Exhibit H

Highly Confidential Detailed Factual and Legal Basis for Mylan's Opinion That U.S. Patent No. 11,084,865 B2 Is Invalid, Unenforceable, and/or Will Not Be Infringed

I. Introduction.

Pursuant to 42 U.S.C. § 262(*l*)(3)(B)(ii)(I), this document is the detailed factual and legal basis for Mylan's[1] opinion that U.S. Patent No. 11,084,865 B2 ("865 patent") is invalid, unenforceable, and/or will not be infringed by the commercial marketing of the biological product described in Mylan's BLA No. 761274. Mylan specifically reserves all rights to raise any additional defenses should litigation ensue.

II. Mylan's BLA Product.

Mylan's product, M710, 2 mg, Solution for Intravitreal Injection, as described in Mylan's BLA No. 761274, is a proposed biosimilar product to EYLEA®, 40 mg/ml Injection for IV Use (aflibercept, BLA No. 125387, Regeneron Pharmaceuticals, United States) (hereinafter "BLA Product").

III. Legal Standards.

A. Patent Non-Infringement.

A patent infringement analysis consists of two steps: (1) determining the scope of the claims, a legal issue for the court; and (2) comparing the accused product to the claims, a factual question. *Carroll Touch, Inc. v. Electro Mech. Sys., Inc.*, 15 F.3d 1573, 1576-78 (Fed. Cir. 1993). A claim may be infringed either: (1) literally; or (2) under the judicially-created doctrine of equivalents. *See id.* Moreover, because a dependent claim incorporates all of the elements and limitations of the independent claim on which it depends, a dependent claim cannot be infringed unless each and every element of the underlying independent claim is also infringed. *Forest Labs., Inc. v. Abbott Labs.*, 239 F.3d 1305, 1310-11 & n.3 (Fed. Cir. 2001).

1. Claim Construction.

"It is axiomatic that the claims mark the outer boundaries of the patent right to exclude." *Astrazeneca AB v. Mut. Pharm. Co., Inc.*, 384 F.3d 1333, 1336 (Fed. Cir. 2004). The "goal of claim construction is to determine what an ordinary artisan would deem the invention claimed by the patent, taking the claims together with the rest of the specification." *Id.* at 1337; *see also DeMarini Sports, Inc. v. Worth, Inc.*, 239 F.3d 1314, 1322 (Fed. Cir. 2001) (noting that claim construction "is simply a way of elaborating the normally terse claim language in order to understand and explain, but not to change, the scope of the claims" (internal quotation marks and citation omitted)).

The intrinsic evidence, including the claims, the specification, and the prosecution history, is the primary source for determining claim meaning. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1315-18 (Fed. Cir. 2005) (en banc); *Astrazeneca*, 384 F.3d at 1336; *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979-80 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370

[1] As used herein, "Mylan" refers to Mylan Pharmaceuticals Inc., the applicant of BLA No. 761274.

(1996). The claim construction inquiry begins with the plain and ordinary meaning of the claims, which define the scope of the right to exclude. *See Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). "When construing patent claims, there is a heavy presumption that the language in the claim carries its ordinary and customary meaning amongst artisans of ordinary skill in the relevant art at the time of the invention." *Housey Pharm., Inc. v. Astrazeneca UK Ltd.*, 366 F.3d 1348, 1352 (Fed. Cir. 2004) (citation and internal quotation marks omitted).

A patentee may assign a claim term a meaning "other than its ordinary and accustomed meaning . . . if the patentee has chosen to be his or her own lexicographer by clearly setting forth an explicit definition for a claim term." *Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985, 990-91 (Fed. Cir. 1999) (examining the scope of the term "heading" through its use by the patentee throughout the specification); *see also Markman*, 52 F.3d at 979-80; *Schering Corp. v. Amgen Inc.*, 222 F.3d 1347, 1353 (Fed. Cir. 2000). The Federal Circuit has made clear that rigid formalism in this regard is not required. *See Astrazeneca*, 384 F.3d at 1339 (rejecting argument that lexicography requires rigid formalism and explicit statements of definition). Lexicography does not require a "statement in the form 'I define _____ to mean ____,'" but rather can be accomplished in a more subtle manner or even by implication. *Id*. at 1349-1350; *see also Bell Atl. Network Servs., Inc. v. Covad Commc'ns Grp., Inc.*, 262 F.3d 1258, 1268 (Fed. Cir. 2001) ("[A] claim term may be clearly redefined without an explicit statement of redefinition. . . . [T]he specification may define claim terms 'by implication' such that the meaning may be 'found in or ascertained by a reading of the patent documents.'").

The specification also should be consulted to determine whether the patentee has disavowed or relinquished claim scope. *See SciMed Life Sys., Inc. v. Advanced Cardiovascular Sys., Inc.*, 242 F.3d 1337, 1340-41 (Fed. Cir. 2001) ("Where the specification makes clear that the invention does not include a particular feature, that feature is deemed to be outside the reach of the claims of the patent, even though the language of the claims . . . might be considered broad enough to encompass the feature in question.").

In addition, a patentee cannot recapture in litigation a claim scope surrendered during the prosecution of the patent, either by amendment or argument. *See Pharmacia & Upjohn Co. v. Mylan Pharm., Inc.*, 170 F.3d 1373, 1376-77 (Fed. Cir. 1999). "Claims may not be construed one way in order to obtain their allowance and in a different way against accused infringers." *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995).

Further, the Federal Circuit has approved reliance upon statements in foreign prosecutions where the statements constituted "blatant admission[s]" directed at the claim scope, *see Gillette Co. v. Energizer Holdings, Inc.*, 405 F.3d 1367, 1374 (Fed. Cir. 2005), and where the statements proved otherwise "consistent with the claims and the invention described in the specification" at issue. *Apple Inc. v. Motorola, Inc.*, 757 F.3d 1286, 1313 (Fed. Cir. 2014), *overruled on other grounds by Williamson v. Citrix Online, LLC*, 729 F.3d 1339 (Fed. Cir. 2015).

2. Comparison of the Accused Product to the Properly Construed Claims.

a. Literal Infringement.

Under 35 U.S.C. § 271(a),[2] "whoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent." Literal infringement requires a patentee to prove "that every limitation of the asserted claim is literally met by the accused device." *Enercon GmbH v. Int'l Trade Comm'n*, 151 F.3d 1376, 1384 (Fed. Cir. 1998); *see also Amhil Enters. Ltd. v. Wawa, Inc.*, 81 F.3d 1554, 1562 (Fed. Cir. 1996) (literal infringement occurs "when the properly construed claim reads on the accused device exactly"). The failure to meet even a single element within a claim mandates a finding that the accused product does not literally infringe the patent. *Laitram Corp. v. Rexnord, Inc.*, 939 F.2d 1533, 1535 (Fed. Cir. 1991). A prior commercial use of claimed "subject matter consisting of a process, or consisting of a machine, manufacture, or composition of matter used in a manufacturing or other commercial process" may provide an infringement defense if the "commercial use occurred at least 1 year before the earlier of either . . . the effective filing date of the claimed invention; or . . . the date on which the claimed invention was disclosed to the public in a manner that qualified for the exception from prior art under [AIA] section 102(b)." AIA 35 U.S.C. § 273.

35 U.S.C. § 271(f) contains two subsections. Section 271(f)(1) addresses exporting a substantial portion of an invention's components:

> Whoever without authority supplies or causes to be supplied in or from the United States all or a substantial portion of the components of a patented invention, where such components are uncombined in whole or in part, in such manner as to actively induce the combination of such components outside of the United States in a manner that would infringe the patent if such combination occurred within the United States, shall be liable as an infringer.

WesternGeco LLC v. ION Geophysical Corp., 138 S. Ct. 2129, 2134 (2018). "[S]ubstantial portion" has a "quantitative, not a qualitative meaning" and "a single component does not constitute a substantial portion of the components that can give rise to liability under § 271(f)(1)." *Life Techs. Corp. v. Promega Corp.*, 137 S. Ct. 734, 737, 743 (2017). Section 271(f)(2) addresses exporting components that are specially adapted for an invention:

> Whoever without authority supplies or causes to be supplied in or from the United States any component of a patented invention that is especially made or especially adapted for use in the invention and not a staple article or commodity of commerce suitable for substantial noninfringing use, where such component is uncombined in whole or in part, knowing that such component is so made or adapted and intending that such component will be combined outside of the United States in a manner that would infringe the patent if such combination occurred within the United

[2] Unless otherwise indicated, citations to Title 35 of the U.S. Code refer to statutes in force prior to the effective date of the America Invents Act ("AIA").

States, shall be liable as an infringer.

WesternGeco, 138 S. Ct. at 2135.

Under 35 U.S.C. § 271(g):

> Whoever without authority imports into the United States or offers to sell, sells, or uses within the United States a product which is made by a process patented in the United States shall be liable as an infringer, if the importation, offer to sell, sale, or use of the product occurs during the term of such process patent. In an action for infringement of a process patent, no remedy may be granted for infringement on account of the noncommercial use or retail sale of a product unless there is no adequate remedy under this title for infringement on account of the importation or other use, offer to sell, or sale of that product. A product which is made by a patented process will, for purposes of this title, not be considered to be so made after (1) it is materially changed by subsequent processes; or (2) it becomes a trivial and nonessential component of another product.

"[W]hen read as a whole, the two parts of section 271(g) require the plaintiff to demonstrate (1) that a product is produced pursuant to a patented process, (2) that the product is then imported into this country, and (3) that the product made by the patented process is neither materially changed by subsequent processes nor a trivial and nonessential component of another product." *Eli Lilly & Co. v. Am. Cyanamid Co.*, 896 F. Supp. 851, 855-56 (S.D. Ind. 1995), *aff'd*, 82 F.3d 1568 (Fed. Cir. 1996); *see also Bayer AG v. Housey Pharm., Inc.*, 340 F.3d 1367, 1377 (Fed. Cir. 2003).

A determination of what "products will be considered to have been 'made by' the patented process" is determined on a case-by-case basis. *Bio-Tech. Gen. Corp. v. Genentech, Inc.*, 80 F.3d 1553, 1561 (Fed. Cir. 1996). Courts have held "the ordinary meaning of 'made' as used in § 271(g) means 'manufacture,'" and thus "extends to the creation or transformation of a product, such as by synthesizing, combining components, or giving raw materials new properties." *Momenta Pharm., Inc. v. Teva Pharm. USA Inc.*, 809 F.3d 610, 616 (Fed. Cir. 2015). The process must not be "too far removed from the actual making of the product." *Id.* at 617.

When examining whether a product has been "materially changed" courts "look [] to the substantiality of the change between the product of the patented process and the product that is being imported." *Eli Lilly*, 82 F.3d at 1573. "The 'materially changed' exception of § 271(g) requires, at a minimum, that there be a real difference between the product imported, offered for sale, sold, or used in the United States and the products produced by the patented process." *Bio-Tech.*, 80 F.3d at 1560. Courts will also examine whether the differences are material where "[m]ateriality is context-dependent." *Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340, 1379 (Fed. Cir. 2009). "Whether a change in a product is material is a factual determination, and is properly for the trier of fact." *Biotec Biologische Naturverpackungen GmbH & Co. v. Biocorp, Inc.*, 249 F.3d 1341, 1352 (Fed. Cir. 2001).

"In the chemical context, a 'material' change in a compound is most naturally viewed as a significant change in the compound's structure and properties." *Eli Lilly*, 82 F.3d at 1573. "[A] change in the physical or chemical properties of a product, even though minor, may be 'material' if the change relates to a physical or chemical property which is an important feature of the product produced by the patented process." *Id.* at 1577. "In the biotechnology context, a significant change in a protein's structure and/or properties would constitute a material change." *Amgen*, 580 F.3d at 1379. Additionally, the determination of whether a "product of a patented process is a 'trivial and nonessential component' of another product is necessarily a question of degree." *Eli Lilly*, 82 F.3d at 1572.

Certain activity is exempt from infringement under the "safe harbor" provision. 35 U.S.C. § 271(e)(1) states: "[i]t shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs." The Supreme Court has stated that "§ 271(e)(1)'s exemption from infringement extends to all uses of patented inventions that are reasonably related to the development and submission of *any* information under the [Federal Food, Drug, and Cosmetic Act]." *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 202 (2005).

b. Doctrine of Equivalents.

Infringement under the doctrine of equivalents requires the patentee to show, for each claim asserted, the presence of each and every claim element or its substantial equivalent in the accused device. *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 732-33 (2002); *Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 40 (1997); *Wolverine World Wide, Inc. v. Nike, Inc.*, 38 F.3d 1192, 1199 (Fed. Cir. 1994). An equivalent of a missing claim element or limitation is found only if "'insubstantial differences' distinguish the missing claim element from the corresponding aspects of the accused [product]." *Abbott Labs. v. Novopharm Ltd.*, 323 F.3d 1324, 1329 (Fed. Cir. 2003) (alteration in original) (quoting *Sage Prods., Inc. v. Devon Indus., Inc.*, 126 F.3d 1420, 1423 (Fed. Cir. 1997)).

The scope and application of this doctrine, however, are limited. The Supreme Court has warned that "[i]t is important to ensure that the application of the doctrine, even as to an individual element, is not allowed such broad play as to effectively eliminate that element in its entirety." *Warner-Jenkinson*, 520 U.S. at 29. Under this "all elements rule, there can be no infringement under the doctrine of equivalents if even one limitation of a claim or its equivalent is not present in the accused device." *Lockheed Martin Corp. v. Space Sys./Loral, Inc.*, 324 F.3d 1308, 1321 (Fed. Cir. 2003). Furthermore, "if a theory of equivalence would entirely vitiate a particular claim element, partial or complete judgment should be rendered by the court, as there would be no further material issue for the jury." *Warner-Jenkinson*, 520 U.S. at 39 n.8. In addition, the scope of permissible equivalents cannot encompass or ensnare what is already in the prior art. *See, e.g.*, *Jang v. Boston Sci. Corp.*, 872 F.3d 1275, 1285 (Fed. Cir. 2017); *Marquip, Inc. v. Fosber Am., Inc.*, 198 F.3d 1363, 1367 (Fed. Cir. 1999).

Likewise, under the doctrine of prosecution history estoppel, an equivalent cannot be extended to include subject matter surrendered by the patentee either in amendments to

overcome patentability rejections or in arguments to secure allowance of a claim. *See Warner-Jenkinson*, 520 U.S. at 33; *Wang Labs., Inc. v. Mitsubishi Elecs. Am., Inc.*, 103 F.3d 1571, 1577-78 (Fed. Cir. 1997); *Haynes Int'l, Inc. v. Jessop Steel Co.*, 8 F.3d 1573, 1577-78 (Fed. Cir. 1993), *reh'g granted on other grounds*, 15 F.3d 1076 (Fed. Cir. 1994). Pursuant to the disclosure-dedication rule, a patentee can disclaim an equivalent by disclosing subject matter in the specification without claiming it. *SanDisk Corp. v. Kingston Tech. Co.*, 695 F.3d 1348, 1363 (Fed. Cir. 2012); *Johnson & Johnston Assocs., Inc. v. R.E. Serv. Co.*, 285 F.3d 1046, 1054 (Fed. Cir. 2002) (en banc).

In addition, a patentee's arguments during the prosecution of a patent regarding a "critical feature" of an invention used to overcome a prior art rejection can give rise to argument-based prosecution history estoppel. *See, e.g.*, *Pharmacia & Upjohn*, 170 F.3d at 1377-78 (finding that "key feature of the present invention" statement during prosecution surrendered claim scope). Further, a patentee's "failure to challenge the Examiner's understanding amounts to a disclaimer." *Sandbox Logistics v. Proppant Express*, No. 19-1684, 2020 WL 2517113, at *4 (Fed. Cir. 2020).

c. Indirect Infringement.

Where a particular entity has not directly committed an act of infringement but has acted in a manner leading to the direct infringement by another, that entity may be held liable for "indirect infringement" for inducement of infringement under 35 U.S.C. § 271(b) and/or for contributory infringement under 35 U.S.C. § 271(c). *See, e.g.*, *Joy Techs., Inc. v. Flakt, Inc.*, 6 F.3d 770, 774 (Fed. Cir. 1993). Liability for either inducement of infringement or contributory infringement requires direct infringement by another as a prerequisite. *See, e.g.*, *Deepsouth Packing Co. v. Laitram Corp.*, 406 U.S. 518, 526 (1972) ("[I]f there is no (direct) infringement of a patent there can be no contributory infringer."), *superseded by statute on other grounds by* 35 U.S.C. § 271(f); *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336, 341 (1961) ("Aro I"); *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1303 (Fed. Cir. 2006); *Joy Techs.*, 6 F.3d at 774 ("Liability for either active inducement of infringement or for contributory infringement is dependent upon the existence of direct infringement."); *C.R. Bard, Inc. v. Advanced Cardiovascular Sys., Inc.*, 911 F.2d 670, 673 (Fed. Cir. 1990) ("[A] finding of induced or contributory infringement must be predicated on a direct infringement of [the asserted] claim."); *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 134 S. Ct. 2111, 2117 (2014) ("[A]s both the Federal Circuit and respondents admit, where there has been no direct infringement, there can be no inducement of infringement under § 271(b)."). Direct infringement of a method claim "occurs where all steps of a claimed method are performed by or attributable to a single entity." *Akamai Techs., Inc. v. Limelight Networks, Inc.*, 797 F.3d 1020, 1022 (Fed. Cir. 2015) (en banc). An entity is responsible for others' performance of method steps "where that entity directs or controls others' performance" and/or "where the actors form a joint enterprise." *Id.* Courts rely on general principles of vicarious liability to determine if a single entity controls the acts of another. *Id.* However, according to the Federal Circuit, indirect infringement based on direction and control requires that customers do more than merely take a vendor's guidance and act independently on their own. *Id.* at 1025.

Moreover, inducing infringement under 35 U.S.C. § 271(b) requires "actively and knowingly aiding and abetting another's direct infringement." *C.R. Bard*, 911 F.2d at 675; *accord*

Rodime PLC v. Seagate Tech., Inc., 174 F.3d 1294, 1306 (Fed. Cir. 1999). The patentee must prove that the defendant's "actions induced infringing acts *and* that [it] knew or should have known [its] actions would induce actual infringements." *Manville Sales Corp. v. Paramount Sys., Inc.*, 917 F.2d 544, 553 (Fed. Cir. 1990). Proof of mere knowledge of the acts alleged to constitute infringement is insufficient; rather, the plaintiff must prove specific intent and action to induce infringement. *See, e.g.*, *DSU*, 471 F.3d at 1305; *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1469 (Fed. Cir. 1990) (holding that "proof of actual intent to cause the acts which constitute the infringement is a necessary prerequisite to finding active inducement"); *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 937 (2005) (the inducement rule in the copyright context "premises liability on purposeful, culpable expression and conduct"). Furthermore, the patentee or patent owner also must prove that the defendant was responsible for the "commission of an affirmative act" in furtherance of the direct infringement of another. *Beverly Hills Fan Co. v. Royal Sovereign Corp.*, 21 F.3d 1558, 1569 & n.25 (Fed. Cir. 1994). In general, "inducement has connotations of *active steps knowingly taken*—knowingly at least in the sense of purposeful, intentional as distinguished from accidental or inadvertent." *Tegal Corp. v. Tokyo Electron Co.*, 248 F.3d 1376, 1378 (Fed. Cir. 2001).

The Federal Circuit has made clear that the patentee must prove that an applicant (here, a BLA applicant) will actually promote or encourage others, such as pharmacists, physicians, nurses or other end users, to infringe the patent by using the drug for the patented use. *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1364-65 (Fed. Cir. 2003); *Takeda Pharm. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015) ("The label must encourage, recommend, or promote infringement."). The "mere existence of direct infringement . . . is not sufficient for inducement"; the inquiry instead focuses on whether "the instructions reflect an 'affirmative' or 'specific intent to encourage infringement.'" *HZNP Meds. LLC v. Actavis Labs. UT, Inc.*, 940 F.3d 680, 702 (Fed. Cir. 2019) (alteration in original); *Takeda*, 785 F.3d at 633 (finding insufficient evidence that instructions would inevitably lead doctors to practice claimed method); *see also United Therapeutics Corp. v. Sandoz, Inc.*, Nos. 12-1617, 13-316, 2014 WL 4259153, at *19-21 (D.N.J. Aug. 29, 2014). Moreover, intent to induce infringement cannot be inferred when there are substantial non-infringing uses for the drug. *Warner-Lambert*, 316 F.3d at 1365; *see also Allergan, Inc. v. Alcon Labs., Inc.*, 324 F.3d 1322, 1332-33 (Fed. Cir. 2003).

In addition, contributory infringement arises when there is a sale or offer for sale of a component of a patented apparatus or a material for use in a patented process if the material or apparatus constitutes a material part of the invention and the person supplying it knows that it is especially made or adapted for use in the infringement of a patent. 35 U.S.C. § 271(c). The Supreme Court in *Aro Manufacturing Co. v. Convertible Top Replacement Co.*, 377 U.S. 476 (1964) ("Aro II") addressed the knowledge requirement of § 271(c). The Court held that § 271(c) requires a showing that the alleged contributory infringer knew that the combination for which his component was especially designed was both patented and infringing. *Aro II*, 377 U.S. at 488; *see also Golden Blount, Inc. v. Robert H. Peterson Co.*, 365 F.3d 1054, 1061 (Fed. Cir. 2004).

Furthermore, a party is liable for contributory infringement only if its product is not a "staple article . . . of commerce suitable for substantial noninfringing use." 35 U.S.C. § 271(c). If a product is "suitable for substantial noninfringing use," it would be, by definition, a "staple

article" of commerce, the sale of which would not create liability for contributory infringement. *C.R. Bard*, 911 F.2d at 673-74 (determining whether product was "staple article" by examining whether it had substantial non-infringing uses). The threshold for what constitutes a "substantial noninfringing use" is not high. Indeed, "[u]nless a commodity 'has no use except through practice of the patented method,' the patentee has no right to claim that its distribution constitutes contributory infringement." *Sony Corp. of Am. v. Universal City Studios, Inc.*, 464 U.S. 417, 441 (1984) (citation omitted) (quoting *Dawson Chem. Co. v. Rohm & Haas Co.*, 448 U.S. 176, 199 (1980)); *see also Fina Research, S.A. v. Baroid Ltd.*, 141 F.3d 1479, 1481-82 (Fed. Cir. 1998) (finding that "suit may not be brought . . . for contributory infringement, because . . . [the product at issue] is a 'staple article or commodity of commerce suitable for substantial noninfringing use'").

Thus, judgment of non-infringement on a claim of contributory infringement is proper where the defendant proffers competent evidence that the product is used in a non-infringing manner. *See Alloc, Inc. v. Int'l Trade Comm'n*, 342 F.3d 1361, 1374 (Fed. Cir. 2003) (affirming judgment of no contributory infringement where evidence was introduced that accused product could be installed without infringing the claim); *Warner-Lambert*, 316 F.3d at 1365 (concluding that product used in non-infringing manner had substantial non-infringing uses); *Universal Elecs., Inc. v. Zenith Elecs. Corp.*, 846 F. Supp. 641, 652 (N.D. Ill. 1994) (granting summary judgment in favor of alleged contributory infringer based on evidence that accused remote control was sold to owners of devices, which when used with the remote control, would not directly infringe the patent).

B. Patent Invalidity.

Patent invalidity is a complete defense to a charge of infringement. *See, e.g.*, 35 U.S.C. § 282 (stating that invalidity and unenforceability are defenses to any action involving infringement of a patent); *TypeRight Keyboard Corp. v. Microsoft Corp.*, 374 F.3d 1151, 1157 (Fed. Cir. 2004); *Viskase Corp. v. Am. Nat'l Can Co.*, 261 F.3d 1316, 1323 (Fed. Cir. 2001); *Weatherchem Corp. v. J.L. Clark, Inc.*, 163 F.3d 1326, 1335 (Fed. Cir. 1998) ("[I]nvalidity operates as a complete defense to infringement for any product, forever . . . ."). A patent is invalid if it fails to satisfy any of the conditions for patentability found in 35 U.S.C. § 101 *et seq*. Furthermore, a patent claim may be invalid for being an obvious variation of a patented claim under the judicially-created doctrine of obviousness-type double patenting. *Georgia-Pacific Corp. v. U.S. Gypsum Co.*, 195 F.3d 1322, 1326 (Fed. Cir. 1999).

1. Burden of Proof and Presumption of Validity.

The burden of proving invalidity rests with the party asserting it.

> A patent, though presumed valid, 35 U.S.C. § 282 (1988), is actually a fragile entity, and must be propped up by a myriad of supports, each representative of one of the legal requirements of validity. If even a single one of these supports is removed, the patent will fall. For example, a patent may be declared invalid . . . if it is found to be anticipated by a prior art reference, *see id.* § 102; if it is rendered obvious by a combination of the prior art, *see*

> *id*. § 103; or if it fails to satisfy any one of a variety of other conditions.

Morton Int'l, Inc. v. Cardinal Chem. Co., 5 F.3d 1464, 1471-72 (Fed. Cir. 1993) (Mayer, J., concurring).

The statutory presumption of validity merely assumes the U.S. Patent and Trademark Office ("PTO") properly did its job by considering all prior art or other evidence material to patentability. *See Lannom Mfg. Co. v. U.S. Int'l Trade Comm'n*, 799 F.2d 1572, 1575 (Fed. Cir. 1986). "[W]here the PTO has not considered facts relevant to an issue in suit, there is no reason to give deference to its action in issuing the patent and a court may find those facts controlling in determining whether the burden of proof has been sustained." *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 773 n.3 (Fed. Cir. 1983), *overruled in part on other grounds by SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107 (Fed. Cir. 1985) (en banc). Thus, "[t]he courts are the final arbiter of patent validity and, although courts may take cognizance of, and benefit from, the proceedings before the patent examiner, the question is ultimately for the courts to decide, without deference to the rulings of the patent examiner." *Quad Envtl. Techs. Corp. v. Union Sanitary Dist.*, 946 F.2d 870, 876 (Fed. Cir. 1991).

2. 35 U.S.C. § 101—Lack of Utility.

35 U.S.C. § 101 provides that "[w]hoever invents . . . any new and useful process . . . or composition of matter . . . may obtain a patent therefor." A patent claim is invalid if no substantial or practical utility for the invention claimed is disclosed. *Cross v. Iizuka*, 753 F.2d 1040, 1044 (Fed. Cir. 1985). As noted by the Supreme Court:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.

Brenner v. Manson, 383 U.S. 519, 534-35 (1966). Utility generally goes hand in hand with the enablement inquiry. "If a patent claim fails to meet the utility requirement because it is not useful or operative, then it also fails to meet the how-to-use aspect of the enablement requirement." *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) (quoting *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1358 (Fed. Cir. 1999)). The utility requirement thus serves as a gatekeeper to ensure that mere ideas are not patented. "The utility requirement also prevents the patenting of a mere research proposal or an invention that is simply an object of research." *Id*. In other words, an invention that is simply an object of further research, without assurance that anything useful will result, does not meet the utility requirement. *See id*.

3. 35 U.S.C. § 101—Unpatentable Subject Matter.

Patentable subject matter is limited to "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." 35 U.S.C. § 101. "[L]aws of nature, physical phenomena, and abstract ideas" are not patentable subject matter under 35 U.S.C. § 101. *Bilski v. Kappos*, 561 U.S. 593, 601 (2010); *see also INO Therapeutics LLC v. Praxair Distribution Inc.*, 782 F. App'x 1001, 1006 (Fed. Cir. 2019) (holding "claim . . . directed to detecting the presence of [an adverse event] in a patient and then doing nothing" claims a natural phenomenon). As set forth in *Alice Corp. v. CLS Bank International*, "distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts" is accomplished via a two-step analysis. 573 U.S. 208, 217-18 (2014). The first step requires "determin[ing] whether the claims at issue are directed to one of those patent-ineligible concepts" (i.e., laws of nature, natural phenomena, and abstract ideas). *Id*. at 217. If the claims at issue are directed to patent-ineligible concepts, then the second step involves an analysis of "the elements of each claim both individually and 'as an ordered combination' to determine whether the additional elements 'transform the nature of the claim' into a patent-eligible application." *Id.* (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 78-79 (2012)). That is, "[a] claim that recites an abstract idea must include 'additional features' to ensure 'that the [claim] is more than a drafting effort designed to monopolize the [abstract idea]." *Id* at 221 (alterations in original) (quoting *Mayo*, 566 U.S. at 77); *see also INO Therapeutics*, 782 F. App'x at 1010-11 (finding additional prior art limitations of claimed method "routine and conventional" and unable to transform the "naturally occurring phenomena into a patent-eligible application").

4. 35 U.S.C. § 101—Statutory Double Patenting.

Only one patent, i.e., "a patent," can issue for each patentable invention. *See Miller v. Eagle Mfg. Co.*, 151 U.S. 186, 197 (1894). "The double patenting doctrine generally prevents a patentee from receiving two patents for the same invention." *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1372 (Fed. Cir. 2005). The double patenting doctrine prevents "the extension of the statutory period of monopoly that would occur if successive patents were allowed on the same basic concept" and reduces the potential for harassment by multiple assignees. 3A DONALD S. CHISUM, CHISUM ON PATENTS § 9.01 (2020); *In re Robeson*, 331 F.2d 610, 615 (C.C.P.A. 1964). Furthermore, the filing of a terminal disclaimer does not cure invalidity due to double patenting under 35 U.S.C. § 101. *In re Vogel*, 422 F.2d 438, 441 (C.C.P.A. 1970).

5. 35 U.S.C. § 102—Anticipation.

Under current 35 U.S.C. § 102 (i.e., AIA 35 U.S.C. § 102), a person shall be entitled to a patent unless "the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention," AIA 35 U.S.C. § 102(a)(1), or "the claimed invention was described in a patent . . . or in an application for a patent published or deemed published . . . in which the patent or

application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention," *id.*, AIA § 102(a)(2).[3]

Under pre-AIA 35 U.S.C. § 102, a person shall be entitled to a patent unless "the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent," 35 U.S.C. § 102(a), or "the invention was patented or described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States," *id.* § 102(b).

A patent claim is said to be anticipated (i.e., not novel) if a comparison of the claim with a prior art reference reveals that every element of the claim is described, either expressly or inherently, in the prior art reference. *See Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003); *Rockwell Int'l Corp. v. United States*, 147 F.3d 1358, 1363 (Fed. Cir. 1998); *In re King*, 801 F.2d 1324, 1326 (Fed. Cir. 1986); *In re Mousa*, 479 F. App'x 348, 352 (Fed. Cir. 2012). "Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates." *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999); *see also In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1373 (Fed. Cir. 2007) (citing *Bristol–Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) ("newly discovered results of known processes are not patentable because those results are inherent in the known processes"); *In re Montgomery*, 677 F.3d 1375, 1381 (Fed. Cir. 2012). In addition, where a specific numerical claim limitation is encompassed by a numerical range in the prior art, the claim is anticipated absent a showing of criticality of the specific numerical claim limitation. *ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1344-45 (Fed. Cir. 2012).

Application of the on-sale bar under 35 U.S.C. § 102(b) requires that (1) "the product must be the subject of a commercial offer for sale" and (2) "the invention must be ready for patenting." *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 67 (1998). To determine if there was an offer for sale, courts generally apply the law of contracts and "focus on those activities that would be understood to be commercial sales and offers for sale 'in the commercial community.'" *Meds. Co. v. Hospira, Inc.*, 827 F.3d 1363, 1373 (Fed. Cir. 2016) (en banc) (quoting *Grp. One, Ltd. v. Hallmark Cards, Inc.*, 254 F.3d 1041, 1047 (Fed. Cir. 2001)). "A sale occurs when there is a 'contract between parties to give and to pass rights of property for consideration which the buyer pays or promises to pay the seller for the thing bought or sold.'" *Helsinn Healthcare S.A. v. Teva Pharm. USA, Inc.*, 855 F.3d 1356, 1364 (Fed. Cir. 2017) (quoting *Trading Techs. Int'l, Inc. v. eSpeed, Inc.*, 595 F.3d 1340, 1361 (Fed. Cir. 2010)).

Regarding invalidity due to prior public use, "[t]he proper test . . . is whether the purported use: (1) was accessible to the public; or (2) was commercially exploited." *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 424 F.3d 1374, 1380 (Fed. Cir. 2005). In evaluating a purported

[3] AIA 35 U.S.C. § 102 is applicable to any patent or patent application "that contains or contained at any time" a claim that has an effective filing date on or after March 16, 2013. *See* 35 U.S.C. § 100 (note).

public use, a court will consider such factors as "evidence relevant to experimentation, . . . the nature of the activity that occurred in public; public access to the use; confidentiality obligations imposed on members of the public who observed the use; and commercial exploitation." *Id.*; *Pronova Biopharma Norge AS v. Teva Pharms. USA, Inc.*, 549 F. App'x 934, 939 (Fed. Cir. 2013) (finding shipment and testing of product samples disclosing all aspects of the claimed invention and unprotected by confidentiality restrictions triggered public use bar).

Under pre-AIA 35 U.S.C. § 102(f), a person shall be entitled to a patent unless "he did not himself invent the subject matter sought to be patented." 35 U.S.C. § 102(f). In other words, if the conception of an invention is derived from another source rather than the named inventors, the patent is said to be invalid under § 102(f). *Price v. Symsek*, 988 F.2d 1187, 1190 (Fed. Cir. 1993). In order to demonstrate derivation under § 102(f), both prior conception of an invention by another and communication of that conception to the patentee must be established. *Id.*

6. 35 U.S.C. § 103(a)—Obviousness.

Under AIA 35 U.S.C. § 103:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.[4]

AIA 35 U.S.C. § 103.

Under pre-AIA 35 U.S.C. § 103(a):

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

35 U.S.C. § 103(a); *see KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

Obviousness is ultimately a legal conclusion, based upon underlying factual inquiries. *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1368 (Fed. Cir. 2003). The required

[4] AIA 35 U.S.C. § 103 is applicable to any patent or patent application "that contains or contained at any time" a claim that has an effective filing date on or after March 16, 2013. *See* AIA 35 U.S.C. § 100 (note).

factual inquiry considers: (1) the level of ordinary skill in the pertinent art; (2) the scope and content of the prior art; and (3) the differences between the prior art and the asserted claims. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Objective evidence of nonobviousness, i.e., so-called "secondary considerations," if any, is considered where relevant. *See id.* at 17-18; *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-39 (Fed. Cir. 1983).

Additionally, it is well settled "that objective evidence [of] non-obviousness must be commensurate in scope with the claims which the evidence is offered to support." *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983) (quoting *In re Tiffin*, 448 F.2d 791, 792 (C.C.P.A. 1971)); *see also In re Kulling*, 897 F.2d 1147, 1149 (Fed. Cir. 1990); *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1468 (Fed. Cir. 1990). A patentee offering objective evidence of non-obviousness bears the burden of demonstrating this "nexus." *See In re Paulsen*, 30 F.3d 1475, 1482 (Fed. Cir. 1994). That is, the patentee must demonstrate "a legally and factually sufficient connection" between the evidence and the patented invention to demonstrate that the evidence does in fact corroborate the invention's non-obviousness. *See id.*; *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1327-28 (Fed. Cir. 2008), *abrogated on other grounds by Travel Sentry, Inc. v. Tropp*, 877 F.3d 1370 (Fed. Cir. 2017).

When, from the perspective of a person of ordinary skill in the art, the differences between the prior art and the claimed invention as a whole would be obvious, a *prima facie* case of obviousness is established under § 103, thus rendering the subject claim invalid. *See In re Dillon*, 919 F.2d 688, 692-93 (Fed. Cir. 1990) (en banc).

Obviousness may be based on one or more references. However, either the prior art as a whole, or knowledge generally available to one of ordinary skill in the art, should suggest the desirability, and thus the obviousness of combining and modifying the prior art to arrive at the claimed invention. *See SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1356 (Fed. Cir. 2000). This requirement for a showing of motivation to combine references ensures that a combination is not improperly made in hindsight. *See In re Gartside*, 203 F.3d 1305, 1318-19 (Fed. Cir. 2000). However, it is not necessary that the references be combined for the same reasons as the inventor. *In re Beattie*, 974 F.2d 1309, 1312 (Fed. Cir. 1992) ("As long as some motivation or suggestion to combine the references is provided by the prior art taken as a whole, the law does not require that the references be combined for the reasons contemplated by the inventor."). Moreover, a "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416. More specifically, "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *Id.* at 417. Further, "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (quoting *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955). Further, "[i]t is long settled that in the context of obviousness, the 'mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not distinguish a claim drawn to those things from the prior art.'" *Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1190 (Fed. Cir. 2019) (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)).

Yet, the mere fact that results are not entirely predictable in advance, and must be confirmed through testing, does not mean that subject matter is nonobvious. "[A] rule of law equating unpredictability to patentability" is improper because "the expectation of success need only be reasonable, not absolute." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). That is, "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Id.*

Where "there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 550 U.S. at 421. "If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *Id.* In such instances "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.*

7. 35 U.S.C. § 112—Lack of Written Description and Enablement.

An inventor is obligated to set forth in the specification "a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention." 35 U.S.C. § 112, ¶ 1; *see also* AIA 35 U.S.C. § 112(a). The test for satisfying the written description requirement is "whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). "Put another way, one skilled in the art, reading the original disclosure, must immediately discern the limitation at issue in the claims." *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000); *see also id.* at 1326-27 ("[O]ne cannot disclose a forest in the original application, and then later pick a tree out of the forest and say here is my invention. In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure."). "[T]o satisfy the written description requirement for a claimed genus, a specification must describe the claimed invention in such a way that a person of skill in the art would understand that the genus that is being claimed has been invented, not just a species of the genus." *Carnegie Mellon Univ. v. Hoffman-La Roche Inc.*, 541 F.3d 1115, 1124 (Fed. Cir. 2008); *see also AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300-02 (Fed. Cir. 2014) (finding description of one type of structurally similar antibodies not representative of full scope of claimed genus); *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1378-79 (Fed. Cir. 2017) (finding that identifying an antigen, by itself, is not sufficient to satisfy written description requirement).

To satisfy the enablement requirement, the claimed invention must be set forth within the specification such that any person skilled in the art can make and use the full scope of the invention without undue experimentation. *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). Thus, one of the purposes of the specification and drawings is to provide one of ordinary skill in the art with a sufficient description of the invention to enable him or her to make and use the invention without having to conduct time-consuming experimentation. *See Idenix Pharms. LLC v. Gilead Scis. Inc.*, 941 F.3d 1149, 1154, 1156-57 (Fed. Cir. 2019); *Enzo Biochem, Inc. v. Calgene,*

Inc., 188 F.3d 1362, 1371 (Fed. Cir. 1999). Whether undue experimentation is required "is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010) (citing *Wands*, 858 F.2d at 737). Specific factors that a court may consider when determining whether a disclosure requires undue experimentation include: (1) how much experimentation is necessary; (2) how much direction or guidance is given; (3) whether working examples are provided; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability of the art; and (8) the breadth of the claims. *Wands*, 858 F.2d at 737. No single factor is outcome-determinative. *Id.* Although illustrative, these factors are not mandatory. *See Enzo*, 188 F.3d at 1371-72 (citing *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991)). A court need not review all of the factors before making an enablement determination. *Id.* at 1371.

8. 35 U.S.C. § 112—Indefiniteness.

"The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112, ¶ 2; *see also* AIA 35 U.S.C. § 112(b). The purpose of this section is to provide clear warning to others as to what constitutes infringement of the patent. *Honeywell Int'l, Inc. v. Int'l Trade Comm'n*, 341 F.3d 1332, 1338 (Fed. Cir. 2003) (recognizing that the definiteness requirement "focuses on whether the claims, as interpreted in view of the written description, adequately perform their function of notifying the public of the [scope of the] patentee's right to exclude") (alteration in original); *accord United Carbon Co. v. Binney & Smith Co.*, 317 U.S. 228, 232 (1942); *Ex parte Oetiker*, 23 U.S.P.Q.2d 1651 (B.P.A.I. 1990), *aff'd sub nom. In re Oetiker*, 951 F.2d 1267 (Fed. Cir. 1991) (unpublished table decision). Otherwise there would be "[a] zone of uncertainty which enterprise and experimentation may enter only at the risk of infringement." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 899 (2014) (quoting *United Carbon*, 317 U.S. at 236). Thus, "a patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Id.* at 901. "If the court determines that a claim is not 'amenable to construction,' then the claim is invalid as indefinite under 35 U.S.C. § 112, ¶ 2." *Honeywell*, 341 F.3d at 1338. Moreover, a claim is indefinite when a given embodiment might simultaneously infringe and not infringe due to differences in the various testing methods that could be used to establish infringement. *See Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1384 (Fed. Cir. 2003); *Dow Chem. Co. v. Nova Chems. Corp.*, 803 F.3d 620, 634 (Fed. Cir. 2015); *Forest Labs., Inc. v. Teva Pharms. USA, Inc.*, 716 F. App'x 987, 994 (Fed. Cir. 2017).

9. 35 U.S.C. § 112—Improper Dependency.

A dependent claim "shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed," and "shall be construed to incorporate by reference all the limitations of the claim to which it refers." 35 U.S.C. § 112, ¶ 4; *see also* AIA 35 U.S.C. § 112(d). If a dependent claim fails to further limit the claim from which it depends, that dependent claim is invalid. *Pfizer, Inc. v. Ranbaxy Labs. Ltd.*, 457 F.3d 1284,

1291-92 (Fed. Cir. 2006). Thus, improper dependency is a valid defense to an allegation of patent infringement. *Id.* at 1292.

10. Obviousness-Type Double Patenting.

"Obviousness-type double patenting is a judicially created doctrine that 'prohibit[s] a party from obtaining an extension of the right to exclude through claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent.'" *Pfizer, Inc. v. Teva Pharm. USA, Inc.*, 518 F.3d 1353, 1363 (Fed. Cir. 2008) (quoting *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 967 (Fed. Cir. 2001)). A later-issued, earlier-expiring, commonly-owned patent may be used as an invalidating obviousness-type double patenting reference. *See, e.g.*, *Gilead Scis., Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208, 1216-17 (Fed. Cir. 2014). Another justification of the doctrine is the prevention of "multiple infringement suits by different assignees asserting essentially the same patented invention." *In re Hubbell*, 709 F.3d 1140, 1145 (Fed. Cir. 2013). The doctrine of obviousness-type double patenting is also known as non-statutory double patenting. *Perricone*, 432 F.3d at 1373. Under this doctrine, "'[a] later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim.'" *Pfizer*, 518 F.3d at 1363 (quoting *Eli Lilly*, 251 F.3d at 968).

There are important differences between an obviousness analysis under 35 U.S.C § 103(a) and obviousness-type double patenting analysis. For example, "[o]bviousness compares claimed subject matter to the prior art; nonstatutory double patenting compares claims in an earlier patent to claims in a later patent or application." *Geneva*, 349 F.3d at 1377 n.1. Under some circumstances, an obviousness-type double patenting analysis may also compare the claims of a later patent against the specification of an earlier patent. For example, "a 'claim to a method of using a composition is not patentably distinct from an earlier claim to the identical composition in a patent disclosing the identical use.'" *Sun Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 611 F.3d 1381, 1385 (Fed. Cir. 2010) (quoting *Pfizer*, 518 F.3d at 1363; *Geneva*, 349 F.3d at 1385-86).

Obviousness-type double patenting based on anticipation does not require a motivation to modify the prior art. *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1297-98 (Fed. Cir. 2012) (construing *Geneva*, 349 F.3d at 1377 n.1), *cert. denied,* 568 U.S. 1123 (2013); *see also Perricone*, 432 F.3d at 1374 (affirming that "the earlier species renders the later genus claims invalid under non-statutory double patenting").

35 U.S.C. § 121 "shields patents that issue on applications filed as a result of a restriction requirement from double patenting invalidation." *Amgen v. F. Hoffman-La Roche*, 580 F.3d at 1350. Because the § 121 "safe harbor provision" applies to applications filed as a result of restriction requirements (i.e., divisional applications), it "does not protect continuation applications or patents descending from only continuation applications." *Id.* at 1352-53. Moreover, even divisional applications must maintain "consonance," a judicially created concept which "specifies that the line of demarcation between the independent and distinct inventions that prompted the restriction requirement be maintained." *St. Jude Med., Inc. v. Access Closure, Inc.*, 729 F.3d 1369, 1377 (Fed. Cir. 2013) (internal quotation marks omitted). "The requirement for consonance applies to both the patent challenged for double patenting (the challenged patent) and

the patent being used as a reference against the challenged patent (the reference patent)." *Id*. (citing *Boehringer Ingelheim Int'l GmbH v. Barr Labs., Inc.*, 592 F.3d 1340, 1352 (Fed. Cir. 2010)).

C. Unenforceability—Inequitable Conduct.

Those involved with prosecuting a patent application before the U.S. Patent and Trademark Office ("PTO") owe an affirmative duty of candor and good faith. *See* 37 C.F.R. § 1.56; *Manual of Patent Examining Procedures* § 2000 *et seq*. The duty of candor and good faith stems from, among other things, the fact that the patent application process is an *ex parte* process. "In light of the ex parte nature of patent prosecution, the number of applications filed, and the limited capacity of the PTO to ascertain the facts necessary to adjudge the patentable merits of each application, . . . the highest standards of honesty and candor on the part of applicants presenting such facts to the office are ... necessary elements in a working patent system." *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1310 (Fed. Cir. 2011) (en banc) (internal quotations omitted). Indeed, the idea that participants in the patent application process must at all times act with candor and in good faith when before the PTO is "essential" to the patent system's ability to operate properly, as the Federal Circuit's predecessor court explained long ago:

> The ex parte prosecution and examination of a patent application must not be considered as an adversary proceeding and should not be limited to the standards required in inter partes proceedings. With the seemingly ever-increasing number of applications before it, the Patent Office has a tremendous burden. While being a fact finding as well as an adjudicatory agency, it is necessarily limited in the time permitted to ascertain the facts necessary to adjudge the patentable merits of each application. In addition, it has no testing facilities of its own. Clearly, it must rely on applicants for many of the facts upon which its decisions are based. *The highest standards of honesty and candor on the part of applicants in presenting such facts to the office are thus necessary elements in a working patent system. We would go so far as to say they are essential.*

Norton v. Curtiss, 433 F.2d 779, 793-94 (C.C.P.A. 1970) (emphasis added); *see also Envtl. Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 698 (Fed. Cir. 1983) ("[P]rosecution of a patent application is ex parte, involving PTO reliance on the candor and good faith of a patent applicant.").

"Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the [Patent] Office." 37 C.F.R. § 1.56(a); *see also* M.P.E.P. § 2000.01. Inequitable conduct occurs when the duty of candor and good faith is breached. *See Ferring B.V. v. Barr Labs., Inc.*, 437 F.3d 1181, 1194-95 (Fed. Cir. 2006) (declaring brand patent in an ANDA case unenforceable due to inequitable conduct before the PTO). A patent obtained through inequitable conduct is unenforceable. *See, e.g.*, *id.* at 1186; *Aventis Pharma S.A. v. Hospira, Inc.*, 675 F.3d 1324, 1337 (Fed. Cir. 2012) (declaring brand patent in an ANDA case unenforceable due to inequitable conduct before the PTO); *Aventis Pharma v.*

Amphastar Pharm., Inc., 525 F.3d 1334, 1349 (Fed. Cir. 2008) (same); *Pharmacia Corp. v. Par. Pharm. Inc.*, 417 F.3d 1369, 1373-75 (Fed. Cir. 2005) (same).

"To prevail on a claim of inequitable conduct, the accused infringer must prove that the patentee acted with the specific intent to deceive the PTO. . . . In other words, the accused infringer must prove by clear and convincing evidence that the applicant knew of the reference, knew that it was material, and made a deliberate decision to withhold it." *Therasense*, 649 F.3d at 1290. "[T]he materiality required to establish inequitable conduct is but-for materiality. When an applicant fails to disclose prior art to the PTO, that prior art is but-for material if the PTO would not have allowed a claim had it been aware of the undisclosed prior art." *Id.* at 1291. The Federal Circuit, however, "recognizes an exception in cases of affirmative egregious misconduct":

> This exception to the general rule requiring but-for proof incorporates elements of the early unclean hands cases before the Supreme Court, which dealt with deliberately planned and carefully executed scheme[s] to defraud the PTO and the courts. When the patentee has engaged in affirmative acts of egregious misconduct, such as the filing of an unmistakably false affidavit, the misconduct is material.

Id. at 1292 (alteration in original) (citation and internal quotation marks omitted).

IV. The 865 Patent.

The 865 patent, titled *VEGF Antagonist Formulations Suitable for Intravitreal Administration*, issued on August 10, 2021, from U.S. Patent Application No. 16/739,559 ("the 559 application"), filed on January 10, 2020.[5]

The 559 application was filed as a purported continuation application of U.S. Patent Application No. 16/582,486, filed on September 25, 2019 (now U.S. Patent No. 11,066,458), which is a purported continuation of application No. 16/159,269, filed on October 12, 2018 (now U.S. Patent No. 10,464,992), which is a purported continuation of application No. 15/879,294, filed on January 24, 2018 (now U.S. Patent No. 10,400,025), which is a purported continuation of application No. 15/095,606, filed on April 11, 2016 (now U.S. Patent No. 9,914,763), which is a purported continuation of application No. 14/330,096, filed on July 14, 2014 (now U.S. Patent No. 9,340,594), which is a purported continuation of application No. 13/914,996, filed on June 11, 2013 (now U.S. Patent No. 8,802,107), which is a purported continuation of application No. 13/329,770, filed on December 19, 2011 (now U.S. Patent No. 8,481,046), which is a purported continuation of application No. 12/833,417, filed on July 9, 2010 (now U.S. Patent No. 8,092,803), which is a purported continuation of application No. 12/560,885, filed on September 16, 2009 (now U.S. Patent No. 7,807,164), which is a purported division of application No. 11/818,463, filed on June 14, 2007 (now U.S. Patent No. 7,608,261), and which purports to claim priority to U.S. Provisional Application No. 60/814,484, filed on June 16, 2006.

[5] Mylan does not concede or otherwise admit that any proper claim of priority to any earlier-filed application has been made or supported.

The face of the 865 patent identifies Eric Furfine, Daniel Dix, Kenneth Graham and Kelly Frye as the purported inventors and Regeneron Pharmaceuticals, Inc. as the purported assignee.

A. Claims.

The 865 patent issued with 64 claims, which recite:

We claim:

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/ml, and wherein said organic co-solvent comprises polysorbate.

3. The vial of claim 2, wherein said organic co-solvent comprises 0.01% to 3% polysorbate.

4. The vial of claim 2, wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20.

5. The vial of claim 2, wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20.

6. The vial of claim 5, wherein said buffer comprises a phosphate buffer.

7. The vial of claim 5, wherein said buffer comprises 5-25 mM buffer.

8. The vial of claim 5, wherein said buffer comprises a pH between about 5.8-7.0.

9. The vial of claim 5, wherein said buffer comprises a pH about 6.2-6.3.

10. The vial of claim 5, wherein said stabilizing agent comprises a sugar.

11. The vial of claim 10, wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.

12. The vial of claim 5, wherein said stabilizing agent comprises 1.0-7.5% of sucrose.

13. The vial of claim 5, wherein said formulation further comprises a tonicity agent.

14. The vial of claim 5, 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.

15. The vial of claim 5, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C.

16. The vial of claim 5, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography.

17. The vial of claim 5, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography.

18. The vial of claim 5, wherein said formulation does not contain phosphate.

19. The vial of claim 5, wherein said formulation does not contain trehalose.

20. The vial of claim 5, wherein said stabilizing agent comprises 1.0-10% of sucrose.

21. The vial of claim 20, wherein said formulation further comprises a tonicity agent.

22. The vial of claim 20, 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.

23. The vial of claim 20, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C.

24. The vial of claim 20, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography.

25. The vial of claim 20, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography.

26. A pre-filled syringe comprising an ophthalmic formulation suitable for intravitreal administration comprising:

a vascular endothelial growth factor (VEGF) antagonist fusion protein,

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 said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography.

27. The pre-filled syringe of claim **26**, wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate.

28. The pre-filled syringe of claim **27**, wherein said organic co-solvent comprises 0.01% to 3% polysorbate.

29. The pre-filled syringe of claim **27**, wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20.

30. The pre-filled syringe of claim **27**, wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20.

31. The pre-filled syringe of claim **30**, wherein said buffer comprises a phosphate buffer.

32. The pre-filled syringe of claim **30**, wherein said buffer comprises 5-25 mM buffer.

33. The pre-filled syringe of claim **30**, wherein said buffer comprises a pH between about 5.8-7.0.

34. The pre-filled syringe of claim **30**, wherein said buffer comprises a pH about 6.2-6.3.

35. The pre-filled syringe of claim **30**, wherein said stabilizing agent comprises a sugar.

36. The pre-filled syringe of claim **35**, wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.

37. The pre-filled syringe of claim **30**, wherein said stabilizing agent comprises 1.0-7.5% of sucrose.

38. The pre-filled syringe of claim **30**, wherein said formulation further comprises a tonicity agent.

39. The pre-filled syringe of claim **30**, 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.

40. The pre-filled syringe of claim **30**, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C.

41. The pre-filled syringe of claim **30**, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography.

42. The pre-filled syringe of claim **30**, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography.

43. The pre-filled syringe of claim **30**, wherein said formulation does not contain phosphate.

44. The pre-filled syringe of claim **30**, wherein said formulation does not contain trehalose.

45. The pre-filled syringe of claim **30**, wherein said stabilizing agent comprises 1.0-10% of sucrose.

46. The pre-filled syringe of claim **45**, wherein said formulation further comprises a tonicity agent.

47. The pre-filled syringe of claim **45**, 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.

48. The pre-filled syringe of claim **45**, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C.

49. The pre-filled syringe of claim **45**, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography.

50. The pre-filled syringe of claim **45**, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography.

51. An ophthalmic formulation comprising:

(a) 40 mg/ml of a glycosylated VEGF antagonist fusion protein comprising amino acids 27-457 of SEQ ID NO:4;

(b) 0.03% to 0.1% polysorbate;

(c) 5-40 mM of sodium phosphate buffer, pH between 5.8-7.0; and

(d) sucrose;

wherein the ophthalmic formulation is suitable for intravitreal administration; and

wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for 2 months as measured by size exclusion chromatography.

52. The formulation of claim **51**, wherein said formulation comprises at least 5% sucrose.

53. The formulation of claim **51**, wherein said formulation comprises 1-10% sucrose.

54. A pre-filled syringe suitable for intravitreal administration comprising the formulation of claim **51**.

55. A vial suitable for intravitreal administration comprising the formulation of claim **51**.

56. The formulation of claim **51**, wherein said formulation comprises 10 mM sodium phosphate buffer, 0.03% polysorbate, 5% sucrose, and a pH between 6.2-6.3.

57. A pre-filled syringe suitable for intravitreal administration comprising the formulation of claim **56**.

58. A vial suitable for intravitreal administration comprising the formulation of claim **56**.

59. The formulation of claim **56**, wherein said formulation further comprises 40 mM NaCl.

60. A pre-filled syringe suitable for intravitreal administration comprising the formulation of claim **59**.

61. A vial suitable for intravitreal administration comprising the formulation of claim **59**.

62. The formulation of claim **59**, 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.

63. A pre-filled syringe suitable for intravitreal administration comprising the formulation of claim **62**.

64. A vial suitable for intravitreal administration comprising the formulation of claim **62**.

* * * * *

(865 patent at 19:29-22:60).

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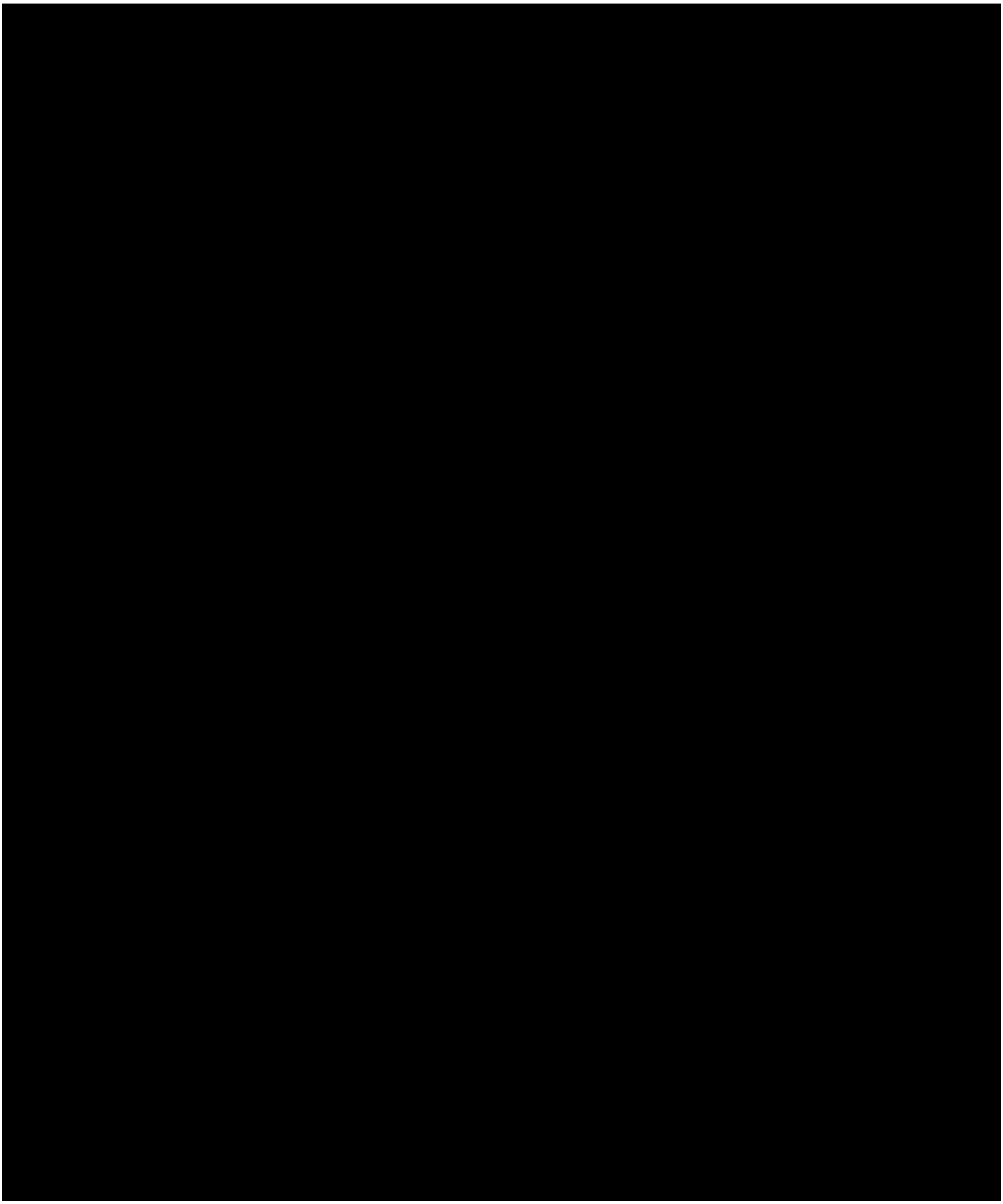

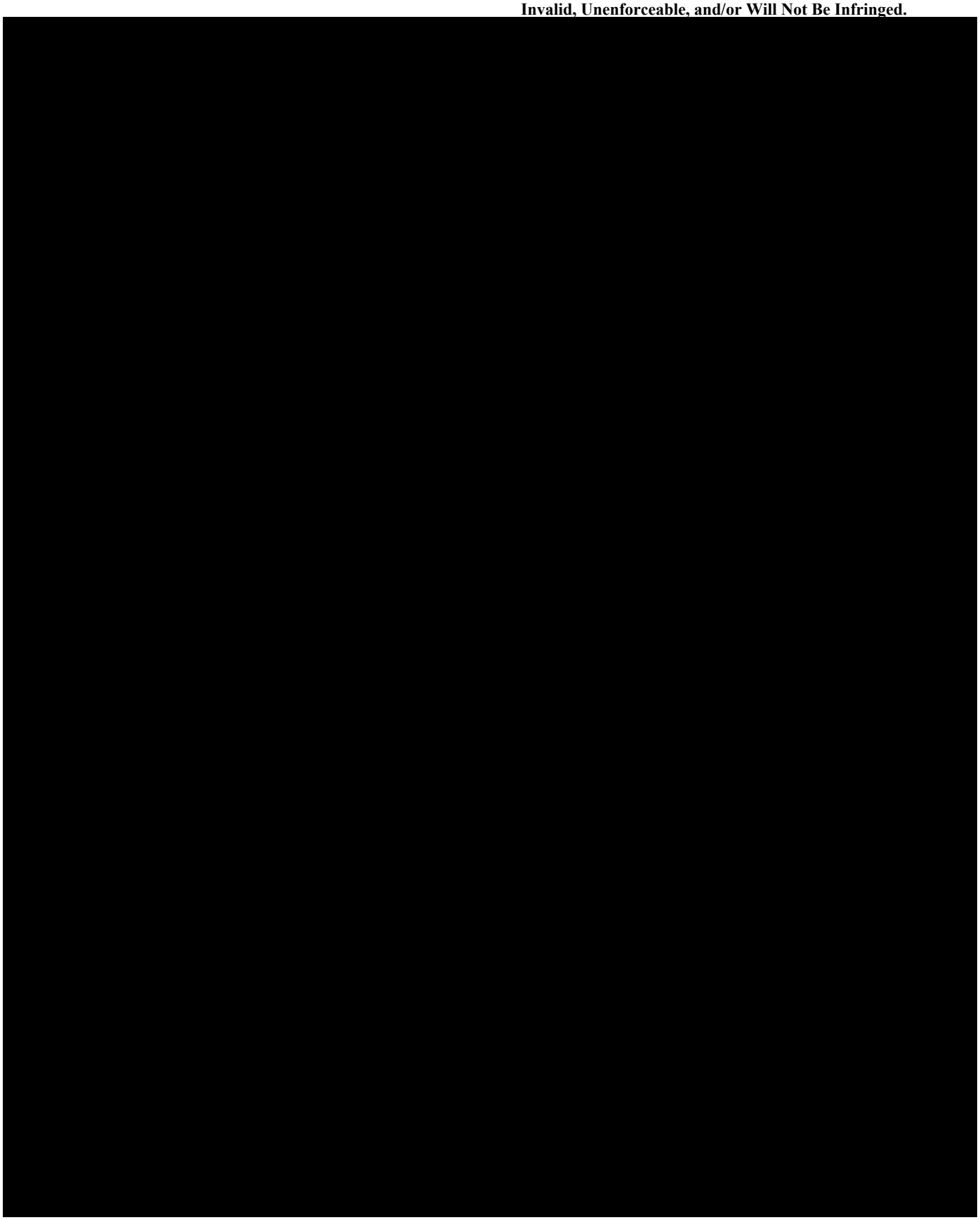

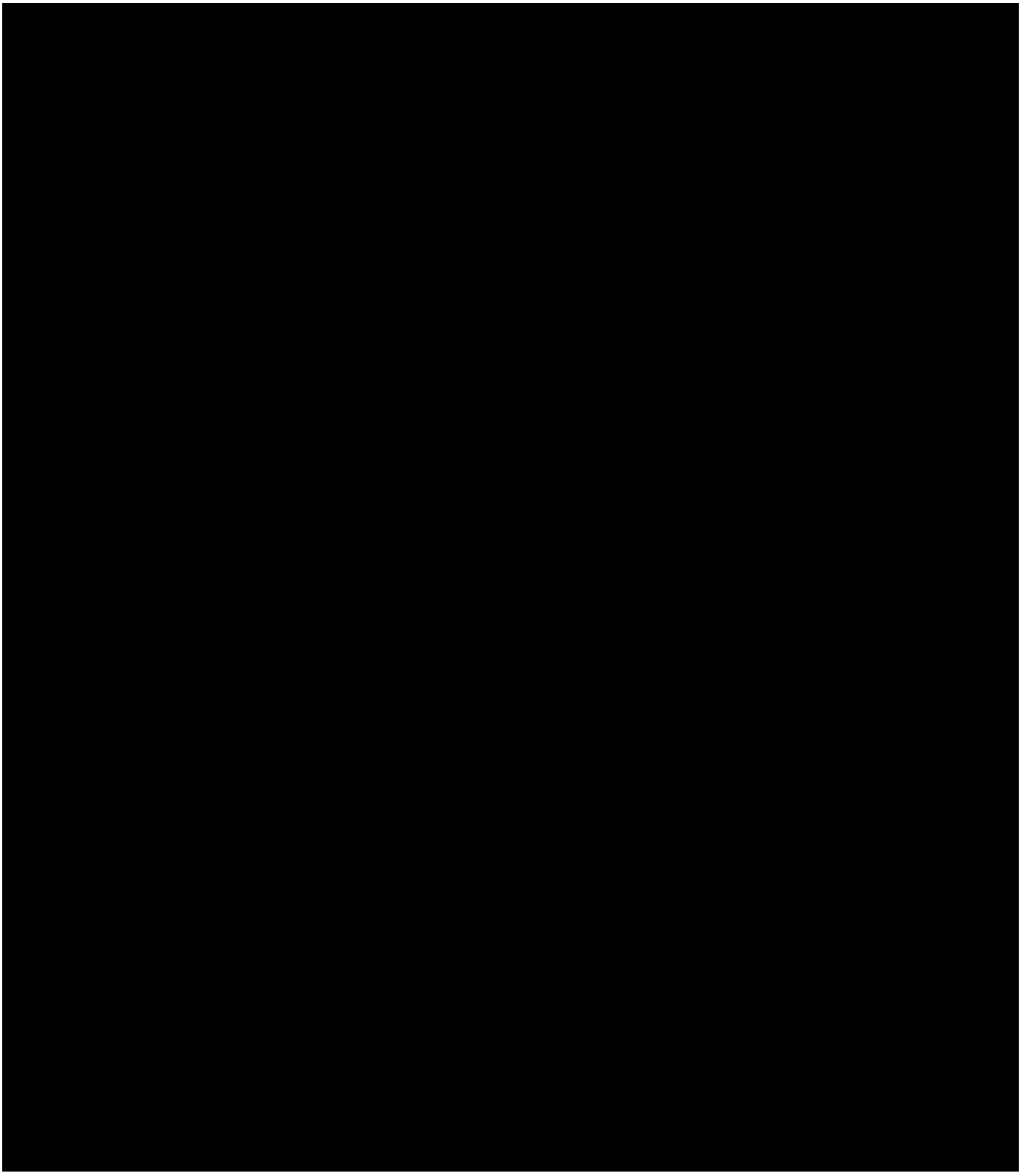

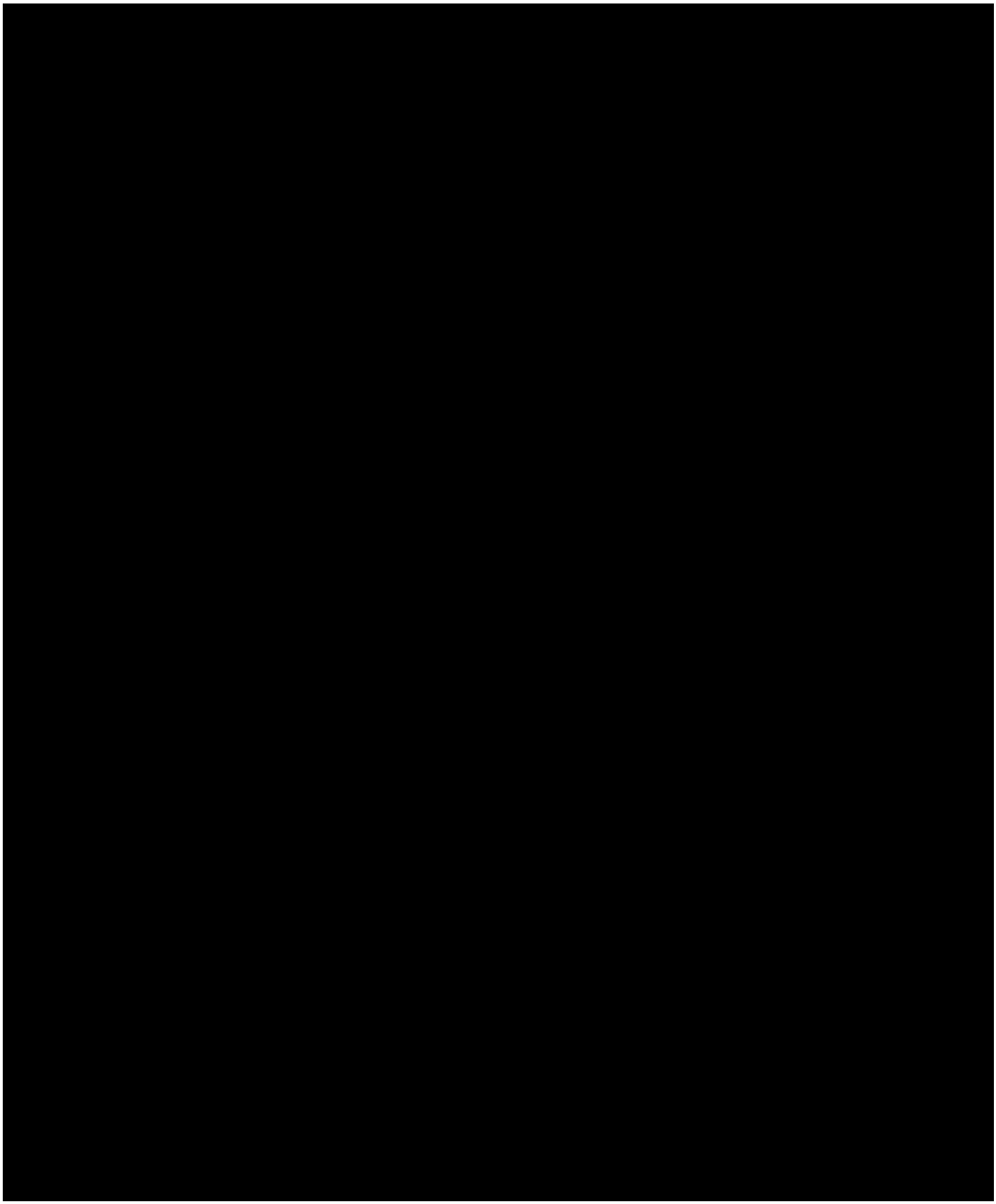

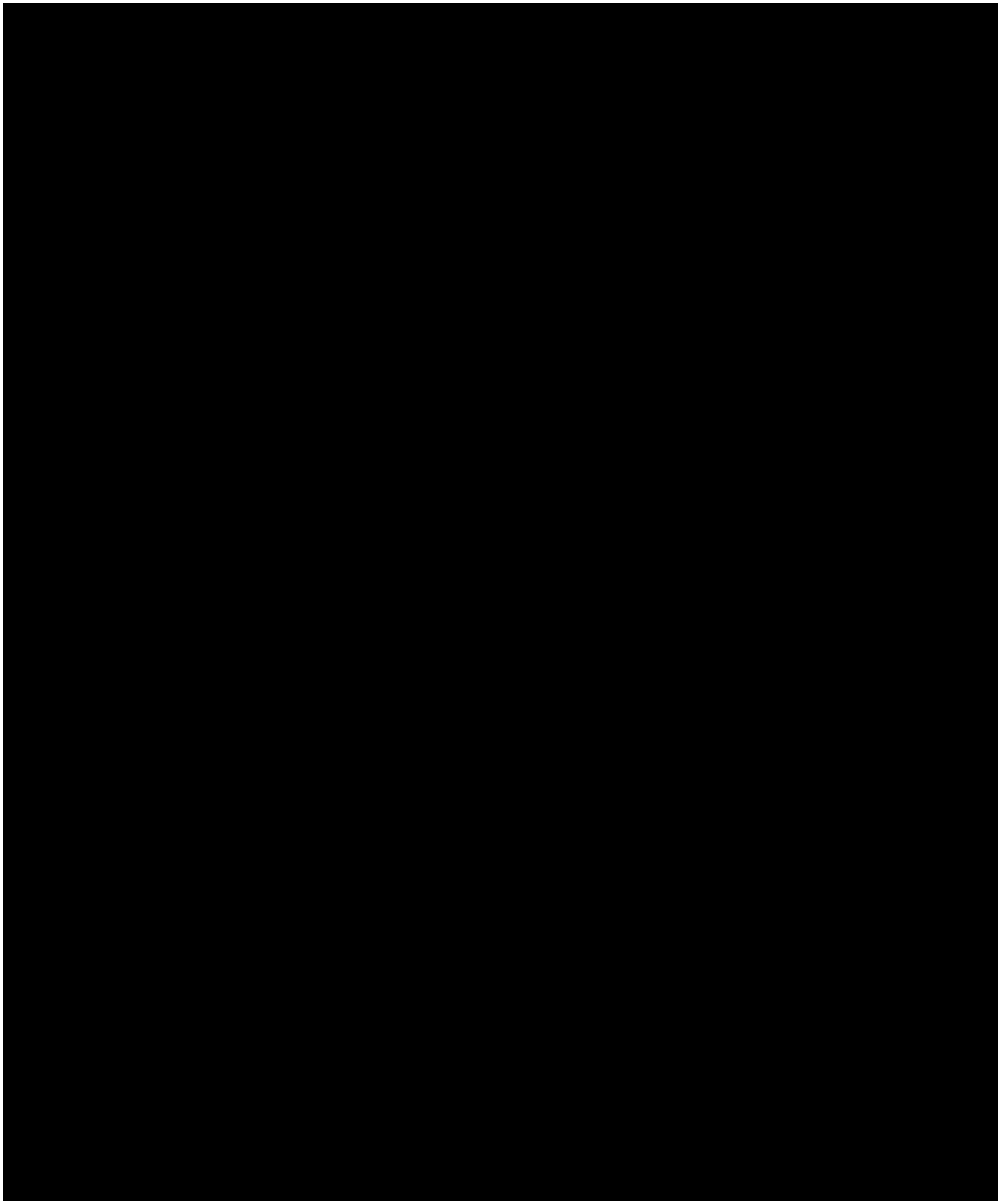

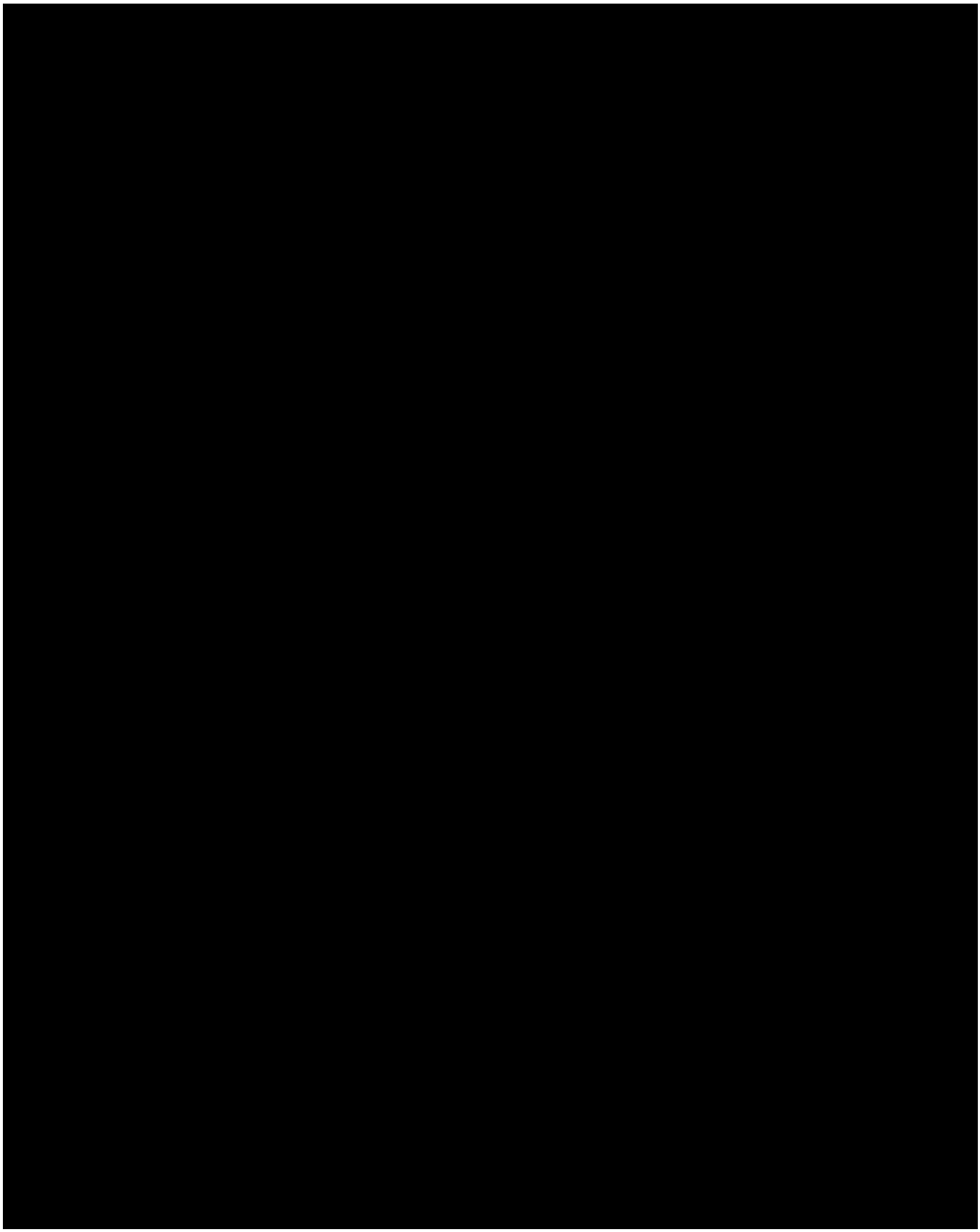

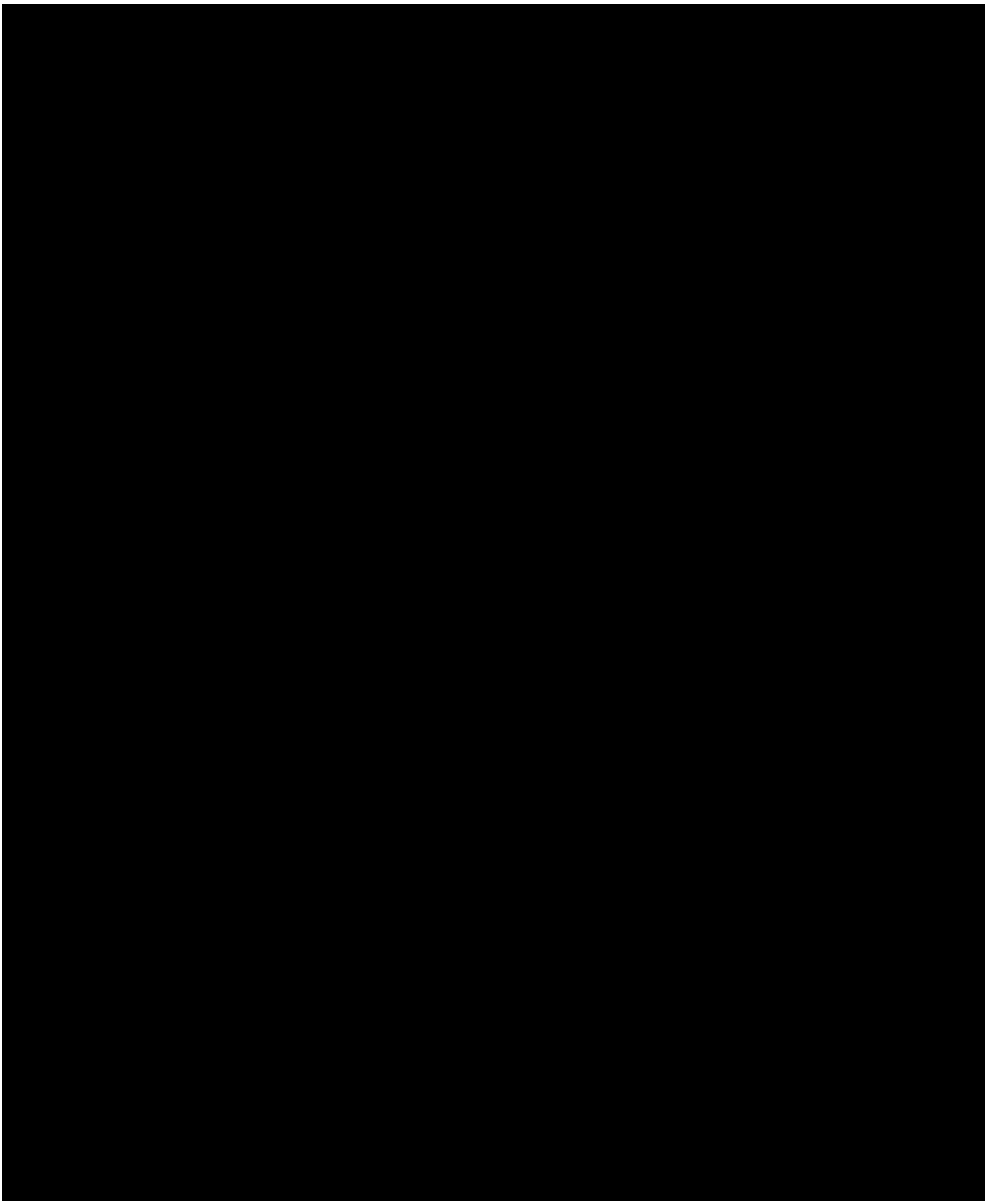

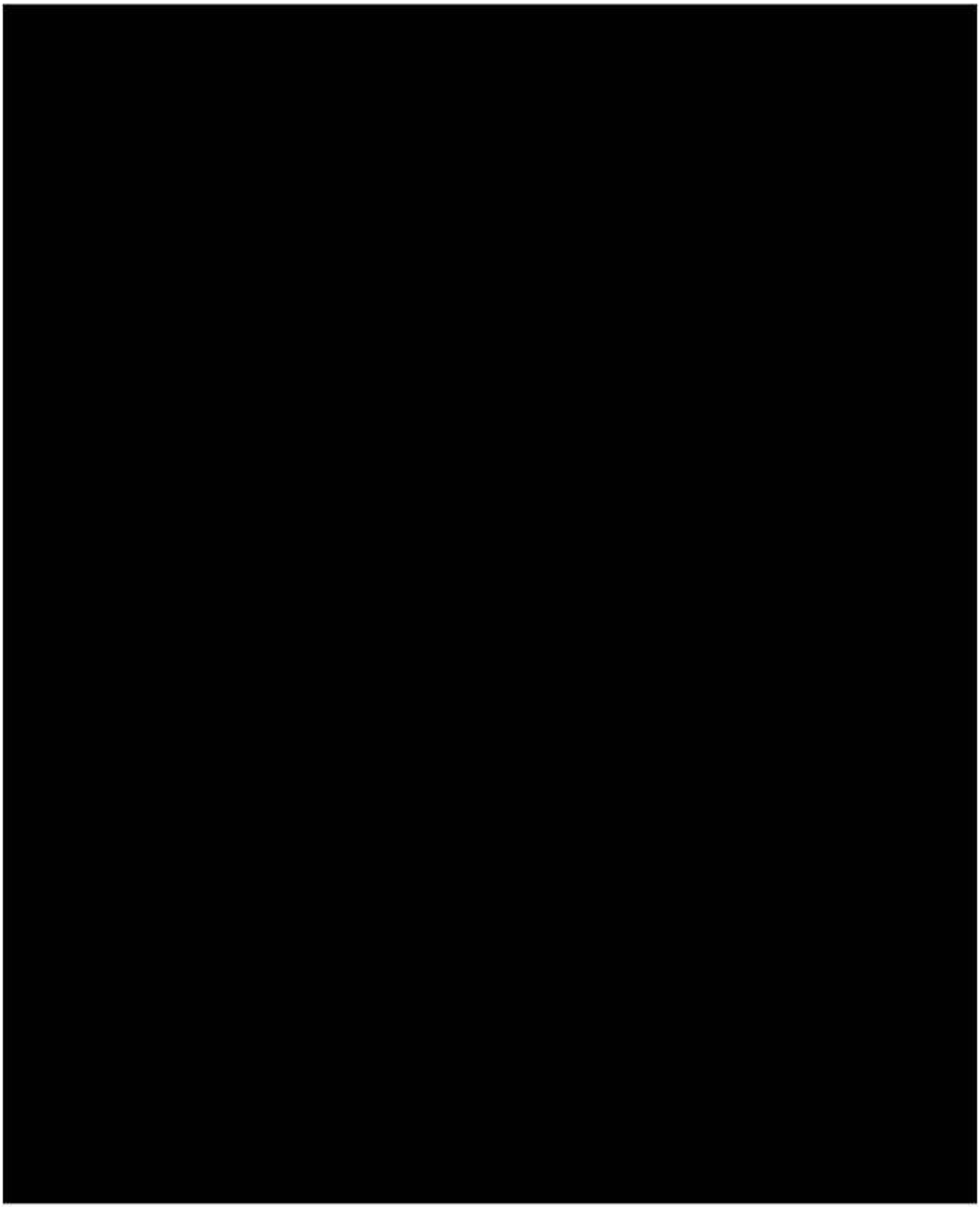

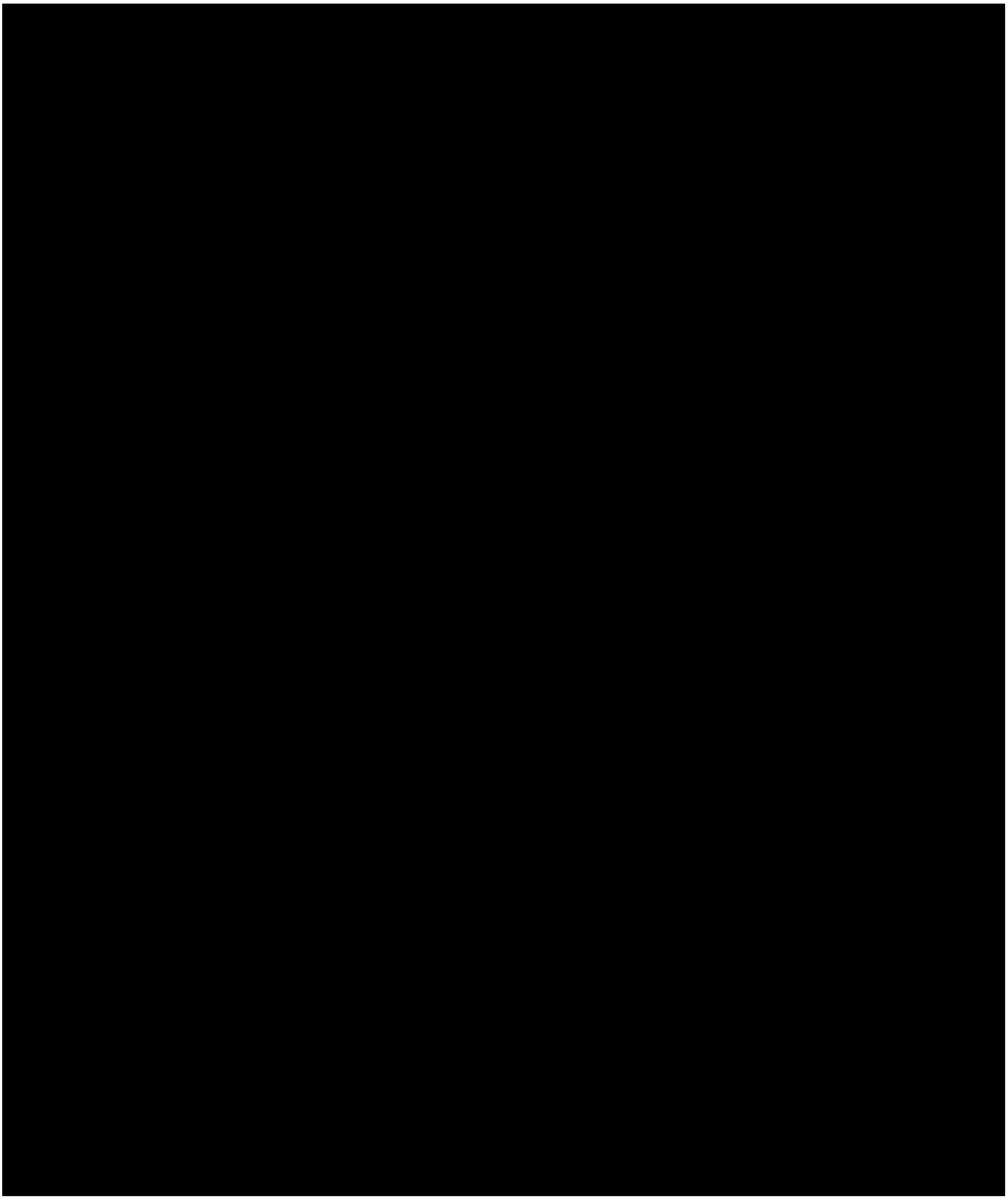

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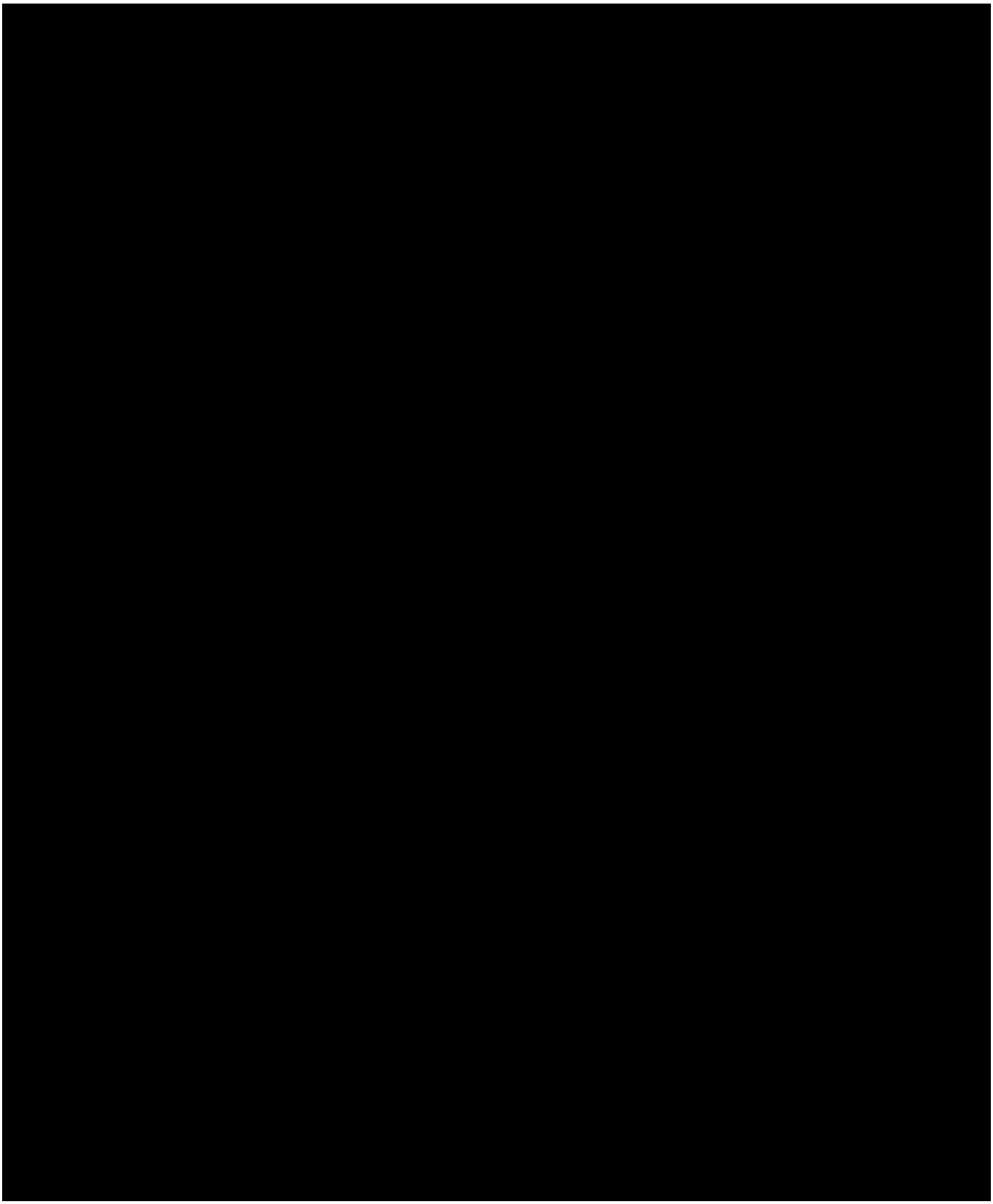

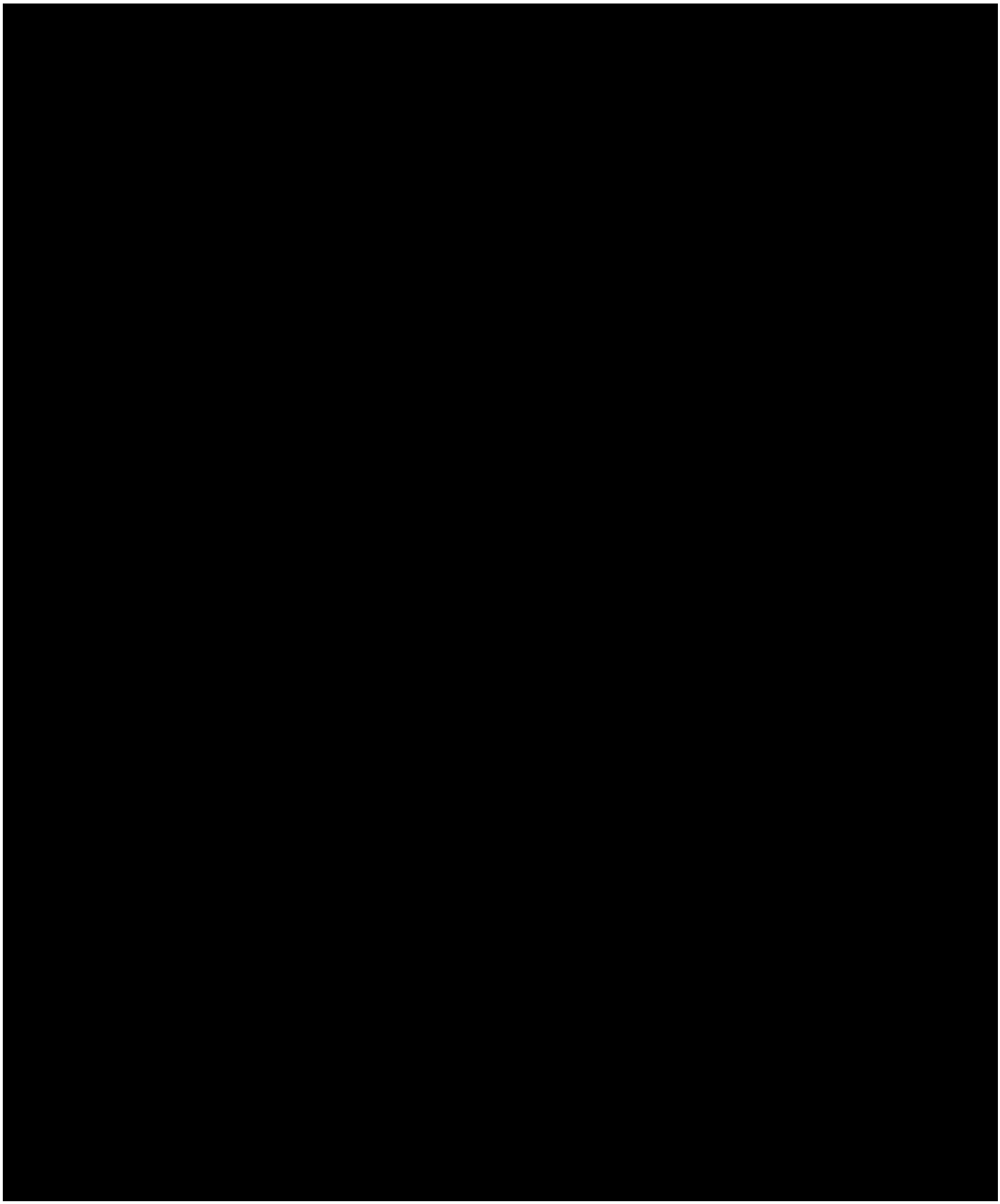

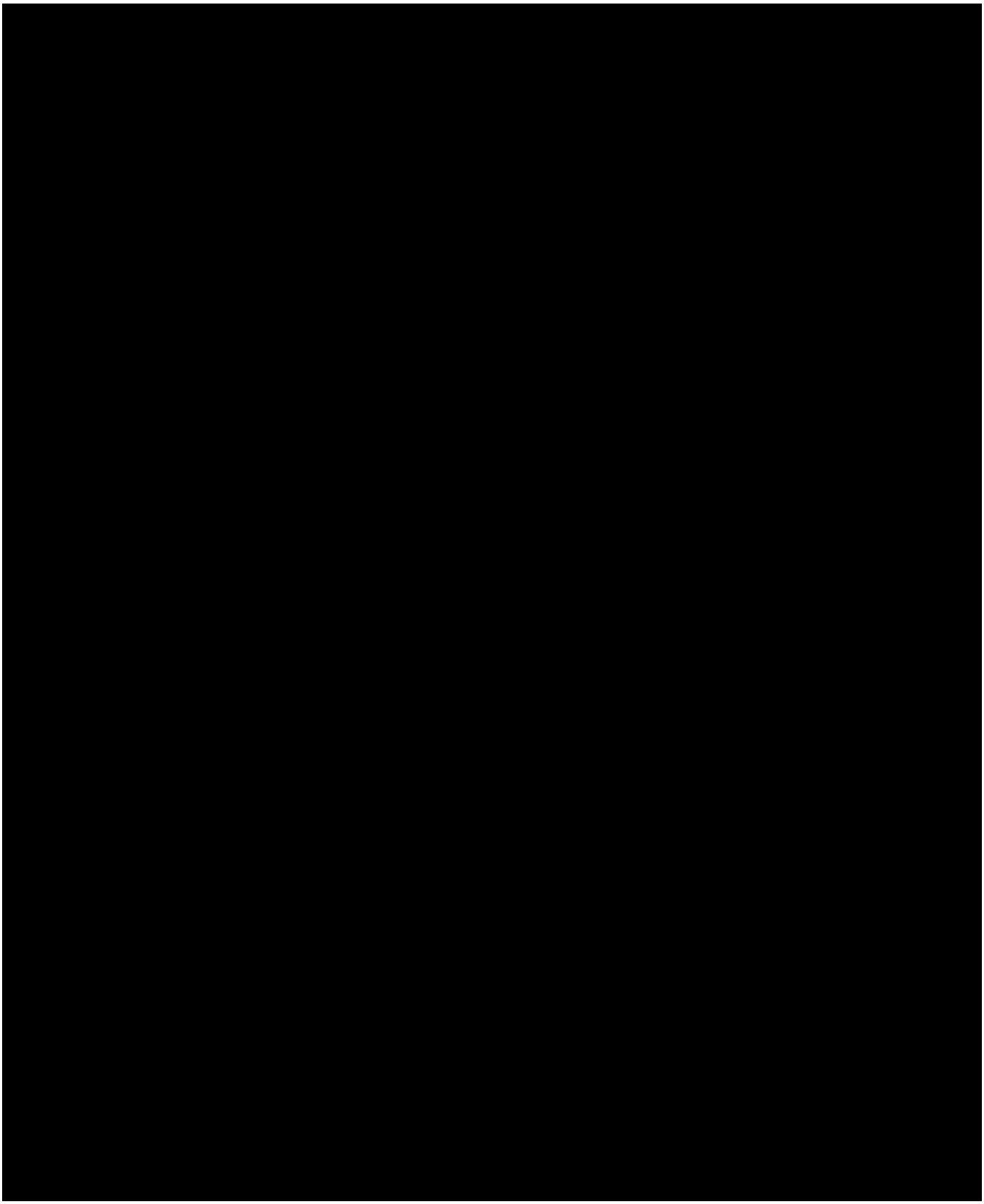

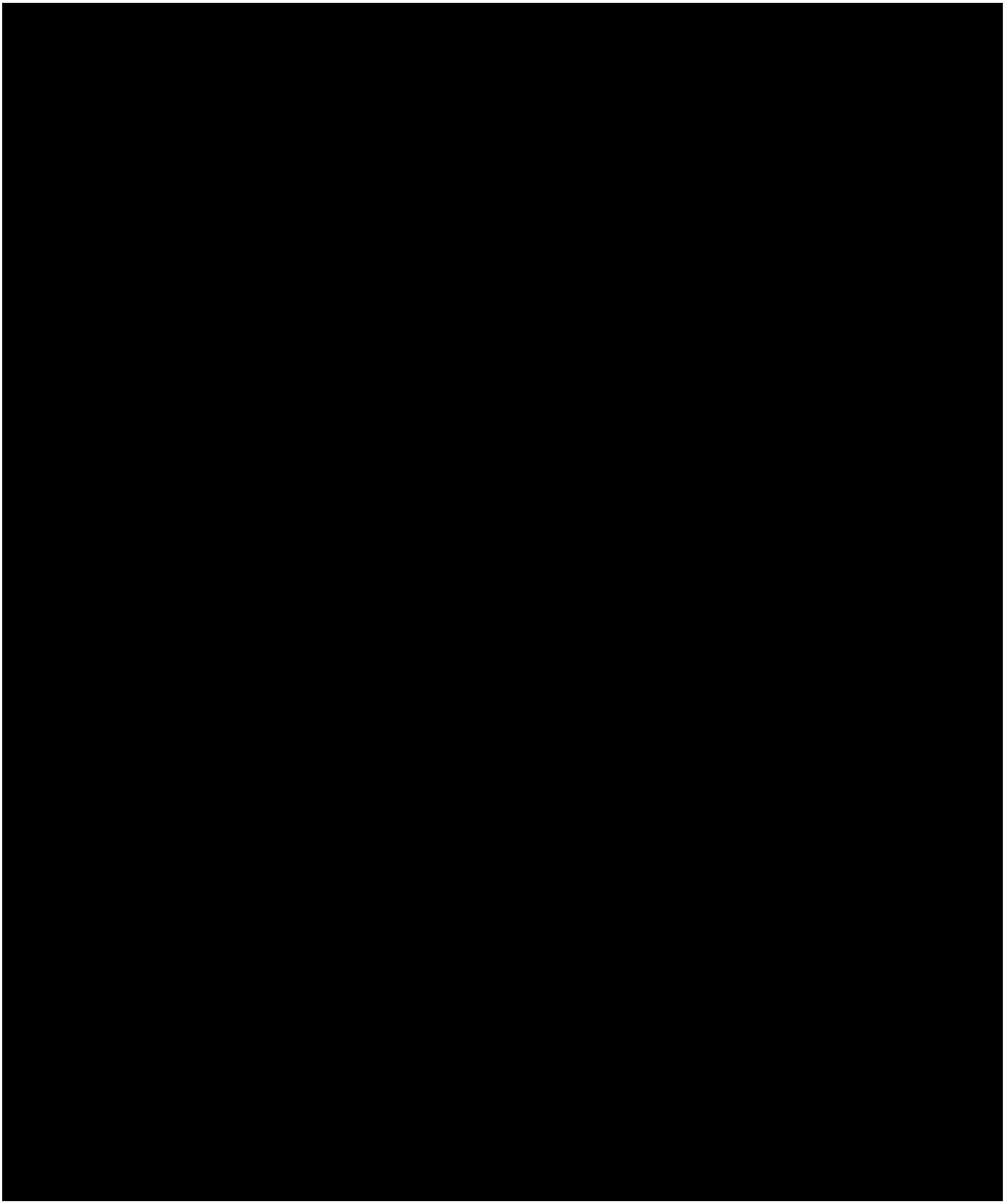

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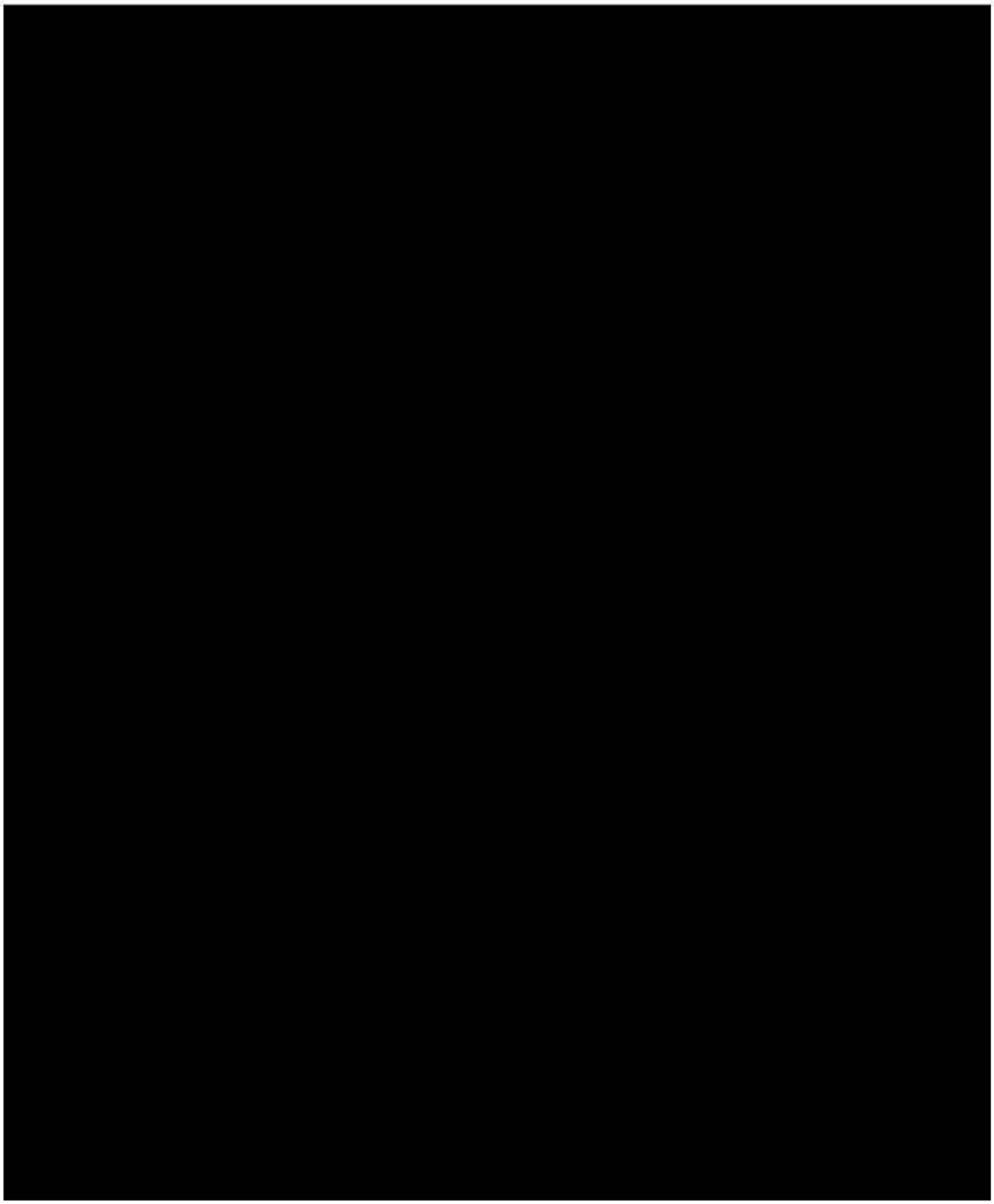

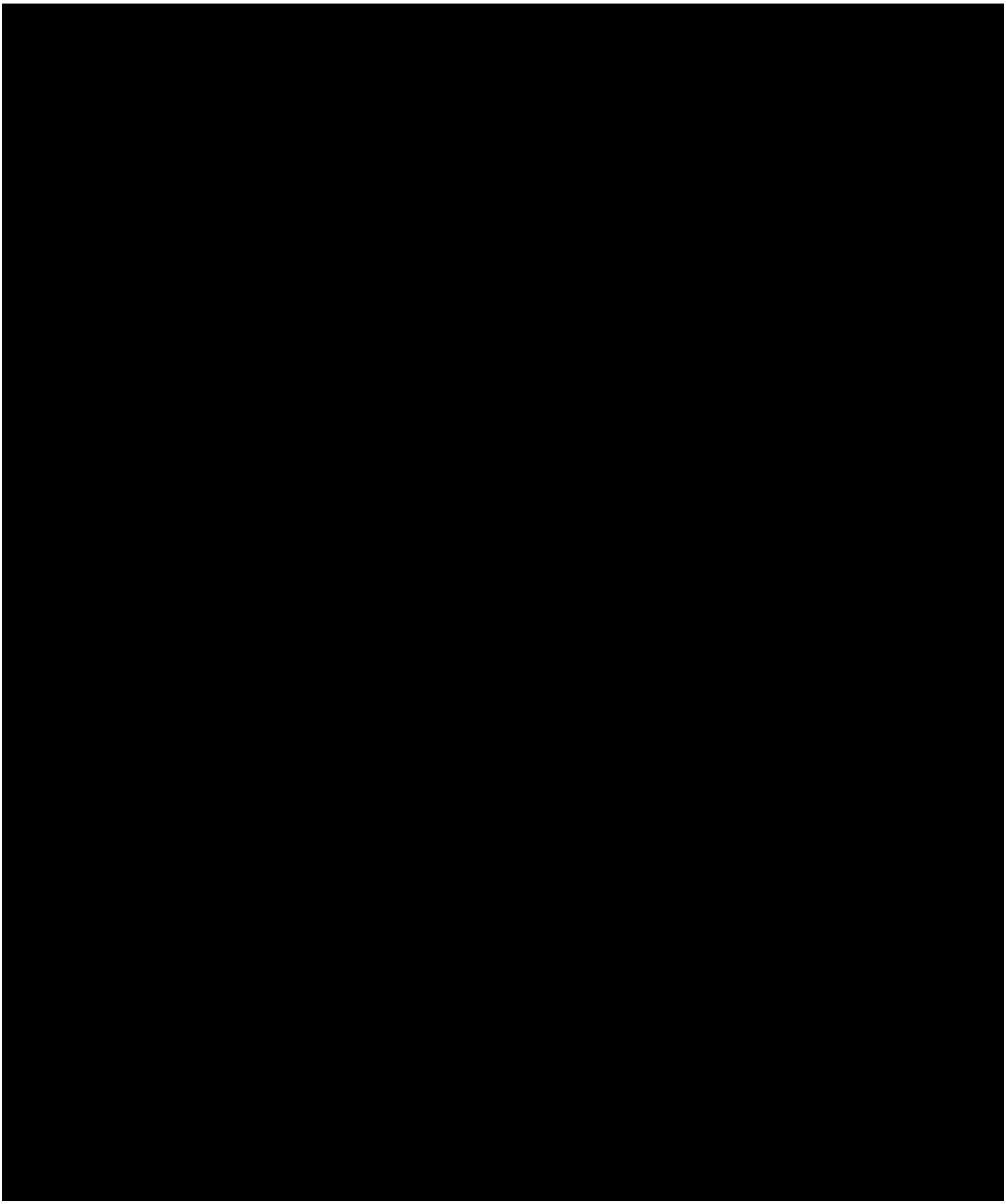

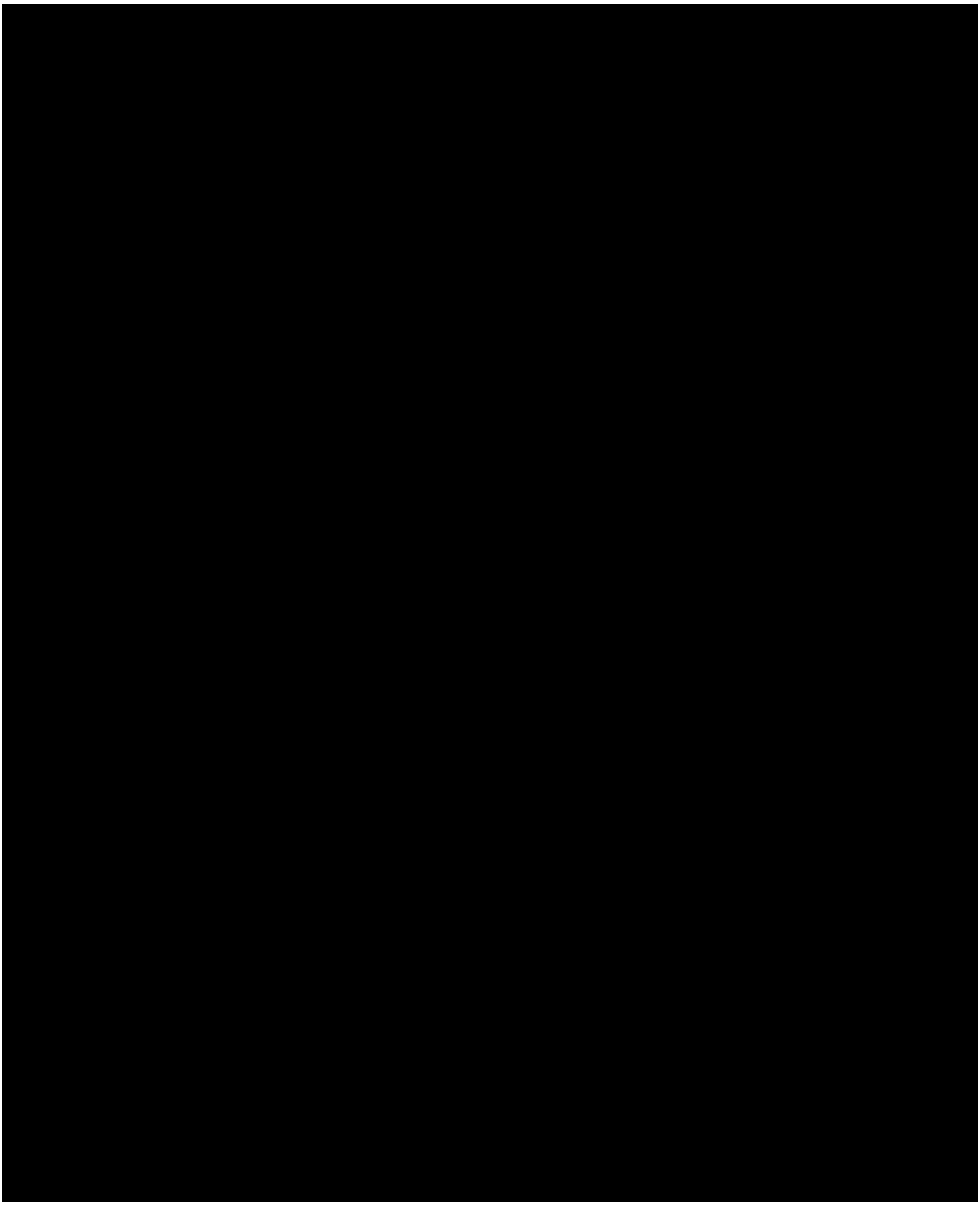

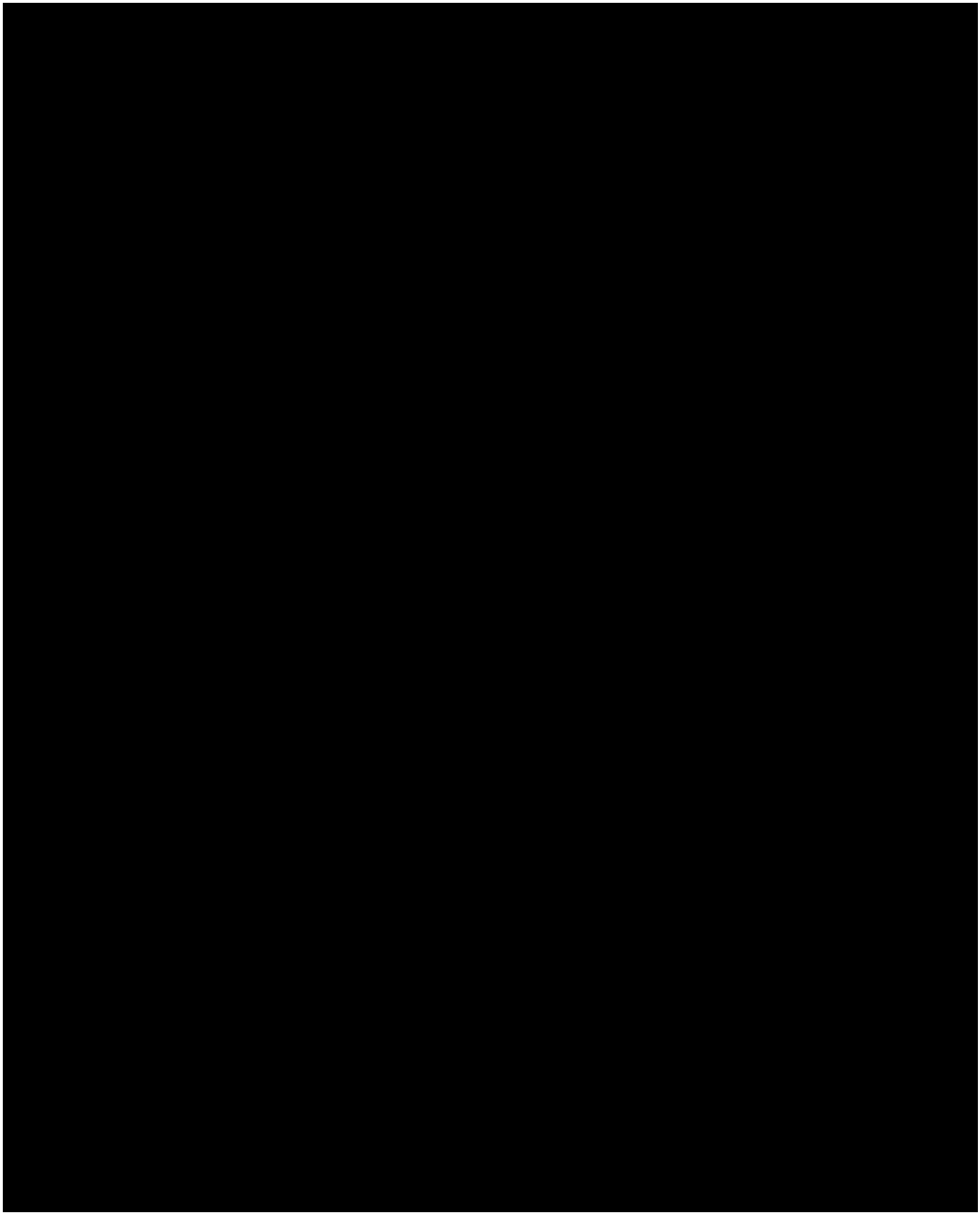

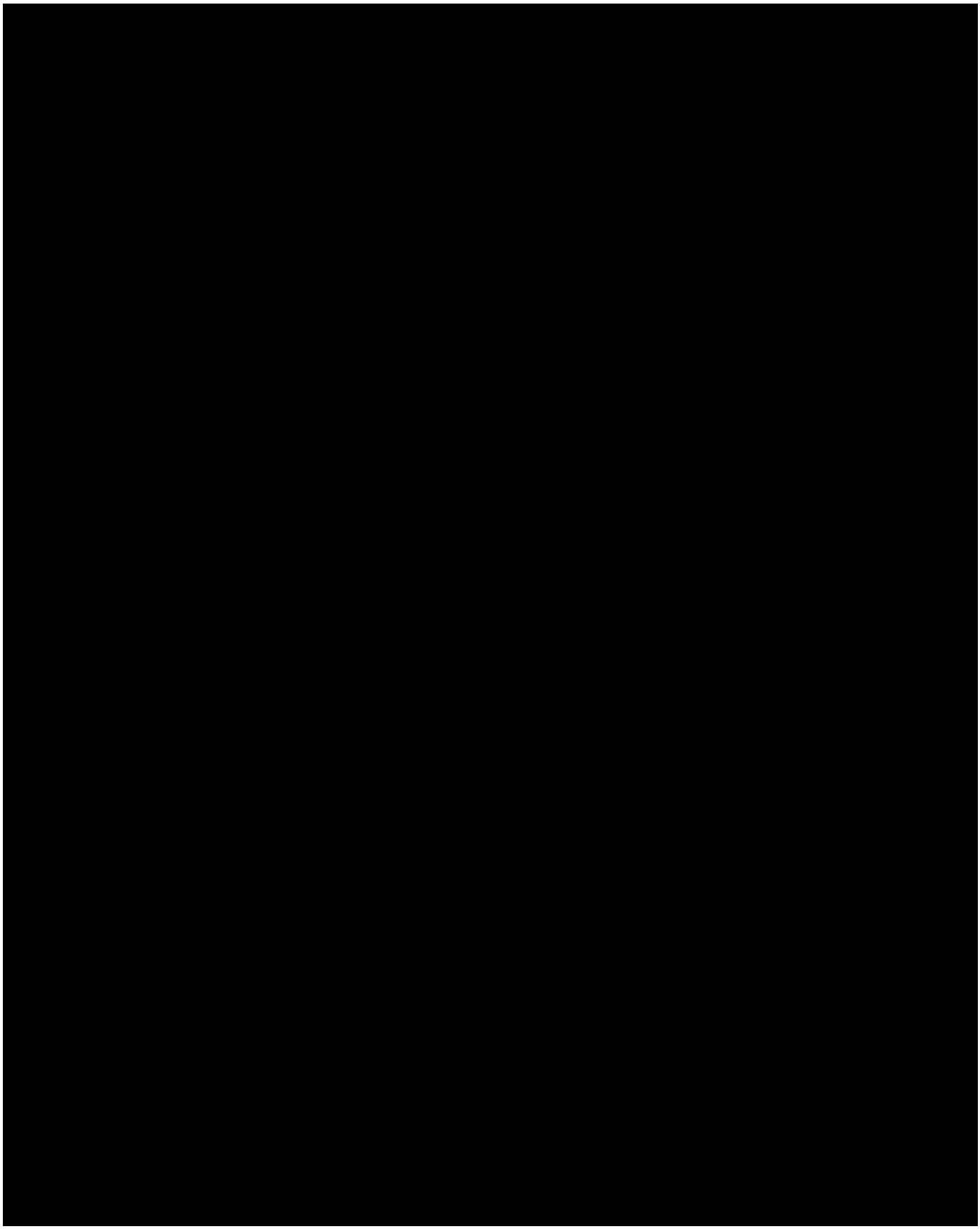

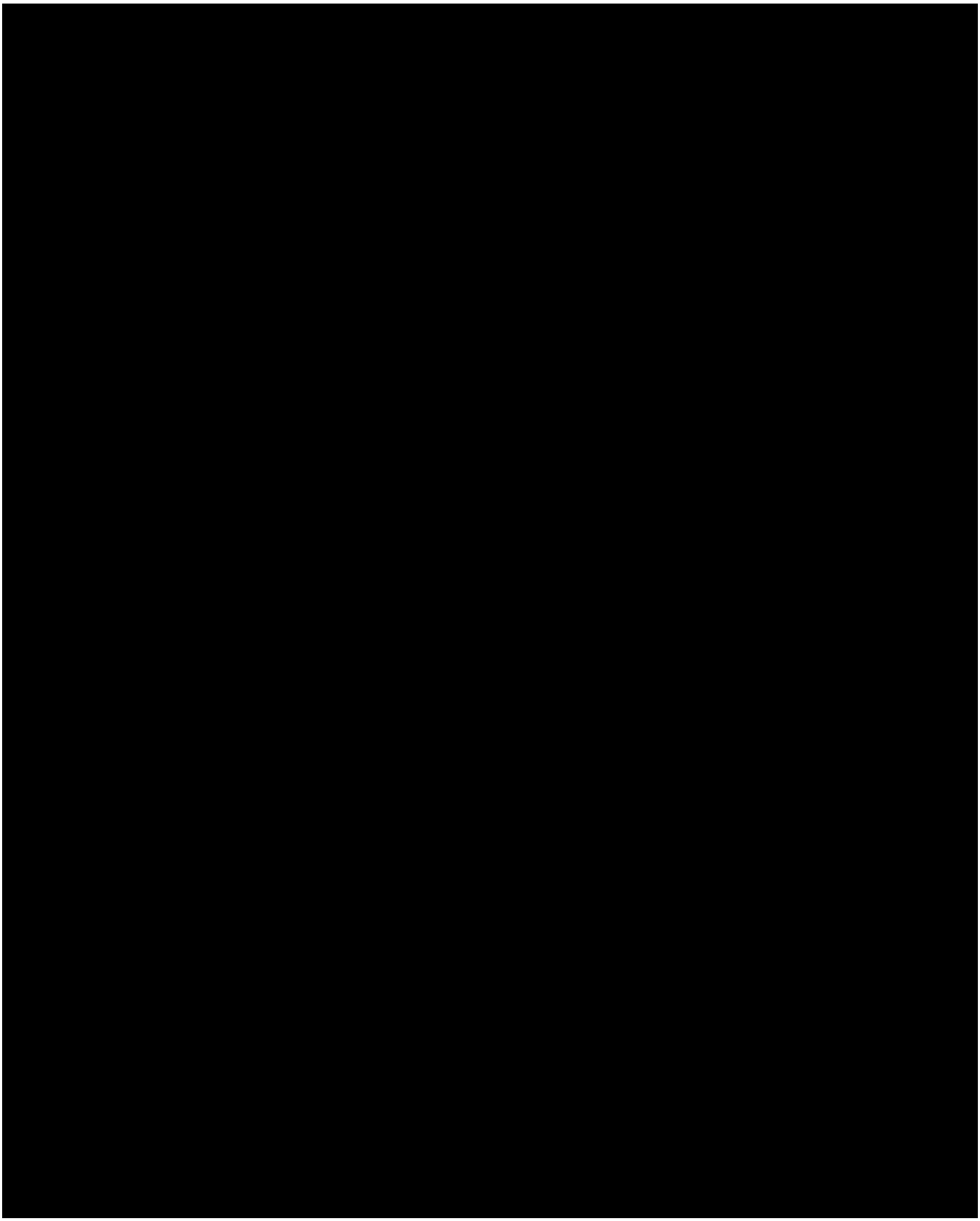

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C. Invalidity.

1. Claims 1-64 of the 865 patent are invalid for at least anticipation, obviousness, obviousness-type double-patenting, lack of enablement, lack of written description, and indefiniteness. [6]

a. The Scope and Content of the Prior Art.

Claims 1-64 of the 865 patent are invalid for at least anticipation and/or obviousness.

[6] Should litigation ensue, Mylan reserves its right to, *inter alia*, raise additional invalidity defenses based upon, among other things, the patentee's disclosure of the asserted claims; the patentee's disclosure of its alleged infringement proofs; the patentee's disclosure of its proposed construction

In the context of the anticipation and/or obviousness analysis, the scope of the prior art is directed to the field of endeavor of the alleged invention. The content of the prior art is dictated by the alleged priority date for the claimed invention.

Here, the 865 patent issued from the 559 application, filed on January 10, 2020, which was filed as a purported continuation application of U.S. Patent Application No. 16/582,486, filed on September 25, 2019 and purports to claim priority to a number of other United States patent applications, including U.S. Patent Application No. 16/159,269, filed on October 12, 2018, which is a purported continuation of application No. 15/879,294, filed on January 24, 2018, which is a purported continuation of application No. 15/095,606, filed on April 11, 2016, which is a purported continuation of U.S. Patent Application No. 14/330,096, filed on July 14, 2014, which is a purported continuation of U.S. Patent Application No. 13/914,996, filed on June 11, 2013, which is a purported continuation application of U.S. Patent Application No. 13/329,770, filed on December 19, 2011, which is a purported continuation application of U.S. Patent Application No. 12/833,417, filed on July 9, 2010, which is a purported continuation application of U.S. Patent Application No. 12/560,885, filed September 16, 2009, which is a purported divisional application of U.S. Patent Application No. 11/818,463, filed on June 14, 2007, which purports to claim priority to U.S. Provisional Application No. 60/814,484, filed on June 16, 2006.

Therefore, without conceding that the 865 patent properly claims priority to these applications, which priority claims Mylan reserves all rights to challenge, any teachings known to those of ordinary skill in the art as of June 16, 2006, at the earliest, make up the content of the prior art under at least 35 U.S.C. § 102 (AIA and/or pre-AIA).

Claims 1-64 of the 865 patent are invalid for anticipation and/or obviousness over at least the references shown in Appendix B.[7] The references therein are prior art to the 865 patent under at least 35 U.S.C. § 102(a) and/or (b) and 35 U.S.C. § 103.[8] Mylan expressly reserves the

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of the claims of the 865 patent; any claim construction ruling by a court, should the court be able to construe the claims of the 865 patent; the patentee's response to any of Mylan's defenses, including, but not limited to, the patentee's interpretation of the prior art; the discovery (fact or expert) that Mylan obtains during any such litigation, including any third party discovery that results in additional grounds of invalidity or unenforceability; and/or further investigation. Mylan further reserves the right to assert any and all invalidity defenses and/or prior art previously or concurrently asserted against any claim of the '865 patent in any prior or concurrent litigation or proceeding including, *inter alia*, IPR2021-00402, *Chengdu Kanghong Biotechnology Co., LTD., v. Regeneron Pharmaceuticals, Inc.*

[7] To the extent that any specific limitation is found not to be explicitly or inherently disclosed in these references, it would have been achieved through routine optimization by one of ordinary skill in the art.

[8] In the event of litigation, to the extent that the patentee and/or inventors attempt to swear behind or otherwise remove as prior art any of the art identified herein, Mylan specifically reserves its right to, *inter alia*, add additional prior art to the list. Furthermore, to the extent that the patentee argues that any of the cited references are not prior art under 35 U.S.C. § 102 or § 103, many of the referenced patents and/or patent applications have foreign or U.S. equivalents which also

right to modify and/or supplement the above list. The above references are prior art to the 865 patent under at least 35 U.S.C. § 102(a) and/or (b) and 35 U.S.C. § 103.

b. Comparison of Patent Claims and the Prior Art.

i. Independent claim 1.

The language of independent claim 1 of the 865 patent is set forth above.

a) Claim 1 is anticipated by Fraser.

Claim 1 of the 865 patent is invalid as anticipated by Fraser.

Fraser is titled "Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function." Fraser's study was aimed at evaluating the effect of VEGF on pituitary-ovarian function. (Fraser at 1114.) In the study, macaques were given an injection of a VEGF antagonist. (*Id.*) In Fraser's experiments, "VEGF was inhibited by administration of VEGF $Trap_{R1R2}$, a recombinant, chimeric protein comprising Ig domain 2 of human VEGF-R1 and Ig domain 3 of human VEGF-R2, expressed in sequence with the human Fc." (*Id.* at 1115). Fraser cites to, and incorporates by reference, Wulff (i.e., reference number 17) and Holash (i.e., reference number 21). (*See* Fraser at 1114-15 1119, 1122). Wulff further incorporates by reference Papadopoulos (WO 00/75319 Al). (*See* Wulff at 2798 n.1).

Fraser expressly discloses the VEGF antagonist, co-solvent, buffer and stabilizing agent elements of claim 1. (*See, e.g.*, Fraser at 1115 ("VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose.")).[9] Accordingly, Fraser expressly discloses the "vial comprising an ophthalmic formulation suitable for intravitreal administration

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qualify as prior art. Such foreign and U.S. equivalents are incorporated herein, and Mylan reserves the right to rely upon them. Additionally, as previously noted, should litigation ensue, Mylan reserves its right to, *inter alia*, supplement or amend its list of prior art references based upon, among other things, the patentee's disclosure of the asserted claims; the patentee's disclosure of its alleged infringement proofs; disclosure of the patentee's proposed construction of the claims of the 865 patent; issuance of a claim construction ruling by a court; the patentee's response to any of Mylan's defenses, including, but not limited to, the patentee's interpretation of the prior art; the discovery (fact or expert) during any such litigation; and/or further investigation. Moreover, Mylan does not admit, or otherwise concede, that the claims of the 865 patent are entitled to an effective filing date earlier than the patent's filing date, and therefore reserves the right to, *inter alia*, challenge the effective filing date of the patent and to assert additional prior art references and/or products based on any such challenge. Nevertheless, as discussed herein, each claim of the patent is invalid even if the 865 patent had made a proper claim of priority to an earlier-filed application.

[9] Tween-20 is a commercial brand name for polysorbate-20. (*See* Andya at [0123]).

that comprises: a vascular endothelial growth factor (VEGF) antagonist[,] an organic co-solvent, a buffer, and a stabilizing agent" elements of claim 1.

Fraser also expressly discloses the first "wherein" clause of claim 1. The limitation "wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4," does not distinguish the claim from the prior art. Specifically, the references outlined above either explicitly or inherently disclose VEGF antagonist fusion proteins posttranslationally glycosylated at one or more asparagine residues. First, Fraser expressly cites to, and incorporates by reference, Holash for its VEGF antagonist. Holash discloses production of the VEGF antagonist in a CHO cell: "VEGF-Trap$_{R1R2}$ was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2. All of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells." (Holash at 11393-94). Second, Fraser expressly cites to, and incorporates by reference, Wulff for its VEGF antagonist, and Wulff cites to, and incorporates by reference, Papadopoulos. A person of ordinary skill in the art would have known that Papadopoulos teaches that the fusion proteins in Fraser and claimed by the 865 patent are glycosylated at five asparagine residues when the protein is expressed in CHO cells. (Papadopoulos at 81:20 – 82:2 ("There are five possible N-linked glycosylation sites in Flt1D2.Flk1D3.FcΔC1(a). All five of them are found to be glycosylated to varying degrees [following expression in CHO cells.]"), Fig. 36 (underlining the five asparagine residues in SEQ ID NO: 2 that are glycosylation sites)).

Fraser and Wulff incorporate by reference, Papadopoulos, which teaches the amino acid sequence of SEQ ID NO: 4, its production in CHO cells, and methods of purifying from CHO cells. Specifically, Papadopoulos teaches methods of producing VEGF antagonist fusion proteins for use in formulations and prefilled syringes, and these methods included isolating and purifying the protein product by affinity and size exclusion chromatography. (Papadopoulos at 67:25 – 68:5 ("The process for production of Flt1D2.Flk1D3.FcΔC1(a) protein … involves suspension culture of recombinant Chinese hamster ovary (CHO K1/E1A) cells which constitutively express the protein product. The cells are grown in bioreactors and the protein product is isolated and purified by affinity and size exclusion chromatography."), Examples 21-22)). As described in Example 20, Papadopoulos teaches methods for producing the VEGF-specific fusion protein of SEQ ID NO: 4 from CHO cells. (Papadopoulos at 67:4-17). Papadopoulos teaches VEGFR1R2-FcΔC1(a) (i.e., SEQ ID NO: 4) and that it "was constructed by insertion of DNA encoding amino acids SDT (corresponding to amino acids 27-29 of Figure 24A-24C) between Flt1d2-Flk1d3-FcΔC1(a) amino acids 26 and 27 of Figure 21A-21C (GG) and removal of DNA encoding amino acids GPG corresponding to amino acids 229-231 of Figure [21A-21C]." (Papadopoulos at 67:7-12). Further, Papadopoulos discloses that the purification methods applied to SEQ ID NO: 2 are useful for purifying SEQ ID NO: 4 and other similar fusion proteins. (Papadopoulos at Fig. 24A-24C, 69:15-19 (stating that "the same methodologies as described [] for Flt1D2.Flk1D3.FcΔC1(a) were used to produce [the related fusion protein] Flt1D2.VEGFR3D3.FcΔC1(a).")). Papadopoulos describes using size exclusion chromatography "[t]o remove aggregates and other contaminants." (Papadopoulos at 39:15-19).

A person of ordinary skill in the art reading the prior art (e.g., Holash, Papadopoulos, Vitti) therefore would have understood that SEQ ID NO: 4 is encompassed by VEGF-Trap$_{R1R2}$. Moreover, a person of ordinary skill in the art would have known that the prior

art compositions comprised a VEGF antagonist fusion protein that "comprises amino acids 27-457 of SEQ ID NO:4." (*See, e.g.*, Papadopoulos at 67:4-17 (Example 20)).

Claim 1 adds the element "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 merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g., In re Copaxone Consol. Cases,* 906 F.3d 1013, 1023-24 (Fed. Cir. 2018); *Bristol-Myers Squibb Co. v. Ben Venue Lab'ys., Inc.,* 246 F.3d 1368, 1375-76 (Fed. Cir. 2001). Notwithstanding, even if some limiting effect is granted to the "98% ... native conformation" element, it is inherent in Fraser's formulation and therefore does not distinguish the claimed "vial" from the prior art. For example, Dix (U.S. Patent No. 8,110,546) discloses (among other results) over 99% VEGF antagonist remaining in "[n]ative [c]onfiguration" after storage at 5º C for two months (Table 9) for Dix's 25 mg/ml formulation, which the patentee has conceded is the identical formulation and possesses the same stability properties as Fraser. (*See* 546 patent PH 11/22/2011 Response to 7/13/2011 Office Action at 2-4 (the patentee describing Dix formulation and admitting it is identical to Fraser)).

For at least these reasons, Fraser anticipates, claim 1.

b) Claim 1 is anticipated by Wulff.

Claim 1 of the 865 patent is also invalid as anticipated by Wulff.

Wulff evaluated the VEGF TrapR1R2 protein and its biological activity in inhibiting VEGF. (Wulff at 2797, Abstract). Wulff describes the VEGF antagonist used in the experiments as follows:

> a recombinant chimeric protein comprising portions of the extracellular, ligand binding domains of the human VEGF receptors Flt-1 (VEGF-R1, Ig domain 2) and KDR (VEGF-R2, Ig domain 3) expressed in sequence with the Fc portion of human IgG (Fig. 1). The presence of the Fc domain results in homodimerization of the recombinant protein, thereby creating a high affinity (KD1–5pM) VEGF Trap. The VEGF trap was expressed in CHO cells and was purified by protein A affinity chromatography followed by size-exclusion chromatography. The specificity of VEGF binding and the affinity to VEGF of VEGF Trap R1R2 were determined by Biacore (Uppsala, Sweden).

(Wulff at 2798).

Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Wulff discloses that a dose of the VEGF Trap was injected subcutaneously into marmosets. (*Id.*). Accordingly, Wulff expressly discloses the "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" elements of claim 1.

Wulff also expressly discloses the first "wherein" clause of claim 1. The limitation "wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4," does not distinguish the claim from the prior art. Specifically, the references outlined above either explicitly or inherently disclose VEGF antagonist fusion proteins posttranslationally glycosylated at one or more asparagine residues. Wulff cites to, and incorporates by reference, Papadopoulos. A person of ordinary skill in the art would have known that Papadopoulos teaches that the fusion proteins in Wulff and claimed by the 865 patent are glycosylated at five asparagine residues when the protein is expressed in CHO cells. (Papadopoulos at 81:20 – 82:2 ("There are five possible N-linked glycosylation sites in Flt1D2.Flk1D3.FcΔC1(a). All five of them are found to be glycosylated to varying degrees [following expression in CHO cells.]"), Fig. 36 (underlining the five asparagine residues in SEQ ID NO: 2 that are glycosylation sites)).

Wulff further discloses that the VEGF TrapR1R2 was administered subcutaneously to the monkeys "[t]o inhibit vascular endothelial growth factor (VEGF)," (Wulff at 2797-98), and that "VEGF Trap R1R2 may be more efficient in inhibiting VEGF, because it contains an additional domain of the second VEGF receptor KDR." (*Id*. at 2804). Wulff also expressly cites to, and incorporates by reference, Papadopoulos (WO 00/75319 Al). (*See* Wulff at 2798, n.1). Papadopoulos teaches amino acid sequences encoding VEGF antagonist fusion proteins that fall within the scope of claim 1, including a protein called "Flt1D2.Flk1D3.FcΔC1(a)," which corresponds to SEQ ID NO: 2 of the 865 patent, and a protein called "VEGFRIR2-FcΔC1(a)," which corresponds to SEQ ID NO: 4 of the 865 patent (also known as "aflibercept").[10] The nucleotide and amino acid sequences of VEGFRIR2-FcΔC1(a) are provided in Papadopoulos Figs. 24A-24C. The amino acid sequence of the VEGFRIR2-FcΔC1(a) protein in Papadopoulos is identical to SEQ ID NO: 4 of the 865 patent. Papadopoulos also teaches that these VEGF antagonist fusion proteins were produced in recombinant Chinese hamster ovary (CHO) cells. (*See* 67:25 - 68:5 ("The process for production of Flt1D2.Flk1D3.FcΔC1(a) [*i.e.,* the protein of SEQ ID NO: 2 of the 865 patent] protein ... involves suspension culture of recombinant Chinese hamster ovary (CHO K1/E1A)) cells which constitutively express the protein product. The cells are grown in bioreactors and the protein product is isolated and purified by affinity and size exclusion chromatography."). Papadopoulos also discloses that "CHO transiently expressed VEGFRIR2-

[10] U.S. Pub. No. 2016/0144025 ("Vitti") confirms that "VEGFRIR2-FcΔC1(a)" is "also known as aflibercept." (Vitti at [0086]). Vitti teaches that aflibercept is "encoded by the amino acid sequence of SEQ ID NO: 11," (*id.*), which is identical to SEQ ID NO:4 of the 865 patent. Vitti also explains that aflibercept "consists of a dimer of two polypeptides consisting of amino acids 27-457 of [SEQ ID NO:4 of the 865 patent]." (*Id.* at [0197]). The complete SEQ ID NO:4 includes, *inter alia,* a signal peptide that is removed during protein production, and an Fe sequence of human IgG that causes the protein to dimerize. (*See* Papadopoulos at Fig. 24A (identifying the signal sequence at amino acids 1-26 of SEQ ID NO: 4); *id.* at Figs. 24B-C (identifying the human Fe region "hFCΔClA" at amino acids 232-458). Accordingly, the VEGF fusion protein of SEQ ID NO:4 and the dimerized VEGF fusion protein consisting of amino acids 27-457 of SEQ ID NO:4 both refer to aflibercept, as known in the prior art.

FcΔC1(a) [*i.e.,* the protein of SEQ ID NO: 4 of the 865 patent]. (*Id.* at 82:12-13). As described above, the element "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 merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g., In re Copaxone*, 906 F.3d at 1023-24; *Bristol-Myers Squibb*, 246 F.3d at 1375-76. Notwithstanding, even if some limiting effect is granted to the "98% ... native conformation" element, it is inherent in Wulff's formulation and therefore does not distinguish the claimed "vial" from the prior art. Papadopoulos teaches that the fusion proteins of the 865 patent are glycosylated at five asparagine residues when the protein is expressed in CHO cells. (Papadopoulos at 81:20 -82:2 ("There are five possible N-linked glycosylation sites in Flt1D2.Flk1D3.FcΔC1(a). All five of them are found to be glycosylated to varying degrees [following expression in CHO cells.]"), Fig. 36 (underlining the five asparagine residues in SEQ ID NO: 2 that are glycosylation sites)). Accordingly, Wulff discloses, either expressly or inherently, every element of the two "wherein" clauses of claim 1.

For at least these reasons, Wulff anticipates claim 1.

c) Claim 1 is anticipated by the 226 patent.

Claim 1 of the 865 patent is also invalid as anticipated by the 226 patent.

The 226 patent discloses the same VEGF antagonist disclosed in the 865 patent, the structure of which is described in claim 1 of the 865 patent. (*See, e.g.*, 226 patent at claim 3, 2:3-19). The 226 patent also discloses that in specific embodiments, "the VEGF antagonist is expressed in a mammalian cell line such as a CHO cell." (*See, e.g.*, *id.* at 5:37-39).

The 226 patent also discloses a number of formulations of the VEGF antagonist, each of which comprises "an organic co-solvent," a "buffer," and a "stabilizing agent," as those terms are defined in the 865 patent. (*See, e.g.*, 226 patent at 2:15 – 3:34, 7:5-18, 7:60 – 12:10).

The 226 patent also discloses formulations that resulted in at least 98% of the VEGF antagonist being present in native conformation following storage at 5° C for two months as measured by SEC. (*See, e.g.*, 226 patent at 7:63 - 8:19).

For at least these reasons, the 226 patent anticipates claim 1.

d) Claim 1 is invalid for public use.

Claim 1 of the 865 patent is invalid for being in public use, on sale, or otherwise available to the public before the earliest effective filing date to which claim 1 of the 865 patent is entitled. For example, the formulation of EYLEA meets each and every limitation of claim 1, either expressly or inherently. (*See, e.g.*, EYLEA Prescribing Information (Nov. 2011) at 9). EYLEA was on the market as of Nov. 2011, and was being utilized in publicly disclosed pre-clinical and clinical trials well before that date.[11]

[11] In addition to the evidence cited herein, Mylan reserves the right to modify and supplement this defense based on information and documents obtained through discovery in litigation.

For at least these reasons, claim 1 is invalid for being in public use, on sale, or otherwise available to the public before the earliest effective filing date to which claim 1 of the 865 patent is entitled.

e) Claim 1 is invalid as obvious.

Additionally, claim 1 of the 865 patent would have been obvious over at least the following: (i) Fraser, either alone or in combination with Dix and/or Holash and/or Liu, in view of the knowledge of a person of ordinary skill in the art; and (ii) Wulff either alone or in combination with Liu, in view of the knowledge of a person of ordinary skill in the art.[12]

As explained, Dix (U.S. Patent No. 8,110,546) discloses the identical formulation as Fraser. Dix further confirms that the Fraser formulation[13] inherently comprises a VEGF antagonist "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." Specifically, Dix discloses that over 99% of the VEGF antagonist in the Fraser, 25 mg/ml formulation remained in "[n]ative [c]onfiguration" (i.e., native conformation) after storage at 5ºC for two months. (Dix at 11:15 – 12:20, Table 9).

Holash describes "a very potent high-affinity VEGF blocker that has prolonged *in vivo* pharmacokinetics and pharmacodynamics, lacks nonspecific toxicities, and can effectively suppress the growth and vascularization of a number of different types of tumors *in vivo*." (Holash at 11393). Holash further describes that "VEGF-Trap$_{R1R2}$ was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2." (*Id*. at 11393-94). A person of ordinary skill in the art reading Holash therefore would have understood that SEQ ID NO: 4 is encompassed by VEGF-Trap$_{R1R2}$. Holash also describes that "[a]ll of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells." (*Id*. at 11394). A person of ordinary skill in the art would have understood that a protein "produced and purified from Chinese hamster ovary cells," especially in order to be targeted for treatment of diabetic retinopathy (i.e., injection into the eye), must be as pure as possible and would have expected the protein to be a fusion protein wherein at least 98% is in native conformation.

To the extent the BLA product could somehow satisfy the claim limitations, those limitations are also met by the prior art. For example, Liu (US2004/0197324) discloses optimizing formulations having a co-solvent (e.g., polysorbate 20), a buffer (e.g., histidine-HCl), and a stabilizer (e.g., trehalose or Arginine HCl) to achieve stable liquid protein formulations having at least 98% "native conformation" after storage at 5° C for two months. (*See, e.g.*, Liu at [0013] ("[T]he present invention concerns a highly concentrated antibody formulations of low turbidity comprising antibody (40-150 mg/ml), histidine (10-100 mM), sugar (e.g., trehalose or sucrose, 20-350 mM) and polysorbate (0.01%-0.1%)."); *id.* at Table 1 (reporting two liquid protein

[12] To the extent that any specific limitation is found not to be explicitly or inherently disclosed in these references, it would have been achieved through routine optimization by one of ordinary skill in the art.

[13] The patentee has conceded that the Fraser formulation is one of Dix's two tested formulations. (*See* 546 patent PH 11/22/2011 Response to 7/13/2011 Office Action at 2-4).

formulations—both containing polysorbate 20 and either Arginine HCl or trehalose—having >98% monomer after storage at 5° C for 3 months (i.e., 99.3% and 98.8% respectively) or longer). A person of ordinary skill in the art would have been highly motivated to combine the aforementioned teachings to achieve the "vial" of claim 1. Furthermore, a person of ordinary skill in the art would have reasonably expected success combining the aforementioned teachings to achieve a "vial" with the stability characteristics (i.e., "98%...native conformation") of claim 1. Accordingly, claim 1 of the 865 patent would have been obvious to a person of ordinary skill in the art over any one of the aforementioned combinations.

Additionally, claim 1 of the 865 patent would have been obvious over at least one or more references describing the LUCENTIS formulation, in combination with one or more references disclosing aflibercept or VEGF Trap-Eye, further in view of the knowledge of a person of ordinary skill in the art.

For example, U.S. Patent No. 7,303,747 describes the structure and sequence of the VEGF antagonist recited in the claims of the 865 patent. (*See, e.g.*, 747 patent at 5:3-26, SEQ ID NO:6). The 747 patent also discloses the use of said VEGF antagonists for use in treating eye disorders, including macular degeneration and diabetic retinopathy. (*See, e.g.*, 747 patent at 5:27-51, 20:17 – 22:42).

Given the disclosures of the 747 patent and other references disclosing the sequence and structure of aflibercept (i.e., VEGF Trap-Eye, or VEGFR1R2-FcΔC1(a)), and its use in treating eye disorders, a person of ordinary skill in the art would have been motivated to review information about formulations of other VEGF antagonists known to be used in treating eye disorders, and formulated to safely deliver a pharmaceutical active into a patient's eye. Accordingly, one of ordinary skill in the art would have looked to the LUCENTIS formulation. LUCENTIS was provided in a vial, and included a VEGF antagonist, "an organic co-solvent," a "buffer," and a "stabilizing agent," as those terms are defined in the 865 patent. (*See, e.g.*, LUCENTIS Prescribing Information (2006) § 11). Given the approval of the LUCENTIS formulation, a person of ordinary skill in the art would have been motivated to use that formulation in formulating aflibercept/VEGF Trap-Eye. Further, a person of ordinary skill in the art would have had a reasonable expectation of success given the successful formulation and FDA approval of LUCENTIS.

Accordingly, claim 1 of the 865 patent would have been obvious over any of the prior art references disclosing the VEGF antagonist and its use in treating eye disorders, including the 757 patent, in combination with one or more references disclosing the formulation used in the LUCENTIS formulation.

ii. Claim 2.

Claim 2 of the 865 patent depends from claim 1 and thus incorporates the elements of claim 1. For at least the same reasons set forth above with respect to claim 1, said discussion incorporated herein by reference, claim 2 is anticipated and/or obvious.

The limitation, "wherein said organic co-solvent comprises polysorbate," does not distinguish the claim from claim 1 or the prior art that invalidates claim 1. Specifically, the

references outlined above either explicitly or inherently disclose a "vial" "wherein said organic co-solvent comprises polysorbate." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said organic co-solvent comprises polysorbate."

The additional limitation "wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml" does not distinguish the claim from claim 1 or the prior art that invalidates claim 1. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml." For example, Andya specifically discloses that a "lyophilized formulation can be reconstituted to generate a stable reconstituted formulation having a protein concentration which is significantly higher (*e.g.*, from about 2-40 times higher, preferably 3-10 times higher and most preferably 3-6 times higher) than the protein concentration in the pre-lyophilized formulation." (Andya at [0008]). Andya also discloses that "while the protein concentration in the pre-lyophilized formulation may be 5 mg/mL or less, the protein concentration in the reconstituted formulation is generally 50 mg/mL or more." (Andya at [0008]). Given that Fraser formulation's VEGF Trap concentration was 24.3 mg/ml, a person of ordinary skill would have been motivated to generate a stable formulation having a significantly higher protein concentration, *e.g.*, by following Andya's teachings to lyophilize and reconstitute in histidine buffer so as to increase the concentration by at least 2-fold (*e.g.*, from ~25 to ~50 mg/ml).

Claim 2 of the 865 patent is therefore anticipated for the same reasons stated above for claim 1. Additionally, claim 2 would have been obvious over at least, *inter alia*, the combinations identified above for claim 1, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claim 1. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including VEGF antagonist fusion protein at a concentration of 40 mg/ml and with an organic co-solvent comprising polysorbate, and would have reasonably expected success with such formulation.

iii. Claim 3.

Claim 3 of the 865 patent depends from claim 2, which depends from claim 1, and thus claim 3 incorporates the elements of claims 1 and 2. For at least the same reasons set forth above with respect to claims 1 and 2, said discussion incorporated herein by reference, claim 3 is anticipated and/or obvious.

The additional limitation, "wherein said organic co-solvent comprises 0.01% to 3% polysorbate," does not distinguish the claim from claims 1 and 2, or the prior art that invalidates claims 1 and 2. Specifically, the references outlined above either explicitly or inherently disclose

a "vial" "wherein said organic co-solvent comprises 0.01% to 3% polysorbate." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations where "[p]olysorbate 20 was added to the formulations at concentrations of 0.005%, 0.01%, and 0.02%." (Andya at [0175]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said organic co-solvent comprises 0.01% to 3% polysorbate."

Claim 3 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1 and 2. Additionally, claim 3 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1 and 2, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1 and 2. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including an organic co-solvent comprising 0.01% to 3% polysorbate, and would have reasonably expected success with such formulation.

iv. Claim 4.

Claim 4 of the 865 patent depends from claim 2, which depends from claim 1, and thus claim 4 incorporates the elements of claims 1 and 2. For at least the same reasons set forth above with respect to claims 1 and 2, said discussion incorporated herein by reference, claim 4 is anticipated and/or obvious.

The additional limitation, "wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20," does not distinguish the claim from claims 1 and 2 or the prior art that invalidates claims 1 and 2. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations where "[p]olysorbate 20 was added to the formulations at concentrations of 0.005%, 0.01%, and 0.02%." (Andya at [0175]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20."

Claim 4 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1 and 2. Additionally, claim 4 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1 and 2, in view of (or in further combination with) the

knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1 and 2. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including an organic co-solvent comprising about 0.03% to about 0.1% polysorbate 20, and would have reasonably expected success with such formulation.

v. Claim 5.

Claim 5 of the 865 patent depends from claim 2, which depends from claim 1, and thus claim 5 incorporates the elements of claims 1 and 2. For at least the same reasons set forth above with respect to claims 1 and 2, said discussion incorporated herein by reference, claim 5 is anticipated and/or obvious.

The additional limitation, "wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20," does not distinguish the claim from claims 1 and 2, or the prior art that invalidates claims 1 and 2. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations where "[p]olysorbate 20 was added to the formulations at concentrations of 0.005%, 0.01%, and 0.02%." (Andya at [0175]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20."

Claim 5 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1 and 2. Additionally, claim 5 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1 and 2, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1 and 2. Given the prior art teachings, a person of skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including an organic cosolvent comprising 0.01% to 3% polysorbate 20, and would have reasonably expected success with such formulation.

vi. Claim 6.

Claim 6 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 6 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 6 is anticipated and/or obvious.

The additional limitation, "wherein said buffer comprises a phosphate buffer," does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial"

"wherein said buffer comprises a phosphate buffer." For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said buffer comprises a phosphate buffer."

Claim 6 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 6 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a phosphate buffer, and would have reasonably expected success with such formulation.

vii. Claim 7.

Claim 7 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 7 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 7 is anticipated and/or obvious.

The additional limitation, "wherein said buffer comprises 5-25 mM buffer," does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said buffer comprises 5-25 mM buffer." For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said buffer comprises 5-25 mM buffer."

Claim 7 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 7 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with)

the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including 5-25 mM buffer, and would have reasonably expected success with such formulation.

viii. Claim 8.

Claim 8 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 8 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 8 is anticipated and/or obvious.

The additional limitation, "wherein said buffer comprises a pH between about 5.8-7.0," does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said buffer comprises a pH between about 5.8-7.0." For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said buffer comprises a pH between about 5.8-7.0."

Claim 8 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 8 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a pH between about 5.8-7.0, and would have reasonably expected success with such formulation.

ix. Claim 9.

Claim 9 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 9 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 9 is anticipated and/or obvious.

The additional limitation, "wherein said buffer comprises a pH about 6.2-6.3," does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial"

"wherein said buffer comprises a pH about 6.2-6.3." For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said buffer comprises a pH about 6.2-6.3."

Claim 9 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 9 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a pH about 6.2-6.3, and would have reasonably expected success with such formulation.

x. Claim 10.

Claim 10 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 10 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 10 is anticipated and/or obvious.

The additional limitation, "wherein said stabilizing agent comprises a sugar," does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said stabilizing agent comprises a sugar." For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said stabilizing agent comprises a sugar."

Claim 10 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 10 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a sugar, and would have reasonably expected success with such formulation.

xi. Claim 11.

Claim 11 of the 865 patent depends from claim 10, which depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 11 incorporates the elements of claims 1, 2, 5, and 10. For at least the same reasons set forth above with respect to claims 1, 2, 5, and 10, said discussion incorporated herein by reference, claim 11 is anticipated and/or obvious.

The additional limitation, "wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol," does not distinguish the claim from claims 1, 2, 5, and 10, or the prior art that invalidates claims 1, 2, 5, and 10. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol." For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol."

Claim 11 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, 5, and 10. Additionally, claim 11 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, 5, and 10, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, 5, and 10. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a sugar selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol and would have reasonably expected success with such formulation.

xii. Claim 12.

Claim 12 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 12 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 12 is anticipated and/or obvious.

The additional limitation, "wherein said stabilizing agent comprises 1.0-7.5% of sucrose," does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said stabilizing agent comprises 1.0-7.5% of sucrose." For example, Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM" and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said stabilizing agent comprises 1.0-7.5% of sucrose."

Claim 12 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 12 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including 1.0-7.5% of sucrose, and would have reasonably expected success with such formulation.

xiii. Claim 13.

Claim 13 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 13 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 13 is anticipated and/or obvious.

The additional limitation, "wherein said formulation further comprises a tonicity agent," does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said formulation further comprises a tonicity agent." For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said formulation further comprises a tonicity agent."

Claim 13 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 13 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a tonicity agent, and would have reasonably expected success with such formulation.

xiv. Claim 14.

Claim 14 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 14 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 14 is anticipated and/or obvious.

The additional limitation, "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," does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "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." First, Fraser expressly cites to, and incorporates by reference, Holash for its VEGF antagonist. Holash discloses production of the VEGF antagonist in a CHO cell: "VEGF-Trap$_{R1R2}$ was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2. All of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells." (Holash at 11393-94). Second, Fraser expressly cites to, and incorporates by reference, Wulff for its VEGF antagonist, and Wulff cites to, and incorporates by reference, Papadopoulos. A person of ordinary skill in the art would have known that Papadopoulos teaches that the fusion proteins of the 865 patent are glycosylated at five asparagine residues when the protein is expressed in CHO cells. (Papadopoulos at 81:20 - 82:2 ("There are five possible N-linked glycosylation sites in Flt1D2.Flk1D3.FcΔC1(a). All five of them are found to be glycosylated to varying degrees [following expression in CHO cells.]"), Fig. 36 (underlining the five asparagine residues in SEQ ID NO: 2 that are glycosylation sites)). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "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."

Claim 14 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 14 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a VEGF antagonist protein glycosylated at the claimed asparagine residues, and would have reasonably expected success with such formulation.

xv. Claim 15.

Claim 15 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 15 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 15 is anticipated and/or obvious.

The additional limitation, "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C," does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C." First, the element "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C," merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *In re Copaxone*, 906 F.3d at 1023-24; *Bristol-Myers Squibb*, 246 F.3d at 1375-76. Notwithstanding, even if some limiting effect is granted to the "turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C" element, it is inherent in Fraser's formulation and therefore does not distinguish the claimed "vial" from the prior art. For example, Dix (U.S. Patent No. 8,110,546) discloses (among other results) over 99% VEGF antagonist remaining in "[n]ative [c]onfiguration" after storage at 5º C for two months (Table 9) for Dix's 25 mg/ml formulation, which the patentee has conceded is the identical formulation and possesses the same stability properties as Fraser. (*See* 546 patent PH 11/22/2011 Response to 7/13/2011 Office Action at 2-4 (Regeneron describing Dix formulation and admitting it is identical to Fraser)). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C."

Claim 15 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 15 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including being capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C, and would have reasonably expected success with such formulation.

xvi. Claim 16.

Claim 16 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 16 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 16 is anticipated and/or obvious.

The additional limitation, "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography," does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or

inherently disclose a "vial" "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography." First, the element "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography," merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *In re Copaxone*, 906 F.3d at 1023-24; *Bristol-Myers Squibb*, 246 F.3d at 1375-76.Notwithstanding, even if some limiting effect is granted to the "99% ... native conformation" element, it is inherent in Fraser's formulation and therefore does not distinguish the claimed "vial" from the prior art. For example, Dix (U.S. Patent No. 8,110,546) discloses (among other results) over 99% VEGF antagonist remaining in "[n]ative [c]onfiguration after storage at 5º C for two months (Table 9) for Dix's 25 mg/ml formulation, which Regeneron has conceded is the identical formulation and possesses the same stability properties as Fraser. (*See* 546 patent PH 11/22/2011 Response to 7/13/2011 Office Action at 2-4 (Regeneron describing Dix formulation and admitting it is identical to Fraser)). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography."

Claim 16 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 16 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including at least 99% of the VEGF antagonist protein being present in native conformation after 2 month storage at 5° C as measured by size exclusion chromatography, and would have reasonably expected success with such formulation.

xvii. Claim 17.

Claim 17 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 17 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 17 is anticipated and/or obvious.

The additional limitation, "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography," does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography." First, the element "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography," merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *In re Copaxone*, 906 F.3d at 1023-24; *Bristol-Myers Squibb*, 246 F.3d at 1375-76.Notwithstanding, even if some limiting effect is granted to the "98%

... native conformation" element, it is inherent in Fraser's formulation and therefore does not distinguish the claimed "vial" from the prior art.

For example, Dix (U.S. Patent No. 8,110,546) discloses (among other results) over 99% VEGF antagonist remaining in "[n]ative [c]onfiguration" after storage at 5º C for two months (Table 9) for Dix's 25 mg/ml formulation, which the patentee has conceded is the identical formulation and possesses the same stability properties as Fraser. (*See* 546 patent PH 11/22/2011 Response to 7/13/2011 Office Action at 2-4 (Regeneron describing Dix formulation and admitting it is identical to Fraser)). Even more, a person of ordinary skill would have noted that Fraser's formulation was stored at 4° C and discarded within 2 weeks, (Fraser at 1115), and would have been motivated to use histidine to generate a formulation with the longer storage stability as disclosed by Andya's disclosure of histidine-buffered formulations with long-term storage stability of "at least 2 years," (Andya at [0049]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography."

Claim 17 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 17 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including at least 98% of the VEGF antagonist protein being present in native conformation following storage at 5° C for 24 months as measured by size exclusion chromatography, and would have reasonably expected success with such formulation.

xviii. Claim 18.

Claim 18 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 18 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 18 is anticipated and/or obvious.

The additional limitation, "wherein said formulation does not contain phosphate," does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said formulation does not contain phosphate." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya recognized that histidine was one of a small group of commonly used buffers for stabilizing proteinaceous therapeutic formulations and had been used in multiple FDA approved products and particularly useful for formulating high

concentration protein formulations. (*See* Andya at [0096]). It would have been obvious to use histidine because of its usefulness in preventing aggregation and generating a stable formulation having a protein concentration, which is significantly higher than the protein concentration in the pre-lyophilized formulation, improving its lyoprotective properties, and improving long term storage stability. (Andya; U.S. Patent Application Publication No. 2003/0113316 A1 (Kaisheva I); U.S. Patent Application Publication No. 2004-0197324 A1 (Liu)). It would have been obvious to use Andya's histidine buffer in the Fraser/Wulff formulations for the additional reasons that: (1) its pKa provides maximum buffering capacity at pH 6 (the same as Fraser's formulation), (2) it had suitable pKa and buffering capacity for the VEGF TrapR1R2 protein having a pI of approximately 8, (3) it contributes less to osmolarity than Fraser/Wulff's phosphate-citrate buffers, (4) phosphate-citrate buffers were known to cause painful reactions when injected subcutaneously in contrast to histidine buffer, and (5) regulatory agencies had repeatedly approved histidine-buffered proteinaceous therapeutic formulations. A person of ordinary skill would have wanted to retain or improve the stability, binding, and potency of the Wulff/Fraser VEGF TrapR1R2, and would have been motivated to use histidine based on Andya's teaching that it was especially good at preventing degradation including aggregation. (*See* Andya at [0160], Figs. 9-10). A person of ordinary skill would further have had a reasonable expectation of achieving a formulation that maintains the stability, potency, and binding properties of Wulff/Fraser's formulation using this combination of ingredients given the numerous other FDA-approved protein therapeutics containing the same combination of excipients, and in view of Andya's teaching that histidine has an exceptional ability to act as a lyoprotectant and prevent degradation. Histidine was a well-known buffer long before the 865 patent's earliest possible priority date, and its multiple advantages were also well-known and would have motivated a person of ordinary skill to use histidine buffer in Wulff/Fraser's formulation. Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said formulation does not contain phosphate."

Claim 18 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 18 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including not containing phosphate, and would have reasonably expected success with such formulation.

xix. Claim 19.

Claim 19 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 19 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 19 is anticipated and/or obvious.

The additional limitation, "wherein said formulation does not contain trehalose," does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial"

"wherein said formulation does not contain trehalose." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said formulation does not contain trehalose."

Claim 19 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 19 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including not containing trehalose, and would have reasonably expected success with such formulation.

xx. Claim 20.

Claim 20 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 20 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 20 is anticipated and/or obvious.

The additional limitation, "wherein said stabilizing agent comprises 1.0-10% of sucrose," does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said stabilizing agent comprises 1.0-10% of sucrose." For example, Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM" and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said stabilizing agent comprises 1.0-10% of sucrose."

Claim 20 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 20 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for

claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including 1.0-10% of sucrose, and would have reasonably expected success with such formulation.

xxi. Claim 21.

Claim 21 of the 865 patent depends from claim 20, which depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 21 incorporates the elements of claims 1, 2, 5, and 20. For at least the same reasons set forth above with respect to claims 1, 2, 5, and 20, said discussion incorporated herein by reference, claim 21 is anticipated and/or obvious.

The additional limitation, "wherein said formulation further comprises a tonicity agent," does not distinguish the claim from claims 1, 2, 5, and 20, or the prior art that invalidates claims 1, 2, 5, and 20. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said formulation further comprises a tonicity agent." For example, Fraser discloses "VEGF Trap$_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said formulation further comprises a tonicity agent."

Claim 21 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, 5, and 20. Additionally, claim 21 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, 5, and 20, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, 5, and 20. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a tonicity agent, and would have reasonably expected success with such formulation.

xxii. Claim 22.

Claim 22 of the 865 patent depends from claim 20, which depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 22 incorporates the elements of claims 1, 2, 5, and 20. For at least the same reasons set forth above with respect to claims 1, 2, 5, and 20, said discussion incorporated herein by reference, claim 22 is anticipated and/or obvious.

The additional limitation, "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," does not distinguish the claim from claims 1, 2, 5, and 20, or the prior art that invalidates claims 1, 2, 5, and 20. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "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." First, Fraser expressly cites to, and incorporates by reference, Holash for its VEGF antagonist. Holash discloses production of the VEGF antagonist in a CHO cell: "VEGF-Trap$_{R1R2}$ was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2. All of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells." (Holash at 11393-94). Second, Fraser expressly cites to, and incorporates by reference, Wulff for its VEGF antagonist, and Wulff cites to, and incorporates by reference, Papadopoulos. A person of ordinary skill in the art would have known that Papadopoulos teaches that the fusion proteins of the 865 patent are glycosylated at five asparagine residues when the protein is expressed in CHO cells. (Papadopoulos at 81:20 - 82:2 ("There are five possible N-linked glycosylation sites in Flt1D2.Flk1D3.FcΔC1(a). All five of them are found to be glycosylated to varying degrees [following expression in CHO cells.]"), Fig. 36 (underlining the five asparagine residues in SEQ ID NO: 2 that are glycosylation sites)). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "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."

Claim 22 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, 5, and 20. Additionally, claim 22 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, 5, and 20, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, 5, and 20. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a VEGF antagonist protein glycosylated at the claimed asparagine residues, and would have reasonably expected success with such formulation.

xxiii. Claim 23.

Claim 23 of the 865 patent depends from claim 20, which depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 23 incorporates the elements of claims 1, 2, 5, and 20. For at least the same reasons set forth above with respect to claims 1, 2, 5, and 20, said discussion incorporated herein by reference, claim 23 is anticipated and/or obvious.

The additional limitation, "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C," does not distinguish the claim from claims 1, 2, 5, and 20, or the prior art that invalidates claims 1, 2, 5, and 20. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C." First, the element "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C," merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *In re Copaxone*, 906 F.3d at 1023-24; *Bristol-Myers Squibb*, 246 F.3d at 1375-76. Notwithstanding, even if some limiting effect is granted to the "turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C" element, it is inherent in Fraser's formulation and therefore does not distinguish the claimed "vial" from the prior art. For example, Dix (U.S. Patent No. 8,110,546) discloses (among other results) over 99% VEGF antagonist

remaining in "[n]ative [c]onfiguration" after storage at 5º C for two months (Table 9) for Dix's 25 mg/ml formulation, which the patentee has conceded is the identical formulation and possesses the same stability properties as Fraser. (*See* 546 patent PH 11/22/2011 Response to 7/13/2011 Office Action at 2-4 (Regeneron describing Dix formulation and admitting it is identical to Fraser)). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C."

Claim 23 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, 5, and 20. Additionally, claim 23 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, 5, and 20, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, 5, and 20. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including being capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C, and would have reasonably expected success with such formulation.

xxiv. Claim 24.

Claim 24 of the 865 patent depends from claim 20, which depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 24 incorporates the elements of claims 1, 2, 5, and 20. For at least the same reasons set forth above with respect to claims 1, 2, 5, and 20 said discussion incorporated herein by reference, claim 24 is anticipated and/or obvious.

The additional limitation, "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography," does not distinguish the claim from claims 1, 2, 5, and 20, or the prior art that invalidates claims 1, 2, 5, and 20. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography." First, the element "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography," merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *In re Copaxone*, 906 F.3d at 1023-24; *Bristol-Myers Squibb*, 246 F.3d at 1375-76. Notwithstanding, even if some limiting effect is granted to the "99% ... native conformation" element, it is inherent in Fraser's formulation and therefore does not distinguish the claimed "vial" from the prior art. For example, Dix (U.S. Patent No. 8,110,546) discloses (among other results) over 99% VEGF antagonist remaining in "[n]ative [c]onfiguration" after storage at 5º C for two months (Table 9) for Dix's 25 mg/ml formulation, which the patentee has conceded is the identical formulation and possesses the same stability properties as Fraser. (*See* 546 patent PH 11/22/2011 Response to 7/13/2011 Office Action at 2-4 (Regeneron describing Dix formulation and admitting it is identical to Fraser)). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography."

Claim 24 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, 5, and 20. Additionally, claim 24 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, 5, and 20 in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, 5, and 20. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including at least 99% of the VEGF antagonist protein being present in native conformation after 2 month storage at 5° C as measured by size exclusion chromatography, and would have reasonably expected success with such formulation.

xxv. Claim 25.

Claim 25 of the 865 patent depends from claim 20, which depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 25 incorporates the elements of claims 1, 2, 5, and 20. For at least the same reasons set forth above with respect to claims 1, 2, 5, and 20, said discussion incorporated herein by reference, claim 25 is anticipated and/or obvious.

The additional limitation, "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography," does not distinguish the claim from claims 1, 2, 5, and 20, or the prior art that invalidates claims 1, 2, 5, and 20. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography." First, the element "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography," merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *In re Copaxone*, 906 F.3d at 1023-24; *Bristol-Myers Squibb*, 246 F.3d at 1375-76. Notwithstanding, even if some limiting effect is granted to the "98% ... native conformation" element, it is inherent in Fraser's formulation and therefore does not distinguish the claimed "vial" from the prior art.

For example, Dix (U.S. Patent No. 8,110,546) discloses (among other results) over 99% VEGF antagonist remaining in "[n]ative [c]onfiguration" after storage at 5º C for two months (Table 9) for Dix's 25 mg/ml formulation, which the patentee has conceded is the identical formulation and possesses the same stability properties as Fraser. (*See* 546 patent PH 11/22/2011 Response to 7/13/2011 Office Action at 2-4 (Regeneron describing Dix formulation and admitting it is identical to Fraser)). Even more, a person of ordinary skill would have noted that Fraser's formulation was stored at 4° C and discarded within 2 weeks, (Fraser at 1115), and would have been motivated to use histidine to generate a formulation with the longer storage stability as disclosed by Andya's disclosure of histidine-buffered formulations with long-term storage stability of "at least 2 years," (Andya at [0049]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography."

Claim 25 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, 5, and 20. Additionally, claim 25 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, 5, and 20, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, 5, and 20. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including at least 98% of the VEGF antagonist protein being present in native conformation following storage at 5° C for 24 months as measured by size exclusion chromatography, and would have reasonably expected success with such formulation.

xxvi. Independent Claim 26.

Claim 26 of the 865 patent is essentially identical to claim 1 with the exceptions being, as highlighted below, that the claim 26 preamble is directed to "[a] pre-filled syringe" as opposed to "[a] vial" and that claim 26 has added the language "fusion protein"; all other elements are the same:

Claim 1	Claim 26
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.	26. A pre-filled syringe comprising an ophthalmic formulation suitable for intravitreal administration comprising: a vascular endothelial growth factor (VEGF) antagonist fusion protein, 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 said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography.

The preamble change from "[a] vial" to "[a] pre-filled syringe" is neither limiting nor does it distinguish claim 26 from claim 1 or the prior art that renders claim 1 invalid as anticipated and/or obvious. Accordingly, for at least the same reasons set forth above with respect to claim 1, said discussion incorporated herein by reference, claim 26 is obvious and/or anticipated.

Notwithstanding, even if the preamble is determined to be a separate limitation, claim 26 is invalid as anticipated and/or obvious for the same reasons set forth above for claim 1 and incorporated by reference herein. For example, Fraser discloses the following formulation: "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20%

(wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Specifically, the references either explicitly or inherently disclose a "pre-filled syringe." Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprise a "pre-filled syringe." Given the prior art teachings, a person of skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including using a pre-filled syringe comprising an ophthalmic formulation, and would have reasonably expected success with such formulation.

Claim 26 of the 865 patent is therefore anticipated for the same reasons stated above for claim 1. Additionally, claim 26 would have been obvious over at least, *inter alia*, the combinations identified above for claim 1, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claim 1.

xxvii. Claim 27.

Claim 27 of the 865 patent depends from claim 26, and thus incorporates the elements of claim 26. For at least the same reasons set forth above with respect to claim 26, said discussion incorporated herein by reference, claim 27 is anticipated and/or obvious.

The limitation, "wherein said organic co-solvent comprises polysorbate," does not distinguish the claim from claim 26 or the prior art that invalidates claim 26. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein said organic co-solvent comprises polysorbate." For example, Fraser discloses "VEGF Trap$_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein said organic co-solvent comprises polysorbate."

The additional limitation, "wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml" does not distinguish the claim from claim 26 or the prior art that invalidates claim 26. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml." For example, Andya specifically discloses that a "lyophilized formulation can be reconstituted to generate a stable reconstituted formulation having a protein concentration which is significantly higher (e.g., from about 2-40 times higher, preferably 3-10 times higher and most preferably 3-6 times higher) than the protein concentration in the pre-lyophilized formulation." (Andya at [0008]). Andya also discloses that "while the protein concentration in the pre-lyophilized formulation may be 5 mg/mL or less, the protein concentration in the reconstituted formulation is generally 50 mg/mL or more." (Andya at [0008]). Given that Fraser formulation's VEGF Trap concentration was 24.3 mg/ml, a person of ordinary skill would have been motivated to generate a stable formulation having a significantly higher protein concentration, *e.g.*, by following Andya's

teachings to lyophilize and reconstitute in histidine buffer so as to increase the concentration by at least 2-fold (*e.g.*, from ~25 to ~50 mg/ml).

Claim 27 of the 865 patent is therefore anticipated for the same reasons stated above for claim 26. Additionally, claim 27 would have been obvious over at least, *inter alia*, the combinations identified above for claim 26, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claim 26. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including VEGF antagonist fusion protein at a concentration of 40 mg/ml and with an organic co-solvent comprising polysorbate, and would have reasonably expected success with such formulation.

xxviii. Claim 28.

Claim 28 of the 865 patent depends from claim 27, which depends from claim 26, and thus claim 28 incorporates the elements of claims 26 and 27. For at least the same reasons set forth above with respect to claims 26 and 27, said discussion incorporated herein by reference, claim 28 is anticipated and/or obvious.

The additional limitation, "wherein said organic co-solvent comprises 0.01% to 3% polysorbate," does not distinguish the claim from claims 26 and 27, or the prior art that invalidates claims 26 and 27. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein said organic co-solvent comprises polysorbate." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations where "[p]olysorbate 20 was added to the formulations at concentrations of 0.005%, 0.01%, and 0.02%." (Andya at [0175]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein said organic co-solvent comprises 0.01% to 3% polysorbate."

Claim 28 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26 and 27. Additionally, claim 28 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26 and 27, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26 and 27. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including an organic co-solvent comprising 0.01% to 3% polysorbate, and would have reasonably expected success with such formulation.

xxix. Claim 29.

Claim 29 of the 865 patent depends from claim 27, which depends from claim 26, and thus claim 29 incorporates the elements of claims 26 and 27. For at least the same reasons set

forth above with respect to claims 26 and 27, said discussion incorporated herein by reference, claim 29 is anticipated and/or obvious.

The additional limitation, "wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20," does not distinguish the claim from claims 26 and 27, or the prior art that invalidates claims 26 and 27. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20." For example, Fraser discloses "VEGF Trap$_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations where "[p]olysorbate 20 was added to the formulations at concentrations of 0.005%, 0.01%, and 0.02%." (Andya at [0175]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20."

Claim 29 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26 and 27. Additionally, claim 29 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26 and 27, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26 and 27. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including an organic co-solvent comprising about 0.03% to about 0.1% polysorbate 20, and would have reasonably expected success with such formulation.

xxx. Claim 30.

Claim 30 of the 865 patent depends from claim 27, which depends from claim 26, and thus claim 30 incorporates the elements of claims 26 and 27. For at least the same reasons set forth above with respect to claims 26 and 27, said discussion incorporated herein by reference, claim 30 is anticipated and/or obvious.

The additional limitation, "wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20," does not distinguish the claim from claims 26 and 27, or the prior art that invalidates claims 26 and 27. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20." For example, Fraser discloses "VEGF Trap$_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations where "[p]olysorbate 20 was added to

the formulations at concentrations of 0.005%, 0.01%, and 0.02%." (Andya at [0175]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20."

Claim 30 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26 and 27. Additionally, claim 30 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26 and 27, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26 and 27. Given the prior art teachings, a person of skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including an organic cosolvent comprising 0.01% to 3% polysorbate 20, and would have reasonably expected success with such formulation.

xxxi. Claim 31.

Claim 31 of the 865 patent depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 31 incorporates the elements of claims 26, 27, and 30. For at least the same reasons set forth above with respect to claims 26, 27, and 30, said discussion incorporated herein by reference, claim 31 is anticipated and/or obvious.

The additional limitation, "wherein said buffer comprises a phosphate buffer," does not distinguish the claim from claims 26, 27, and 30, or the prior art that invalidates claims 26, 27, and 30. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein said buffer comprises a phosphate buffer." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein said buffer comprises a phosphate buffer."

Claim 31 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, and 30. Additionally, claim 31 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, and 30, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, and 30. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a phosphate buffer, and would have reasonably expected success with such formulation.

xxxii. Claim 32.

Claim 32 of the 865 patent depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 32 incorporates the elements of claims 26, 27, and

30. For at least the same reasons set forth above with respect to claims 26, 27, and 30, said discussion incorporated herein by reference, claim 32 is anticipated and/or obvious.

The additional limitation, "wherein said buffer comprises 5-25 mM buffer," does not distinguish the claim from claims 26, 27, and 30, or the prior art that invalidates claims 26, 27, and 30. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein said buffer comprises 5-25 mM buffer." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein said buffer comprises 5-25 mM buffer."

Claim 32 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, and 30. Additionally, claim 32 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, and 30, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, and 30. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including 5-25 mM buffer, and would have reasonably expected success with such formulation.

xxxiii. Claim 33.

Claim 33 of the 865 patent depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 33 incorporates the elements of claims 26, 27, and 30. For at least the same reasons set forth above with respect to claims 26, 27, and 30, said discussion incorporated herein by reference, claim 33 is anticipated and/or obvious.

The additional limitation, "wherein said buffer comprises a pH between about 5.8-7.0," does not distinguish the claim from claims 26, 27, and 30, or the prior art that invalidates claims 26, 27, and 30. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein said buffer comprises a pH between about 5.8-7.0." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which

equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein said buffer comprises a pH between about 5.8-7.0."

Claim 33 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, and 30. Additionally, claim 33 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, and 30, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, and 30. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a pH between about 5.8-7.0, and would have reasonably expected success with such formulation.

xxxiv. Claim 34.

Claim 34 of the 865 patent depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 34 incorporates the elements of claims 26, 27, and 30. For at least the same reasons set forth above with respect to claims 26, 27, and 30, said discussion incorporated herein by reference, claim 34 is anticipated and/or obvious.

The additional limitation, "wherein said buffer comprises a pH about 6.2-6.3," does not distinguish the claim from claims 26, 27, and 30, or the prior art that invalidates claims 26, 27, and 30. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein said buffer comprises a pH about 6.2-6.3." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein said buffer comprises a pH about 6.2-6.3."

Claim 34 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, and 30. Additionally, claim 34 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, and 30, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, and 30. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination

of elements, including a pH about 6.2-6.3, and would have reasonably expected success with such formulation.

xxxv. Claim 35.

Claim 35 of the 865 patent depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 35 incorporates the elements of claims 26, 27, and 30. For at least the same reasons set forth above with respect to claims 26, 27, and 30, said discussion incorporated herein by reference, claim 35 is anticipated and/or obvious.

The additional limitation, "wherein said stabilizing agent comprises a sugar," does not distinguish the claim from claims 26, 27, and 30, or the prior art that invalidates claims 26, 27, and 30. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein said stabilizing agent comprises a sugar." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein said stabilizing agent comprises a sugar."

Claim 35 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, and 30. Additionally, claim 35 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, and 30, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, and 30. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a sugar, and would have reasonably expected success with such formulation.

xxxvi. Claim 36.

Claim 36 of the 865 patent depends from claim 35, which depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 36 incorporates the elements of claims 26, 27, 30, and 35. For at least the same reasons set forth above with respect to claims 26, 27, 30, and 35, said discussion incorporated herein by reference, claim 36 is anticipated and/or obvious.

The additional limitation, "wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol," does not distinguish the claim from claims

26, 27, 30, and 35, or the prior art that invalidates claims 26, 27, 30, and 35. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol."

Claim 36 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, 30, and 35. Additionally, claim 36 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, 30, and 35, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, 30, and 35. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a sugar selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol, and would have reasonably expected success with such formulation.

xxxvii. Claim 37.

Claim 37 of the 865 patent depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 37 incorporates the elements of claims 26, 27, and 30. For at least the same reasons set forth above with respect to claims 26, 27, and 30, said discussion incorporated herein by reference, claim 37 is anticipated and/or obvious.

The additional limitation, "wherein said stabilizing agent comprises 1.0-7.5% of sucrose," does not distinguish the claim from claims 26, 27, and 30, or the prior art that invalidates claims 26, 27, and 30. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein said stabilizing agent comprises 1.0-7.5% of sucrose." For example, Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM" and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein said stabilizing agent comprises 1.0-7.5% of sucrose."

Claim 37 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, and 30. Additionally, claim 37 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, and 30, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, and 30. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including 1.0-7.5% of sucrose, and would have reasonably expected success with such formulation.

xxxviii. Claim 38.

Claim 38 of the 865 patent depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 38 incorporates the elements of claims 26, 27, and 30. For at least the same reasons set forth above with respect to claims 26, 27, and 30, said discussion incorporated herein by reference, claim 38 is anticipated and/or obvious.

The additional limitation, "wherein said formulation further comprises a tonicity agent," does not distinguish the claim from claims 26, 27, and 30, or the prior art that invalidates claims 26, 27, and 30. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein said formulation further comprises a tonicity agent." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein said formulation further comprises a tonicity agent."

Claim 38 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, and 30. Additionally, claim 38 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, and 30, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, and 30. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a tonicity agent, and would have reasonably expected success with such formulation.

xxxix. Claim 39.

Claim 39 of the 865 patent depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 39 incorporates the elements of claims 26, 27, and 30. For at least the same reasons set forth above with respect to claims 26, 27, and 30, said discussion incorporated herein by reference, claim 39 is anticipated and/or obvious.

The additional limitation, "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," does not distinguish the claim from claims 26, 27, and 30, or the prior art that invalidates claims 26, 27, and 30. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "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." First, Fraser expressly cites to, and incorporates by reference, Holash for its VEGF antagonist. Holash discloses production of the VEGF antagonist in a CHO cell: "VEGF-Trap$_{R1R2}$ was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2. All of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells." (Holash at 11393-94). Second, Fraser expressly cites to, and incorporates by reference, Wulff for its VEGF antagonist, and Wulff cites to, and incorporates by reference, Papadopoulos. A person of ordinary skill in the art would have known that Papadopoulos teaches that the fusion proteins of the 865 patent are glycosylated at five asparagine residues when the protein is expressed in CHO cells. (Papadopoulos at 81:20 - 82:2 ("There are five possible N-linked glycosylation sites in Flt1D2.Flk1D3.FcΔC1(a). All five of them are found to be glycosylated to varying degrees [following expression in CHO cells.]"), Fig. 36 (underlining the five asparagine residues in SEQ ID NO: 2 that are glycosylation sites)). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "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."

Claim 39 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, and 30. Additionally, claim 39 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, and 30, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, and 30. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a VEGF antagonist protein glycosylated at the claimed asparagine residues, and would have reasonably expected success with such formulation.

xl. Claim 40.

Claim 40 of the 865 patent depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 40 incorporates the elements of claims 26, 27, and 30. For at least the same reasons set forth above with respect to claims 26, 27, and 30, said discussion incorporated herein by reference, claim 40 is anticipated and/or obvious.

The additional limitation, "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C," does not distinguish the claim from claims 26, 27, and 30, or the prior art that invalidates claims 26, 27, and 30. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C." First, the element "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C," merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *In re Copaxone*, 906 F.3d at 1023-24; *Bristol-Myers*

Squibb, 246 F.3d at 1375-76. Notwithstanding, even if some limiting effect is granted to the "turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C" element, it is inherent in Fraser's formulation and therefore does not distinguish the claimed "vial" from the prior art. For example, Dix (U.S. Patent No. 8,110,546) discloses (among other results) over 99% VEGF antagonist remaining in "[n]ative [c]onfiguration" after storage at 5º C for two months (Table 9) for Dix's 25 mg/ml formulation, which the patentee has conceded is the identical formulation and possesses the same stability properties as Fraser. (*See* 546 patent PH 11/22/2011 Response to 7/13/2011 Office Action at 2-4 (Regeneron describing Dix formulation and admitting it is identical to Fraser)). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C."

Claim 40 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, and 30. Additionally, claim 40 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, and 30, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, and 30. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including being capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C, and would have reasonably expected success with such formulation.

xli. Claim 41.

Claim 41 of the 865 patent depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 41 incorporates the elements of claims 26, 27, and 30. For at least the same reasons set forth above with respect to claims 26, 27, and 30, said discussion incorporated herein by reference, claim 41 is anticipated and/or obvious.

The additional limitation, "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography," does not distinguish the claim from claims 26, 27, and 30, or the prior art that invalidates claims 26, 27, and 30. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography." First, the element "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography," merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *In re Copaxone*, 906 F.3d at 1023-24; *Bristol-Myers Squibb*, 246 F.3d at 1375-76. Notwithstanding, even if some limiting effect is granted to the "99% ... native conformation" element, it is inherent in Fraser's formulation and therefore does not distinguish the claimed "vial" from the prior art. For example, Dix (U.S. Patent No. 8,110,546) discloses (among other results) over 99% VEGF antagonist remaining in "[n]ative [c]onfiguration" after storage at 5º C for two months (Table 9) for Dix's 25 mg/ml formulation, which the patentee has conceded is the identical formulation and possesses the same stability properties as Fraser. (*See* 546 patent PH 11/22/2011 Response to 7/13/2011 Office Action at 2-4 (Regeneron describing Dix formulation and admitting it is identical to Fraser)). Moreover, a person of ordinary skill in

the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography."

Claim 41 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, and 30. Additionally, claim 41 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, and 30, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, and 30. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including at least 99% of the VEGF antagonist protein being present in native conformation after 2 month storage at 5° C as measured by size exclusion chromatography, and would have reasonably expected success with such formulation.

xlii. Claim 42.

Claim 42 of the 865 patent depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 42 incorporates the elements of claims 26, 27, and 30. For at least the same reasons set forth above with respect to claims 26, 27, and 30, said discussion incorporated herein by reference, claim 42 is anticipated and/or obvious.

The additional limitation, "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography," does not distinguish the claim from claims 26, 27, and 30, or the prior art that invalidates claims 26, 27, and 30. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography." First, the element "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography," merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *In re Copaxone*, 906 F.3d at 1023-24; *Bristol-Myers Squibb*, 246 F.3d at 1375-76. Notwithstanding, even if some limiting effect is granted to the "98% ... native conformation" element, it is inherent in Fraser's formulation and therefore does not distinguish the claimed "pre-filled syringe" from the prior art.

For example, Dix (U.S. Patent No. 8,110,546) discloses (among other results) over 99% VEGF antagonist remaining in "[n]ative [c]onfiguration" after storage at 5º C for two months (Table 9) for Dix's 25 mg/ml formulation, which the patentee has conceded is the identical formulation and possesses the same stability properties as Fraser. (*See* 546 patent 11/22/2011 Response to 7/13/2011 Office Action at 2-4 (Regeneron describing Dix formulation and admitting it is identical to Fraser)). Even more, a person of ordinary skill would have noted that Fraser's formulation was stored at 4° C and discarded within 2 weeks, (Fraser at 1115), and would have been motivated to use histidine to generate a formulation with the longer storage stability as disclosed by Andya's disclosure of histidine-buffered formulations with long-term storage stability of "at least 2 years," (Andya at [0049]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein at least 98% of

said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography."

Claim 42 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, and 30. Additionally, claim 42 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, and 30, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, and 30. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including at least 98% of the VEGF antagonist protein being present in native conformation following storage at 5° C for 24 months as measured by size exclusion chromatography, and would have reasonably expected success with such formulation.

xliii. Claim 43.

Claim 43 of the 865 patent depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 43 incorporates the elements of claims 26, 27, and 30. For at least the same reasons set forth above with respect to claims 26, 27, and 30, said discussion incorporated herein by reference, claim 43 is anticipated and/or obvious.

The additional limitation, "wherein said formulation does not contain phosphate," does not distinguish the claim from claims 26, 27, and 30, or the prior art that invalidates claims 26, 27, and 30. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein said formulation does not contain phosphate." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya recognized that histidine was one of a small group of commonly used buffers for stabilizing proteinaceous therapeutic formulations, had been used in multiple FDA approved products, and was particularly useful for formulating high concentration protein formulations. (*See* Andya at [0096]). It would have been obvious to use histidine because of its usefulness in preventing aggregation and generating a stable formulation having a protein concentration, which is significantly higher than the protein concentration in the pre-lyophilized formulation, improving its lyoprotective properties, and improving long term storage stability. (*See* Andya at [0013]; U.S. Patent Application Publication No. 2003/0113316 A1 (Kaisheva I); U.S. Patent Application Publication No. 2004/0197324 A1 (Liu)). It would have been obvious to use Andya's histidine buffer in the Fraser/Wulff formulations for the additional reasons that: (1) its pKa provides maximum buffering capacity at pH 6 (the same as Fraser's formulation), (2) it had suitable pKa and buffering capacity for the VEGF TrapR1R2 protein having a pI of approximately 8, (3) it contributes less to osmolarity than Fraser/Wulff's phosphate-citrate buffers, (4) phosphate-citrate buffers were known to cause painful reactions when injected subcutaneously in contrast to histidine buffer, and (5) regulatory agencies had repeatedly approved histidine-buffered proteinaceous therapeutic formulations. A person of ordinary skill would have wanted to retain or improve the stability,

binding, and potency of the Wulff/Fraser VEGF TrapR1R2, and would have been motivated to use histidine based on Andya's teaching that it was especially good at preventing degradation including aggregation. (*See* Andya at [0160], Figs. 9-10). A person of ordinary skill would further have had a reasonable expectation of achieving a formulation that maintains the stability, potency, and binding properties of Wulff/Fraser's formulation using this combination of ingredients given the numerous other FDA-approved protein therapeutics containing the same combination of excipients, and in view of Andya's teaching that histidine has an exceptional ability to act as a lyoprotectant and prevent degradation. Histidine was a well-known buffer long before the 865 patent's earliest possible priority date and its multiple advantages were also well-known and would have motivated a person of ordinary skill to use histidine buffer in Wulff/Fraser's formulation. Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein said formulation does not contain phosphate."

Claim 43 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, and 30. Additionally, claim 43 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, and 30, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, and 30. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including not containing phosphate, and would have reasonably expected success with such formulation.

xliv. Claim 44.

Claim 44 of the 865 patent depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 44 incorporates the elements of claims 26, 27, and 30. For at least the same reasons set forth above with respect to claims 26, 27, and 30, said discussion incorporated herein by reference, claim 44 is anticipated and/or obvious.

The additional limitation, "wherein said formulation does not contain trehalose," does not distinguish the claim from claims 26, 27, and 30, or the prior art that invalidates claims 26, 27, and 30. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein said formulation does not contain trehalose." For example, Fraser discloses "VEGF Trap$_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein said formulation does not contain trehalose."

Claim 44 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, and 30. Additionally, claim 44 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, and 30, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, and 30. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including not containing trehalose, and would have reasonably expected success with such formulation.

xlv. Claim 45.

Claim 45 of the 865 patent depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 45 incorporates the elements of claims 26, 27, and 30. For at least the same reasons set forth above with respect to claims 26, 27, and 30, said discussion incorporated herein by reference, claim 45 is anticipated and/or obvious.

The additional limitation, "wherein said stabilizing agent comprises 1.0-10% of sucrose," does not distinguish the claim from claims 26, 27, and 30, or the prior art that invalidates claims 26, 27, and 30. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein said stabilizing agent comprises 1.0-10% of sucrose." For example, Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM" and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein said stabilizing agent comprises 1.0-10% of sucrose."

Claim 45 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, and 30. Additionally, claim 45 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, and 30, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, and 30. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including 1.0-10% of sucrose, and would have reasonably expected success with such formulation.

xlvi. Claim 46.

Claim 46 of the 865 patent depends from claim 45, which depends from claim 30, which depends from claim 27, which depends fom claim 26, and thus claim 46 incorporates the elements of claims 26, 27, 30, and 45. For at least the same reasons set forth above with respect to claims 26, 27, 30, and 45, said discussion incorporated herein by reference, claim 46 is anticipated and/or obvious.

The additional limitation, "wherein said formulation further comprises a tonicity agent," does not distinguish the claim from claims 26, 27, 30, and 45, or the prior art that invalidates claims 26, 27, 30, and 45. Specifically, the references outlined above either explicitly

or inherently disclose a "pre-filled syringe" "wherein said formulation further comprises a tonicity agent." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein said formulation further comprises a tonicity agent."

Claim 46 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, 30, and 45. Additionally, claim 46 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, 30, and 45, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, 30, and 45. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a tonicity agent, and would have reasonably expected success with such formulation.

xlvii. Claim 47.

Claim 47 of the 865 patent depends from claim 45, which depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 47 incorporates the elements of claims 26, 27, 30, and 45. For at least the same reasons set forth above with respect to claims 26, 27, 30, and 45, said discussion incorporated herein by reference, claim 47 is anticipated and/or obvious.

The additional limitation, "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," does not distinguish the claim from claims 26, 27, 30, and 45, or the prior art that invalidates claims 26, 27, 30, and 45. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "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." First, Fraser expressly cites to, and incorporates by reference, Holash for its VEGF antagonist. Holash discloses production of the VEGF antagonist in a CHO cell: "VEGF-$Trap_{R1R2}$ was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2. All of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells." (Holash at 11393-94). Second, Fraser expressly cites to, and incorporates by reference, Wulff for its VEGF antagonist, and Wulff cites to, and incorporates by reference, Papadopoulos. A person of ordinary skill in the art would have known that Papadopoulos teaches that the fusion proteins of the 865 patent are glycosylated at five asparagine residues when the protein is expressed in CHO cells. (Papadopoulos at 81:20 - 82:2 ("There are five possible N-linked glycosylation sites in Flt1D2.Flk1D3.FcΔC1(a). All five of them are found to be glycosylated to varying degrees [following expression in CHO cells.]"), Fig. 36 (underlining the five asparagine residues in SEQ ID NO: 2 that are glycosylation sites)). Moreover, a person of

ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "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."

Claim 47 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, 30, and 45. Additionally, claim 47 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, 30, and 45, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, 30, and 45. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a VEGF antagonist protein glycosylated at the claimed asparagine residues, and would have reasonably expected success with such formulation.

xlviii. Claim 48.

Claim 48 of the 865 patent depends from claim 45, which depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 48 incorporates the elements of claims 26, 27, 30, and 45. For at least the same reasons set forth above with respect to claims 26, 27, 30, and 45, said discussion incorporated herein by reference, claim 48 is anticipated and/or obvious.

The additional limitation, "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C" does not distinguish the claim from claims 26, 27, 30, and 45, or the prior art that invalidates claims 26, 27, 30, and 45. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C." First, the element "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C," merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *In re Copaxone*, 906 F.3d at 1023-24; *Bristol-Myers Squibb*, 246 F.3d at 1375-76. Notwithstanding, even if some limiting effect is granted to the "turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C" element, it is inherent in Fraser's formulation and therefore does not distinguish the claimed "vial" from the prior art. For example, Dix (U.S. Patent No. 8,110,546) discloses (among other results) over 99% VEGF antagonist remaining in "[n]ative [c]onfiguration" after storage at 5º C for two months (Table 9) for Dix's 25 mg/ml formulation, which the patentee has conceded is the identical formulation and possesses the same stability properties as Fraser. (*See* 546 patent PH 11/22/2011 Response to 7/13/2011 Office Action at 2-4 (Regeneron describing Dix formulation and admitting it is identical to Fraser)). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C."

Claim 48 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, 30, and 45. Additionally, claim 48 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, 30, and 45, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, 30, and 45. Given the prior art teachings, a person of ordinary skill in the

art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including being capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C, and would have reasonably expected success with such formulation.

xlix. Claim 49.

Claim 49 of the 865 patent depends from claim 45, which depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 49 incorporates the elements of claims 26, 27, 30, and 45. For at least the same reasons set forth above with respect to claims 26, 27, 30, and 45, said discussion incorporated herein by reference, claim 49 is anticipated and/or obvious.

The additional limitation, "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography," does not distinguish the claim from claims 26, 27, 30, and 45, or the prior art that invalidates claims 26, 27, 30, and 45. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography." First, the element "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography," merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *In re Copaxone*, 906 F.3d at 1023-24; *Bristol-Myers Squibb*, 246 F.3d at 1375-76. Notwithstanding, even if some limiting effect is granted to the "99% ... native conformation" element, it is inherent in Fraser's formulation and therefore does not distinguish the claimed "vial" from the prior art. For example, Dix (U.S. Patent No. 8,110,546) discloses (among other results) over 99% VEGF antagonist remaining in "[n]ative [c]onfiguration" after storage at 5º C for two months (Table 9) for Dix's 25 mg/ml formulation, which the patentee has conceded is the identical formulation and possesses the same stability properties as Fraser. (*See* 546 patent PH 11/22/2011 Response to 7/13/2011 Office Action at 2-4 (Regeneron describing Dix formulation and admitting it is identical to Fraser)). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography."

Claim 49 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, 30, and 45. Additionally, claim 49 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, 30, and 45, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, 30, and 45. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including at least 99% of the VEGF antagonist protein being present in native conformation after 2 month storage at 5° C as measured by size exclusion chromatography, and would have reasonably expected success with such formulation.

l. Claim 50.

Claim 50 of the 865 patent depends from claim 45, which depends from claim 30, which depends from claim 27, which depends from claim 26, and thus claim 50 incorporates the elements of claims 26, 27, 30, and 45. For at least the same reasons set forth above with respect to claims 26, 27, 30, and 45, said discussion incorporated herein by reference, claim 50 is anticipated and/or obvious.

The additional limitation, "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography," does not distinguish the claim from claims 26, 27, 30, and 45, or the prior art that invalidates claims 26, 27, 30, and 45. Specifically, the references outlined above either explicitly or inherently disclose a "pre-filled syringe" "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography." First, the element "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography," merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *In re Copaxone*, 906 F.3d at 1023-24; *Bristol-Myers Squibb*, 246 F.3d at 1375-76. Notwithstanding, even if some limiting effect is granted to the "98% ... native conformation" element, it is inherent in Fraser's formulation and therefore does not distinguish the claimed "vial" from the prior art.

For example, Dix (U.S. Patent No. 8,110,546) discloses (among other results) over 99% VEGF antagonist remaining in "native configuration" after storage at 5º C for two months (Table 9) for Dix's 25 mg/ml formulation, which the patentee has conceded is the identical formulation and possesses the same stability properties as Fraser. (*See* 546 patent PH 11/22/2011 Response to 7/13/2011 Office Action at 2-4 (Regeneron describing Dix formulation and admitting it is identical to Fraser)). Even more, a person of ordinary skill would have noted that Fraser's formulation was stored at 4° C and discarded within 2 weeks, (Fraser at 1115), and would have been motivated to use histidine to generate a formulation with the longer storage stability as disclosed by Andya's disclosure of histidine-buffered formulations with long-term storage stability of "at least 2 years," (Andya at [0049]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "pre-filled syringe" "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography."

Claim 50 of the 865 patent is therefore anticipated for the same reasons stated above for claims 26, 27, 30, and 45. Additionally, claim 50 would have been obvious over at least, *inter alia*, the combinations identified above for claims 26, 27, 30, and 45, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 26, 27, 30, and 45. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including at least 98% of the VEGF antagonist protein being present in native conformation following storage at 5° C for 24 months as measured by size exclusion chromatography, and would have reasonably expected success with such formulation.

li. Independent Claim 51.

Claim 51 of the 865 patent recites:

> **51.** An ophthalmic formulation comprising:
> (a) 40 mg/ml of a glycosylated VEGF antagonist fusion protein comprising amino acids 27-457 of SEQ ID NO:4;
> (b) 0.03% to 0.1% polysorbate;
> (c) 5-40 mM of sodium phosphate buffer, pH between 5.8-7.0; and
> (d) sucrose;
> wherein the ophthalmic formulation is suitable for intravitreal administration; and
> wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for 2 months as measured by size exclusion chromatography.

(865 patent at 22:18-31).

Claim 51 is invalid as anticipated and/or obvious for the same reasons set forth above for claim 1 and incorporated by reference herein.

Specifically, Fraser expressly discloses the VEGF antagonist, co-solvent, buffer and stabilizing agent elements of claim 51. (*See, e.g.*, Fraser at 1115 ("VEGF Trap$_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose.")). Accordingly, Fraser expressly discloses the formulation 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 elements of claim 51.

Fraser also expressly discloses the limitation "[a]n ophthalmic formulation comprising … a glycosylated VEGF antagonist fusion protein comprising amino acids 27-457 of SEQ ID NO:4." Specifically, the references outlined above either explicitly or inherently disclose VEGF antagonist fusion proteins posttranslationally glycosylated at one or more asparagine residues. First, Fraser expressly cites to, and incorporates by reference, Holash for its VEGF antagonist. Holash discloses production of the VEGF antagonist in a CHO cell: "VEGF-Trap$_{R1R2}$ was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2. All of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells." (Holash at 11393-94). Second, Fraser expressly cites to, and incorporates by reference, Wulff for its VEGF antagonist, and Wulff cites to, and incorporates by reference, Papadopoulos. A person of ordinary skill in the art would have known that Papadopoulos teaches that the fusion proteins of the 865 patent are glycosylated at five asparagine residues when the protein is expressed in CHO cells. (Papadopoulos at 81:20 - 82:2 ("There are five possible N-linked glycosylation sites in Flt1D2.Flk1D3.FcΔC1(a). All five of them are found to be glycosylated to varying degrees

[following expression in CHO cells.]"), Fig. 36 (underlining the five asparagine residues in SEQ ID NO: 2 that are glycosylation sites)).

Fraser and Wulff incorporate by reference, Papadopoulos, which teaches the amino acid sequence of SEQ ID NO: 4, its production in CHO cells, and methods of purifying from CHO cells. Specifically, Papadopoulos teaches methods of producing VEGF antagonist fusion proteins for use in formulations and prefilled syringes, and these methods included isolating and purifying the protein product by affinity and size exclusion chromatography. (Papadopoulos at 67:25 - 68:5 ("The process for production of Flt1D2.Flk1D3.FcΔC1(a) protein … involves suspension culture of recombinant Chinese hamster ovary (CHO K1/E1A) cells which constitutively express the protein product. The cells are grown in bioreactors and the protein product is isolated and purified by affinity and size exclusion chromatography."), Examples 21-22)). As described in Example 20, Papadopoulos teaches methods for producing the VEGF-specific fusion protein of SEQ ID NO: 4 from CHO cells. (Papadopoulos at 67:4-17). Papadopoulos teaches VEGFR1R2-FcΔC1(a) (i.e., SEQ ID NO: 4) and that it "was constructed by insertion of DNA encoding amino acids SDT (corresponding to amino acids 27-29 of Figure 24A-24C) between Flt1d2-Flk1d3-FcΔC1(a) amino acids 26 and 27 of Figure 21A-21C (GG) and removal of DNA encoding amino acids GPG corresponding to amino acids 229-231 of Figure [21A-21C]." (Papadopoulos at 67:7-12). Further, Papadopoulos discloses that the purification methods applied to SEQ ID NO: 2 are useful for purifying SEQ ID NO: 4 and other similar fusion proteins. (Papadopoulos at Fig. 24A-24C, 69:15-19 (stating that "the same methodologies as described [] for Flt1D2.Flk1D3.FcΔCl(a) were used to produce [the related fusion protein] Flt1D2.VEGFR3D3.FcΔCl(a).")). Papadopoulos describes using size exclusion chromatography "[t]o remove aggregates and other contaminants." (Papadopoulos at 39:15-19).

A person of ordinary skill in the art reading the prior art (e.g., Holash, Papadopoulos, Vitti) therefore would have understood that SEQ ID NO: 4 is encompassed by VEGF-Trap$_{R1R2}$. Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a VEGF antagonist fusion protein that "comprising amino acids 27-457 of SEQ ID NO:4." (*See, e.g.*, Papadopoulos at 67:4-17 (Example 20)).

Wulff evaluated the VEGF TrapR1R2 protein and its biological activity in inhibiting VEGF. (Wulff at 2797, Abstract). Wulff describes the VEGF antagonist used in the experiments as follows:

> A recombinant chimeric protein comprising portions of the extracellular, ligand binding domains of the human VEGF receptors Flt-1 (VEGF-R1, Ig domain 2) and KDR (VEGF-R2, Ig domain 3) expressed in sequence with the Fc portion of human IgG (Fig. 1). The presence of the Fc domain results in homodimerization of the recombinant protein, thereby creating a high affinity (KD1–5pM) VEGF Trap. The VEGF trap was expressed in CHO cells and was purified by protein A affinity chromatography followed by size-exclusion chromatography. The specificity of VEGF binding and the affinity to VEGF of VEGF Trap R1R2 were determined by Biacore (Uppsala, Sweden).

Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Wulff discloses that a dose of the VEGF Trap was injected subcutaneously into marmosets. (*Id.*). Accordingly, Wulff expressly discloses the "ophthalmic formulation comprising: (a) 40 mg/ml of a glycosylated VEGF antagonist fusion protein comprising amino acids 27-457 of SEQ ID NO:4; (b) 0.03% to 0.1% polysorbate; (c) 5-40 mM of sodium phosphate buffer, pH between 5.8-7.0; and (d) sucrose; wherein the ophthalmic formulation is suitable for intravitreal administration" elements of claim 51.

Wulff also expressly discloses the limitation "[a]n ophthalmic formulation comprising … a glycosylated VEGF antagonist fusion protein comprising amino acids 27-457 of SEQ ID NO:4." Specifically, the references outlined above either explicitly or inherently disclose VEGF antagonist fusion proteins posttranslationally glycosylated at one or more asparagine residues. Wulff cites to, and incorporates by reference, Papadopoulos. A person of ordinary skill in the art would have known that Papadopoulos teaches that the fusion proteins of the 865 patent are glycosylated at five asparagine residues when the protein is expressed in CHO cells. (Papadopoulos at 81:20 - 82:2 ("There are five possible N-linked glycosylation sites in Flt1D2.Flk1D3.FcΔC1(a). All five of them are found to be glycosylated to varying degrees [following expression in CHO cells.]"), Fig. 36 (underlining the five asparagine residues in SEQ ID NO: 2 that are glycosylation sites)).

Wulff further discloses that the VEGF TrapR1R2 was administered subcutaneously to the monkeys "[t]o inhibit vascular endothelial growth factor (VEGF)," (Wulff at 2797-98), and that "VEGF Trap R1R2 may be more efficient in inhibiting VEGF, because it contains an additional domain of the second VEGF receptor KDR," *id*. at 2804. Wulff also expressly cites to, and incorporates by reference, Papadopoulos (WO 00/75319 Al). (*See* Wulff at 2798, n.1). Papadopoulos teaches amino acid sequences encoding VEGF antagonist fusion proteins that fall within the scope of the claim 51, including a protein called "Flt1D2.Flk1D3.FcΔC1(a)," which corresponds to SEQ ID NO: 2 of the 865 patent, and a protein called "VEGFRIR2-FcΔC1(a)," which corresponds to SEQ ID NO: 4 of the 865 patent (also known as "aflibercept").[14] The nucleotide and amino acid sequences of VEGFRIR2-FcΔC1(a) are provided in Papadopoulos Figs. 24A-24C. The amino acid sequence of the VEGFRIR2-FcΔC1(a) protein in Papadopoulos is identical to SEQ ID NO: 4 of the 865 patent. Papadopoulos also teaches that these VEGF

[14] U.S. Pub. No. 2016/0144025 ("Vitti") confirms that "VEGFRIR2-FcΔC1(a)" is "also known as aflibercept." (Vitti at [0086]). Vitti teaches that aflibercept is "encoded by the amino acid sequence of SEQ ID NO: 11," (*id.*), which is identical to SEQ ID NO:4 of the 865 patent. Vitti also explains that aflibercept "consists of a dimer of two polypeptides consisting of amino acids 27-457 of [SEQ ID NO:4 of the 865 patent]." (*Id.* at [0197]). The complete SEQ ID NO:4 includes, *inter alia,* a signal peptide that is removed during protein production, and an Fe sequence of human IgG that causes the protein to dimerize. (*See* Papadopoulos at Fig. 24A (identifying the signal sequence at amino acids 1-26 of SEQ ID NO: 4); *id.* at Figs. 24B-C (identifying the human Fe region "hFCΔClA" at amino acids 232-458). Accordingly, the VEGF fusion protein of SEQ ID NO:4 and the dimerized VEGF fusion protein consisting of amino acids 27-457 of SEQ ID NO:4 both refer to aflibercept, as known in the prior art.

antagonist fusion proteins were produced in recombinant Chinese hamster ovary (CHO) cells. (*See* Papadopoulos 67:25 - 68:5 ("The process for production of Flt1D2.Flk1D3.FcΔC1(a) [*i.e.,* the protein of SEQ ID NO: 2 of the 865 patent] protein ... involves suspension culture of recombinant Chinese hamster ovary (CHO K1/E1A)) cells which constitutively express the protein product. The cells are grown in bioreactors and the protein product is isolated and purified by affinity and size exclusion chromatography."). Papadopoulos also discloses that "CHO transiently expressed VEGFRIR2-FcΔC1(a) [*i.e.,* the protein of SEQ ID NO: 4 of the 865 patent]. (*Id.* at 82:12-13). Papadopoulos further teaches that the fusion proteins of the 865 patent are glycosylated at five asparagine residues when the protein is expressed in CHO cells. (Papadopoulos at 81:20 - 82:2 ("There are five possible N-linked glycosylation sites in Flt1D2.Flk1D3.FcΔC1(a). All five of them are found to be glycosylated to varying degrees [following expression in CHO cells.]"), Fig. 36 (underlining the five asparagine residues in SEQ ID NO: 2 that are glycosylation sites)). Accordingly, Wulff discloses, either expressly or inherently, every element of claim 51.

The 226 patent discloses the same VEGF antagonist disclosed in the 865 patent, the structure of which is described in claim 51 of the 865 patent. (*See, e.g.*, 226 patent at claim 3, 2:3-19). The 226 patent also discloses that in specific embodiments, "the VEGF antagonist is expressed in a mammalian cell line such as a CHO cell." (*See, e.g.*, *id.* at 5:37-39).

The 226 patent also discloses a number of formulations of the VEGF antagonist, each of which comprises "an organic co-solvent," a "buffer," and a "stabilizing agent," as those terms are defined in the 865 patent. (*See, e.g.*, 226 patent at 2:15 – 3:34, 7:5-18, 7:60 – 12:10).

The 226 patent also discloses formulations that resulted in at least 98% of the VEGF antagonist being present in native conformation following storage at 5° C for two months as measured by SEC. (*See, e.g.*, 226 patent at 8:6-19). For at least these reasons, the 226 patent anticipates claim 51.

Additionally, claim 51 of the 865 patent would have been obvious over at least the following: (i) Fraser either alone or in combination with Dix and/or Holash and/or Liu, in view of the knowledge of a person of ordinary skill in the art; and (ii) Wulff either alone or in combination with Liu, in view of the knowledge of a person of ordinary skill in the art.[15]

As explained, Dix (U.S. Patent No. 8,110,546) discloses the identical formulation as Fraser. Dix further confirms that the Fraser formulation[16] inherently comprises a VEGF antagonist "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." Specifically, Dix discloses that over 99% of the VEGF antagonist in the Fraser, 25 mg/ml

[15] To the extent that any specific limitation is found not to be explicitly or inherently disclosed in these references, it would have been achieved through routine optimization by one of ordinary skill in the art.

[16] Regeneron has conceded that the Fraser formulation is one of Dix's two tested formulations. (*See* 546 patent PH 11/22/2011 Response to 7/13/2011 Office Action at 2-4).

formulation remained in "[n]ative [c]onfiguration" (i.e., native conformation) after storage at 5º C for two months. (Dix at 11:15-12:20, Table 9).

Holash describes "a very potent high-affinity VEGF blocker that has prolonged *in vivo* pharmacokinetics and pharmacodynamics, lacks nonspecific toxicities, and can effectively suppress the growth and vascularization of a number of different types of tumors *in vivo*." (Holash at 11393). Holash further describes that "VEGF-Trap$_{R1R2}$ was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2." (*Id*. at 11393-94). A person of ordinary skill in the art reading Holash therefore would have understood that SEQ ID NO: 4 is encompassed by VEGF-Trap$_{R1R2}$. Holash also describes that "[a]ll of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells." (*Id*. at 11394). A person of ordinary skill in the art would have understood that a protein "produced and purified from Chinese hamster ovary cells," especially in order to be targeted for treatment of diabetic retinopathy (i.e., injection into the eye), must be as pure as possible and would have expected the protein to be a fusion protein wherein at least 98% is in native conformation.

The limitation "[a]n ophthalmic formulation comprising: (a) 40 mg/ml of a glycosylated VEGF antagonist fusion protein" does not distinguish the claim from the prior art that invalidates claim 51. Specifically, the references outlined above either explicitly or inherently disclose a "formulation" "comprising: (a) 40 mg/ml of a glycosylated VEGF antagonist fusion protein." For example, Andya specifically discloses that a "lyophilized formulation can be reconstituted to generate a stable reconstituted formulation having a protein concentration which is significantly higher (e.g., from about 2-40 times higher, preferably 3-10 times higher and most preferably 3-6 times higher) than the protein concentration in the pre-lyophilized formulation." (Andya at [0008]). Andya also discloses that "while the protein concentration in the pre-lyophilized formulation may be 5 mg/mL or less, the protein concentration in the reconstituted formulation is generally 50 mg/mL or more." (Andya at [0008]). Given that Fraser formulation's VEGF Trap concentration was 24.3 mg/ml, a person of ordinary skill would have been motivated to generate a stable formulation having a significantly higher protein concentration, *e.g.*, by following Andya's teachings to lyophilize and reconstitute in histidine buffer so as to increase the concentration by at least 2-fold (*e.g.*, from ~25 to ~50 mg/ml).

To the extent the BLA product could somehow satisfy the claim limitations, those limitations are also met by the prior art. For example, Liu (US2004/0197324) discloses optimizing formulations having a co-solvent (e.g., polysorbate 20), a buffer (e.g., histidine-HCl), and a stabilizer (e.g., trehalose or Arginine HCl) to achieve stable liquid protein formulations having at least 98% "native conformation" after storage at 5° C for two months. (*See, e.g.*, Liu at [0013] ("the present invention concerns a highly concentrated antibody formulations of low turbidity comprising antibody (40-150 mg/ml), histidine (10-100 mM), sugar (e.g., trehalose or sucrose, 20-350 mM) and polysorbate (0.01%-0.1%)."); *id.* at Table 1 (reporting two liquid protein formulations—both containing polysorbate 20 and either sucrose or trehalose—having >98% monomer after storage at 5º C for 3 months (i.e., 99.3% and 98.8% respectively) or longer). A person of ordinary skill in the art would have been highly motivated to combine the aforementioned teachings to achieve the "formulation" of claim 51. Furthermore, a person of ordinary skill in the art would have reasonably expected success combining the aforementioned teachings to achieve a "formulation" with the stability characteristics (i.e., "98% ... native

conformation") of claim 51. Accordingly, claim 51 of the 865 patent would have been obvious to a person of ordinary skill in the art over any one of the aforementioned combinations.

Additionally, claim 51 of the 865 patent would have been obvious over at least one or more references describing the LUCENTIS formulation, in combination with one or more references disclosing aflibercept or VEGF Trap-Eye, further in view of the knowledge of a person of ordinary skill in the art.

For example, U.S. Patent No. 7,303,747 describes the structure and sequence of the VEGF antagonist recited in the claims of the 865 patent. (*See, e.g.*, 747 patent at 5:3-26, SEQ ID NO:6). The 747 patent also discloses the use of said VEGF antagonists for use in treating eye disorders, including macular degeneration and diabetic retinopathy. (*See, e.g.*, *id.* at 5:27-51, 20:17 – 22:42).

Given the disclosures of the 747 patent and other references disclosing the sequence and structure of aflibercept (i.e., VEGF Trap-Eye, or VEGFR1R2-FcΔC1(a)), and its use in treating eye disorders, a person of ordinary skill in the art would have been motivated to review information about formulations of other VEGF antagonists known to be used in treating eye disorders, and formulated to safely deliver a pharmaceutical active into a patient's eye. Accordingly, one of ordinary skill in the art would have looked to the LUCENTIS formulation. LUCENTIS was provided as a formulation, and included a VEGF antagonist, "an organic co-solvent," a "buffer," and a "stabilizing agent," as those terms are defined in the 865 patent. (*See, e.g.*, LUCENTIS Prescribing Information (2006) § 11). Given the approval of the LUCENTIS formulation, a person of ordinary skill in the art would have been motivated to use that formulation in formulating aflibercept/VEGF Trap-Eye. Further, a person of ordinary skill in the art would have had a reasonable expectation of success given the successful formulation and FDA approval of LUCENTIS.

Accordingly, claim 51 of the 865 patent would have been obvious over any of the prior art references, above, disclosing the VEGF antagonist and its use in treating eye disorders, including the 757 patent, in combination with one or more references disclosing the formulation used in the LUCENTIS formulation.

lii. Claim 52.

Claim 52 of the 865 patent depends from claim 51, and thus claim 52 incorporates the elements of claim 51. For at least the same reasons set forth above with respect to claim 51, said discussion incorporated herein by reference, claim 52 is anticipated and/or obvious.

The additional limitation, "wherein said formulation comprises at least 5% sucrose" does not distinguish the claim from claim 51, or the prior art that invalidates claim 51. Specifically, the references outlined above either explicitly or inherently disclose a "formulation" "wherein said formulation comprises at least 5% sucrose." For example, Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM" and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in

the art would have known that the prior art compositions comprised a "formulation" "wherein said formulation comprises at least 5% sucrose."

Claim 52 of the 865 patent is therefore anticipated for the same reasons stated above for claim 51. Additionally, claim 52 would have been obvious over at least, *inter alia*, the combinations identified above for claim 51, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claim 51. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including having at least 5% sucrose, and would have reasonably expected success with such formulation.

liii. Claim 53.

Claim 53 the 865 patent depends from claim 51, and thus claim 53 incorporates the elements of claim 51. For at least the same reasons set forth above with respect to claim 51, said discussion incorporated herein by reference, claim 53 is anticipated and/or obvious.

The additional limitation, "wherein said formulation comprises 1-10% sucrose," does not distinguish the claim from claim 51, or the prior art that invalidates claim 51. Specifically, the references outlined above either explicitly or inherently disclose a "formulation" "wherein said formulation comprises 1-10% sucrose." For example, Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM" and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "formulation" "wherein said formulation comprises 1-10% sucrose."

Claim 53 of the 865 patent is therefore anticipated for the same reasons stated above for claim 51. Additionally, claim 53 would have been obvious over at least, *inter alia*, the combinations identified above for claim 51, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claim 51. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including 1.0-10% of sucrose, and would have reasonably expected success with such formulation.

liv. Claim 54.

Claim 54 of the 865 patent is essentially identical to claim 51 with the only exception being that claim 54 is directed to "[a] pre-filled syringe suitable for intravitreal administration comprising the formulation of claim 51" as opposed to "[a]n ophthalmic formulation … suitable for intravitreal administration."

The change from "[a] formulation" to "[a] pre-filled syringe" is neither limiting nor does it distinguish claim 54 from claim 51 or the prior art that renders claim 51 invalid as anticipated and/or obvious. Accordingly, for at least the same reasons set forth above with respect

to claim 51, said discussion incorporated herein by reference, claim 54 is obvious and/or anticipated.

lv. Claim 55.

Claim 55 of the 865 patent is essentially identical to claim 51 with the only exception being that claim 55 is directed to "[a] vial suitable for intravitreal administration comprising the formulation of claim 51" as opposed to "[a]n ophthalmic formulation … suitable for intravitreal administration."

The change from "[a] formulation" to "[a] vial" is neither limiting nor does it distinguish claim 55 from claim 51 or the prior art that renders claim 51 invalid as anticipated and/or obvious. Accordingly, for at least the same reasons set forth above with respect to claim 51, said discussion incorporated herein by reference, claim 55 is obvious and/or anticipated.

lvi. Claim 56.

Claim 56 of the 865 patent depends from claim 51, and thus claim 56 incorporates the elements of claim 51. For at least the same reasons set forth above with respect to claim 51, said discussion incorporated herein by reference, claim 56 is anticipated and/or obvious.

The additional limitation, "wherein said formulation comprises 10 mM sodium phosphate buffer," does not distinguish the claim from claim 51, or the prior art that invalidates claim 51. Specifically, the references outlined above either explicitly or inherently disclose a "formulation" "wherein said formulation comprises 10 mM sodium phosphate buffer." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "formulation" "wherein said formulation comprises 10 mM sodium phosphate buffer."

The additional limitation, "wherein said formulation comprises … 0.03% polysorbate," does not distinguish the claim from claim 51, or the prior art that invalidates claim 51. Specifically, the references outlined above either explicitly or inherently disclose a "formulation" "wherein said formulation comprises … 0.03% polysorbate." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose."

(Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations where "[p]olysorbate 20 was added to the formulations at concentrations of 0.005%, 0.01%, and 0.02%." (Andya at [0175]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "formulations" "wherein said formulation comprises … 0.03% polysorbate."

The additional limitation, "wherein said formulation comprises … 5% sucrose," does not distinguish the claim from claim 51, or the prior art that invalidates claim 51. Specifically, the references outlined above either explicitly or inherently disclose a "formulation" "wherein said formulation comprises … 5% sucrose." For example, Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM" and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "formulation" "wherein said formulation comprises … 5% sucrose."

The additional limitation, "wherein said formulation comprises … a pH between 6.2-6.3," does not distinguish the claim from claim 51, or the prior art that invalidates claim 51. Specifically, the references outlined above either explicitly or inherently disclose a "formulation" "wherein said formulation comprises … a pH between 6.2-6.3." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "formulation" "wherein said formulation comprises … a pH between 6.2-6.3."

Claim 56 of the 865 patent is therefore anticipated for the same reasons stated above for claim 51. Additionally, claim 56 would have been obvious over at least, *inter alia*, the combinations identified above for claim 51, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claim 51. Given the prior art teachings, a person of skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements including 10 mM sodium phosphate buffer, 0.03% polysorbate, 5% sucrose, and a pH between 6.2-6.3, and would have reasonably expected success with such formulation.

lvii. Claim 57.

Claim 57 of the 865 patent is essentially identical to claim 56 with the only exception being that claim 57 is directed to "[a] pre-filled syringe suitable for intravitreal administration comprising the formulation of claim 56" as opposed to "[a]n ophthalmic formulation … suitable for intravitreal administration."

The change from "[a] formulation" to "[a] pre-filled syringe" is neither limiting nor does it distinguish claim 57 from claim 56 or the prior art that renders claim 56 invalid as anticipated and/or obvious. Accordingly, for at least the same reasons set forth above with respect to claim 56, said discussion incorporated herein by reference, claim 57 is obvious and/or anticipated.

lviii. Claim 58.

Claim 58 of the 865 patent is essentially identical to claim 56 with the only exception being that claim 58 is directed to "[a] vial suitable for intravitreal administration comprising the formulation of claim 56" as opposed to "[a]n ophthalmic formulation … suitable for intravitreal administration."

The change from "[a] formulation" to "[a] vial" is neither limiting nor does it distinguish claim 58 from claim 56 or the prior art that renders claim 56 invalid as anticipated and/or obvious. Accordingly, for at least the same reasons set forth above with respect to claim 56, said discussion incorporated herein by reference, claim 58 is obvious and/or anticipated.

lix. Claim 59.

Claim 59 of the 865 patent depends from claim 56, which depends from claim 51, and thus claim 59 incorporates the elements of claims 51 and 56. For at least the same reasons set forth above with respect to claims 51 and 56, said discussion incorporated herein by reference, claim 59 is anticipated and/or obvious.

The limitation "formulation of claim 56, wherein said formulation further comprises 40 mM NaCl," does not distinguish the claims from claims 51 or 56, or the prior art that invalidates claims 51 and 56. Specifically, each of Wulff and Fraser discloses a formulation containing sodium chloride. (Wulff at 2798; Fraser at 1115). Thus, Wulff or Fraser in view of Andya renders obvious the "formulation of claim 56, wherein said formulation further comprises 40 mM NaCl."

Claim 59 of the 865 patent is therefore anticipated for the same reasons stated above for claims 51 and 56. Additionally, claim 59 would have been obvious over at least, *inter alia*, the combinations identified above for claims 51 and 56, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 51 and 56. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including 40 mM NaCl, and would have reasonably expected success with such formulation.

lx. Claim 60.

Claim 60 of the 865 patent is essentially identical to claim 59 with the only exception being that claim 60 is directed to "[a] pre-filled syringe suitable for intravitreal administration comprising the formulation of claim 59" as opposed to "[a]n ophthalmic formulation … suitable for intravitreal administration."

The change from "[a] formulation" to "[a] pre-filled syringe" is neither limiting nor does it distinguish claim 60 from claim 59 or the prior art that renders claim 59 invalid as anticipated and/or obvious. Accordingly, for at least the same reasons set forth above with respect to claim 59, said discussion incorporated herein by reference, claim 60 is obvious and/or anticipated.

lxi. Claim 61.

Claim 61 of the 865 patent is essentially identical to claim 59 with the only exception being that claim 61 is directed to "[a] vial suitable for intravitreal administration comprising the formulation of claim 59" as opposed to "[a]n ophthalmic formulation … suitable for intravitreal administration."

The change from "[a] formulation" to "[a] vial" is neither limiting nor does it distinguish claim 61 from claim 59 or the prior art that renders claim 59 invalid as anticipated and/or obvious. Accordingly, for at least the same reasons set forth above with respect to claim 59, said discussion incorporated herein by reference, claim 61 is obvious and/or anticipated.

lxii. Claim 62.

Claim 62 of the 865 patent depends from claim 59, which depends from claim 56, which depends from claim 51, and thus claim 62 incorporates the elements of claims 51, 56, and 59. For at least the same reasons set forth above with respect to claims 51, 56, and 59, said discussion incorporated herein by reference, claim 62 is anticipated and/or obvious.

The additional limitation, "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," does not distinguish the claim from claims 51, 56, and 59, or the prior art that invalidates claims 51, 56, and 59. Specifically, the references outlined above either explicitly or inherently disclose a "formulation" "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." First, Fraser expressly cites to, and incorporates by reference, Holash for its VEGF antagonist. Holash discloses production of the VEGF antagonist in a CHO cell: "VEGF-Trap$_{R1R2}$ was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2. All of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells." (Holash at 11393-94). Second, Fraser expressly cites to, and incorporates by reference, Wulff for its VEGF antagonist, and Wulff cites to, and incorporates by reference, Papadopoulos. A person of ordinary skill in the art would have known that Papadopoulos teaches that the fusion proteins of the 865 patent are glycosylated at five asparagine residues when the protein is expressed in CHO cells. (Papadopoulos at 81:20 - 82:2 ("There are five possible N-linked glycosylation sites in

Flt1D2.Flk1D3.FcΔC1(a). All five of them are found to be glycosylated to varying degrees [following expression in CHO cells.]"), Fig. 36 (underlining the five asparagine residues in SEQ ID NO: 2 that are glycosylation sites)). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "formulation" "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."

Claim 62 of the 865 patent is therefore anticipated for the same reasons stated above for claims 51, 56, and 59. Additionally, claim 62 would have been obvious over at least, *inter alia*, the combinations identified above for claims 51, 56, and 59, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 51, 56, and 59. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a VEGF antagonist protein glycosylated at the claimed asparagine residues and would have reasonably expected success with such formulation.

lxiii. Claim 63.

Claim 63 of the 865 patent is essentially identical to claim 62 with the only exception being that claim 63 is directed to "[a] pre-filled syringe suitable for intravitreal administration comprising the formulation of claim 62" as opposed to "[a]n ophthalmic formulation … suitable for intravitreal administration."

The change from "[a] formulation" to "[a] pre-filled syringe" is neither limiting nor does it distinguish claim 63 from claim 62 or the prior art that renders claim 62 invalid as anticipated and/or obvious. Accordingly, for at least the same reasons set forth above with respect to claim 62, said discussion incorporated herein by reference, claim 63 is obvious and/or anticipated.

lxiv. Claim 64.

Claim 64 of the 865 patent is essentially identical to claim 62 with the only exception being that claim 64 is directed to "[a] vial suitable for intravitreal administration comprising the formulation of claim 62" as opposed to "[a]n ophthalmic formulation … suitable for intravitreal administration."

The change from "[a] formulation" to "[a] vial" is neither limiting nor does it distinguish claim 64 from claim 62 or the prior art that renders claim 62 invalid as anticipated and/or obvious. Accordingly, for at least the same reasons set forth above with respect to claim 62, said discussion incorporated herein by reference, claim 64 is obvious and/or anticipated.

c. Secondary Considerations.

Mylan is unaware of any evidence of secondary considerations that would render non-obvious the particular combination of elements claimed in the 865 patent, as described above and incorporated herein by reference.

Additionally, the patentee must prove the required nexus before relying on *any* secondary considerations of alleged non-obviousness. Mylan is not aware of any evidence that would establish the required nexus for any of the claims of the 865 patent. Further, even if there were any evidence of such secondary considerations[17] and the required nexus, the *prima facie* evidence of obviousness is sufficiently strong that it cannot be rebutted by evidence relevant to secondary considerations of non-obviousness, including any evidence of alleged commercial success.

As a result, all claims of the 865 patent would have been obvious over at least, *inter alia*, Andya, Fraser, Wullf, Holash, Papadopoulos, Vitti, Liu, Dix, Wiegand, or Kaisheva, alone or in combination, in view of the knowledge of a person of ordinary skill in the art.

* * *

Accordingly, for at least these reasons, claims 1-64 of the 865 are invalid for at least anticipation and/or obviousness.

2. Obviousness-Type Double Patenting.

Claims 1-64 of the 865 patent are invalid for obviousness-type double patenting ("OTDP") over at least each of the following, which expire no later than March 7, 2021: (i) U.S. Patent No. 11,066,458 ("458 patent"), claims 1-66, optionally in view of Papadopoulos; (ii) U.S. Patent No. 9,340,594 ("594 patent"), claims 1-9, optionally in view of Papadopoulos; (iii) U.S. Patent No. 9,580,489 ("489 patent"), claims 1-29, optionally in view of Papadopoulos; and (iv) U.S. Patent No. 7,608,261 ("261 patent"), claims 1-5, optionally in view of Papadopoulos.

The 458 patent discloses and claims, *inter alia*, the following:

- Claim 1: "A glass vial comprising an ophthalmic formulation suitable for intravitreal administration comprising:

  a vascular endothelial growth factor (VEGF) antagonist fusion protein,

  an organic co-solvent,

  a buffer, and

[17] Mylan reserves the right to address any evidence of secondary considerations that is raised in litigation by any entity, or entities, attempting to assert the 865 patent.

a stabilizing agent;

wherein said VEGF antagonist fusion protein is glycosylated and comprises an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor that is human Flt1 and Ig domain 3 of a second VEGF receptor selected from the group consisting of human Flk1 and human Flt4, and a multimerizing component; and

wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography.

- Claim 2: "The glass vial of claim 1, wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate."
- Claim 3: "The glass vial of claim 2, wherein said organic co-solvent comprises 0.01% to 3% polysorbate."
- Claim 4: "The glass vial of claim 2, wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20."
- Claim 5: "The glass vial of claim 2, wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20."
- Claim 6: "The glass vial of claim 5, wherein said buffer comprises a phosphate buffer."
- Claim 7: "The glass vial of claim 5, wherein said buffer comprises 5-25 mM buffer."
- Claim 8: "The glass vial of claim 5, wherein said buffer comprises a pH between about 5.8-7.0."
- Claim 9: "The glass vial of claim 5, wherein said buffer comprises a pH about 6.2-6.3."
- Claim 10: "The glass vial of claim 5, wherein said stabilizing agent comprises a sugar."
- Claim 11: "The glass vial of claim 10, wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol."
- Claim 12: "The glass vial of claim 5, wherein said stabilizing agent comprises 1.0-7.5% of sucrose."
- Claim 13: "The glass vial of claim 5, wherein said formulation further comprises a tonicity agent."
- Claim 14: "The glass vial of claim 5, 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."

- Claim 15: "The glass vial of claim 5, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C."

- Claim 16: "The glass vial of claim 5, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography."

- Claim 17: "The glass vial of claim 5, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography."

- Claim 18: "The glass vial of claim 5, wherein said formulation does not contain phosphate."

- Claim 19: "The glass vial of claim 5, wherein said formulation does not contain trehalose."

- Claim 20: "The glass vial of claim 5, wherein said stabilizing agent comprises 1.0-10% of sucrose."

- Claim 21: "The glass vial of claim 20, wherein said formulation further comprises a tonicity agent."

- Claim 22: "The glass vial of claim 20, 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."

- Claim 23: "The glass vial of claim 20, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C."

- Claim 24: "The glass vial of claim 20, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography."

- Claim 25: "The glass vial of claim 20, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography."

- Claim 26: "The glass vial of claim 1, wherein said stabilizing agent comprises sucrose."

- Claim 27: "The glass vial of claim 26, wherein said stabilizing agent comprises 1.0-10% of sucrose."

- Claim 28: "The glass vial of claim 26, wherein the organic co-solvent is polysorbate 20."

- Claim 29: "The glass vial of claim 28, wherein said Ig domain 3 of human VEGF receptor 2 comprises amino acids 131-230 of SEQ ID NO:4."

- Claim 30: "The glass vial of claim 29, wherein said formulation further comprises a tonicity agent."

- Claim 31: "The glass vial of claim 30, wherein said tonicity agent comprises sodium chloride."

- Claim 32: "The glass vial of claim 28, wherein said formulation comprises 10 mg/mL VEGF antagonist fusion protein."

- Claim 33: "The glass vial of claim 28, wherein said formulation does not contain phosphate."

- Claim 34: "A pre-filled syringe comprising an ophthalmic formulation suitable for intravitreal administration comprising:

  a vascular endothelial growth factor (VEGF) antagonist fusion protein,

  an organic co-solvent,

  a buffer, and

  a stabilizing agent;

  wherein said VEGF antagonist fusion protein is glycosylated and comprises an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor that is human Flt1 and Ig domain 3 of a second VEGF receptor selected from the group consisting of human Flk1 and human Flt4, and a multimerizing component; and

  wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography."

- Claim 35: "The pre-filled syringe of claim 34, wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate."

- Claim 36: "The pre-filled syringe of claim 35, wherein said organic co-solvent comprises 0.01% to 3% polysorbate."

- Claim 37: "The pre-filled syringe of claim 35, wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20."

- Claim 38: "The pre-filled syringe of claim 35, wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20."

- Claim 39: "The pre-filled syringe of claim 38, wherein said buffer comprises 5-25 mM buffer."

- Claim 40: "The pre-filled syringe of claim 38, wherein said buffer comprises a pH between about 5.8-7.0."

- Claim 41: "The pre-filled syringe of claim 38, wherein said buffer comprises a pH about 6.2-6.3."

- Claim 42: "The pre-filled syringe of claim 38, wherein said buffer comprises a phosphate buffer."

- Claim 43: "The pre-filled syringe of claim 38, wherein said stabilizing agent comprises a sugar."

- Claim 44: "The pre-filled syringe of claim 43, wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol."

- Claim 45: "The pre-filled syringe of claim 38, wherein said stabilizing agent comprises 1.0-10% of sucrose."

- Claim 46: "The pre-filled syringe of claim 45, wherein said formulation further comprises a tonicity agent."

- Claim 47: "The pre-filled syringe of claim 45, 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."

- Claim 48: "The pre-filled syringe of claim 45, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C."

- Claim 49: "The pre-filled syringe of claim 45, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography."

- Claim 50: "The pre-filled syringe of claim 45, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography."

- Claim 51: "The pre-filled syringe of claim 38, wherein said stabilizing agent comprises 1.0-7.5% of sucrose."

- Claim 52: "The pre-filled syringe of claim 38, wherein said formulation further comprises a tonicity agent."

- Claim 53: "The pre-filled syringe of claim 38, 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."

- Claim 54: "The pre-filled syringe of claim 38, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C."

- Claim 55: "The pre-filled syringe of claim 38, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography."

- Claim 56: "The pre-filled syringe of claim 38, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography."

- Claim 57: "The pre-filled syringe of claim 38, wherein said formulation does not contain phosphate."

- Claim 58: "The pre-filled syringe of claim 38, wherein said formulation does not contain trehalose."

- Claim 59: "The pre-filled syringe of claim 34, wherein said stabilizing agent comprises sucrose."

- Claim 60: "The pre-filled syringe of claim 59, wherein said stabilizing agent comprises 1.0-10% of sucrose."

- Claim 61: "The pre-filled syringe of claim 59, wherein the organic co-solvent is polysorbate 20."

- Claim 62: "The pre-filled syringe of claim 61, wherein said Ig domain 3 of human VEGF receptor 2 comprises amino acids 131-230 of SEQ ID NO:4."

- Claim 63: "The pre-filled syringe of claim 62, wherein said formulation further comprises a tonicity agent."

- Claim 64: "The pre-filled syringe of claim 63, wherein said tonicity agent comprises sodium chloride."

- Claim 65: "The pre-filled syringe of claim 61, wherein said formulation comprises 10 mg/mL VEGF antagonist fusion protein."

- Claim 66: "The pre-filled syringe of claim 61, wherein said formulation does not contain phosphate."

As illustrated above, claims 1-64 of the 865 patent are not patentably distinct from—i.e., are obvious over and/or anticipated by—the 458 patent claims. Indeed, the aforementioned 458 patent claims recite a specific formulation that falls within the scope of every claim of the 865 patent. Consequently, claims 1-64 of the 865 patent are invalid for obviousness-type double patenting.

The 594 patent discloses and claims, *inter alia*, the following:

- Claim 1: "A pre-filled syringe suitable for intravitreal administration comprising a 1 mL luer glass syringe fitted with a plunger and a stable ophthalmic formulation of a vascular endothelial growth factor (VEGF) trap which consists of (i) a receptor component consisting essentially of an immunoglobulin-like domain 2 of a first VEGF receptor and an immunoglobulin-like domain 3 of a second VEGF receptor, and (ii) a multimerizing component, wherein the stable ophthalmic formulation comprises:

  (a) 1-100 mg/ml a VEGF antagonist;

  (b) 0.01-5% of one or more organic co-solvent;

  (c) 5-40 mM of buffer; and

  (d) optionally comprising 1.0-7.5% of a stabilizing agent."

- Claim 2: "The pre-filled syringe of claim 1, wherein the first VEGF receptor is Flt1, and the second VEGF receptor is Flk1 or Flt4."

- Claim 3: "The pre-filled syringe according to claim 2, wherein the VEGF trap is stable for at least 4 months."

- Claim 4: "The pre-filled syringe according to claim 3, wherein the VEGF trap consists of amino acids 27-457 of SEQ ID NO:4."

- Claim 5: "The pre-filled syringe according to claim 4, wherein the stable ophthalmic formulation comprises 40 mg/mL of the VEGF trap, 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, at pH 6.2-6.4."

- Claim 7: "The pre-filled syringe of claim 3, wherein the VEGF trap consists of the amino acid sequence of SEQ ID NO:4."

- Claim 8: "The pre-filled syringe according to claim 2 wherein the VEGF trap is stable for at least 5 months."

- Claim 9: "The pre-filled syringe according to claim 8, wherein the VEGF trap consists of amino acids 27-457 of SEQ ID NO:4."

As illustrated above, claims 1-64 of the 865 patent are not patentably distinct from—i.e., are obvious over and/or anticipated by—the 594 patent claims. Indeed, the aforementioned 594 patent claims recite a specific formulation that falls within the scope of every claim of the 865 patent. Consequently, claims 1-64 of the 865 patent are invalid for obviousness-type double patenting.

The 489 patent discloses and claims, *inter alia*, the following:

- Claim 1: "A formulation comprising:

(a) 1-100 mg/mL of a VEGF-specific fusion protein antagonist;

(b) 5-40 mM of a buffer;

(c) 0.01-5% of an organic co-solvent; and

(d) a stabilizer or 30-150 mM of a tonicity agent,

wherein the VEGF-specific fusion protein antagonist represents at least 90% of the total weight of protein in the composition, at least 90% of the total weight of the VEGF-specific fusion protein antagonist is not present as an aggregate, and the VEGF-specific fusion protein antagonist comprises an Ig domain 2 of human VEGF receptor 1, an Ig domain 3 of human VEGF receptor 2, and a multimerizing component."

- Claim 2: "The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist represents at least 95% of the total weight of protein in the composition."
- Claim 6: "The formulation of claim 1, wherein the buffer comprises a phosphate buffer."
- Claim 7: "The formulation of claim 6, wherein the buffer comprises sodium phosphate present at a concentration of 10 mM."
- Claim 11: "The formulation of claim 1, wherein the organic co-solvent comprises one or more of polysorbate 20, polysorbate 80, polyethylene glycol (PEG) 3350, and propylene glycol."
- Claim 19: "The formulation of claim 1, comprising a stabilizer comprising trehalose or sucrose."
- Claim 22: "The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist does not comprise amino acids 1-26 of SEQ ID NO:4."
- Claim 23: "The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist is a dimer."
- Claim 24: "The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist is expressed in a Chinese hamster ovary (CHO) cell."

(*See also* 489 patent at claims 26-29 (claiming "[a] vial" containing the same formulation(s)). As illustrated above, claims 1-64 of the 865 patent are not patentably distinct from—i.e., are obvious over and/or anticipated by—the 489 patent claims. Indeed, the aforementioned 489 patent claims recite a specific formulation that falls within the scope of every claim of the 865 patent. Consequently, claims 1-64 of the 865 patent are invalid for obviousness-type double patenting.

The 261 patent discloses and claims, *inter alia*, the following:

- Claim 1: "An ophthalmic formulation of a vascular endothelial growth factor (VEGF) antagonist, comprising

  (a) 1-100 mg/ml of a VEGF antagonist comprising the amino acid sequence of SEQ ID NO:4;

  (b) 0.01-5% of one or more organic co-solvent(s) which is one or more of polysorbate, polyethylene glycol (PEG), and propylene glycol;

  (c) 30-150 mM of a tonicity agent selected from sodium chloride or potassium chloride; and

  (d) 5-40 mM of sodium phosphate buffer.

- Claim 2: "The ophthalmic formulation of claim 1, further comprising 1-7.5% of a stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, or mannitol, pH between about 5.8-7.0."

- Claim 3: "The ophthalmic formulation of claim 2, comprising about 1-100 mg/ml of the VEGF antagonist, 10 mM sodium phosphate buffer, 40 mM NaCl, 0.03% polysorbate, and 5% sucrose, pH about 6.2-6.3."

As illustrated above, claims 1-64 of the 865 patent are not patentably distinct from—i.e., are obvious over and/or anticipated by—the 261 patent claims. Indeed, the aforementioned 261 patent claims recite a specific formulation that falls within the scope of every claim of the 865 patent. Consequently, claims 1-64 of the 865 patent are invalid for obviousness-type double patenting.

3. Lack of Enablement.

Claims 1-64 are invalid for lack of enablement because the 865 patent fails to enable the full scope of the claims.

a. Claims 1, 26, and 51.

To the extent claims 1, 26, and 51 are not anticipated or obvious, as discussed above, the 865 patent fails to provide sufficient support for the subject matter claimed in claims 1, 26, and 51. For example, the specification does not describe or enable anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claims 1, 26, and 51 are not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to enable a person of ordinary skill in the art to practice the claimed "vial," "pre-filled syringe," and/or "formulation" without undue experimentation.

Claims 1, 26, and 51 are invalid for lack of enablement for at least the following reasons:

- The nature of the claimed invention(s) relate to extremely broad genera of formulations claimed by their functions.

- The claimed invention(s) is directed to an unpredictable art—biological formulation, wherein slight changes in excipients and concentrations thereof can impact the overall profile of a formulation. The 865 patent does not enable the broad genera of formulations covered by the claims, which encompass an unlimited variety of excipients and concentrations thereof.

- The scope of the claims is broad with the primary limitations being the "wherein" clauses rather than the "vial," "pre-filled syringe," and/or "formulation" components. Further, the claims encompass a formulation suitable for any route of administration. The claims also encompass formulations comprising unlimited combinations of excipients and concentrations thereof. The 865 patent's limited disclosure fails to enable the full scope of these formulation permutations and highly variable concentrations.

- The 865 patent specification fails enable a person of ordinary skill in the art to obtain the claimed "vial," "pre-filled syringe," and/or "formulation" having the requisite stability. The specification further fails to adequately explain the appropriate SEC parameters and/or methodology needed to determine whether a "vial," "pre-filled syringe," and/or "formulation" exhibits the claimed "native conformation."

- The 865 patent disclosure fails to enable the full scope of the formulations having the claimed functionalities. The 865 patent disclosure has not demonstrated possession of all buffers encompassed in the claim term "a buffer." For example, based on a fraudulent disclosure of stability, potency, or binding properties of formulations containing histidine as a buffer in U.S. Patent No. 10,857,231 ("the 231 patent"), the 231 patent was disclaimed. (*See* Exhibit 3001, PGR2021-00117 ("[B]ased on very recently discovered information, Patent Owner has reason to question whether the data presented in Table 7 of the Dix '231 Patent corresponds to the formulation described in Example 4 at column 10, lines 27-38."); Exhibit 2048, PGR2021-00117 (copy of Regeneron's disclaimer of the 231 patent); Paper 16, PGR2021-00117 (order denying institution of Post-Grant Review based on Regeneron's disclaiming all claims of the 231 patent)). Thus, the patentee was not in possession of, at least, formulations using histidine as a buffer. As such, the specification fails to enable the full scope of these formulations and does not enable the person of ordinary skill to make histidine containing formulations (falling within the scope of the claims) that possess the claimed functionalities.

- The quantity of experimentation necessary for a person of ordinary skill in the art to practice the full breadth of claims is not only undue, it is excessive and likely limitless. Among other things, the quantity of experimentation required to test the unlimited combinations of excipients and concentrations to determine whether each formulation meets the claimed "native conformation" limitation is undue and excessive.

Given the breadth of the claims, the lack of guidance in the specification, and the quantity of experimentation required, the 865 patent does not enable one skilled in the art to

practice the full scope of claims 1, 26, and 51 without undue experimentation. Thus, claims 1, 26, and 51 are not enabled such that one of ordinary skill in the art would understand how to practice the claimed invention without undue experimentation.

b. Claims 2-24, 27-50, and 52-64.

Claims 2-24 depend either directly or indirectly from claim 1, and thus incorporate the elements of claim 1. Claims 27-50 depend either directly or indirectly from claim 26, and thus incorporate the elements of claim 26. Claims 52-64 depend either directly or indirectly from claim 51, and thus incorporate the elements of claim 51. As explained above, claims 2-24, 27-50, and 52-64 do not substantially narrow the scope of claims 1, 26, or 51, and the specification fails to provide sufficient guidance for the genera of formulations claimed therein. Therefore, for at least the same reasons set forth above with respect to claims 1, 26, and 51, said discussion incorporated herein by reference, the 865 patent does not enable a person of ordinary skilled in the art to practice the full scope of claims 2-24, 27-50, and 52-64 without undue experimentation.

Accordingly, claims 2-24, 27-50, and 52-64 of the 865 patent are invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

* * *

For at least the reasons discussed above, claims 1-64 of the 865 patent are not enabled such that one of ordinary skill in the art would understand how to practice the claimed invention without undue experimentation.

4. Lack of Written Description.

Claims 1-64 are invalid for lack of written description because the 865 patent does not convey to persons of ordinary skill in the art that the named inventors were in possession of the full scope of the claims.

To the extent claims 1-64 are not anticipated or obvious, as discussed above, the 865 patent fails to provide sufficient support for the subject matter claimed. For example, the specification does not describe anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claims 1-64 are not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to convey to those skilled in the art that the inventor had possession of the claimed subject matter.

The 865 patent disclosure fails to describe formulations having the claimed functionalities. The 865 patent disclosure has not described all buffers encompassed in the claim term "a buffer." For example, based on a fraudulent disclosure of stability, potency, or binding properties of formulations containing histidine as a buffer in the 231 patent, the 231 patent was disclaimed. (*See* Exhibit 3001, PGR2021-00117 ("[B]ased on very recently discovered information, Patent Owner has reason to question whether the data presented in Table 7 of the Dix '231 Patent corresponds to the formulation described in Example 4 at column 10, lines 27-38."); Exhibit 2048, PGR2021-00117 (copy of Regeneron's disclaimer of the 231 patent); Paper 16,

PGR2021-00117 (order denying institution of Post-Grant Review based on Regeneron's disclaiming all claims of the 231 patent)). As such, the specification fails to describe, at least, histidine containing formulations (falling within the scope of the claims) that possess the claimed functionalities.

The 865 patent specification fails to disclose the combination of elements set forth in claims 1-64, which covers unlimited combinations of excipients and concentrations. Further, the claims encompass broad, functionally-defined genera of formulations requiring stability properties. Despite claiming genera of formulations using functional language to define desired results (*e.g.*, stability), the 865 patent specification provides no guidance or common structural features for use in a formulation to obtain the claimed functionalities. The 865 patent does not disclose a sufficient number of species to demonstrate the patentee invented the claimed genera of formulations.

For at least the reasons discussed above, claims 1-64 of the 865 patent are invalid for lack of written description because it does not convey to those skilled in the art that the named inventors were in possession of the full scope of the claims.

5. Indefiniteness.

Claims 1-64 of the 865 patent are invalid for at least indefiniteness pursuant to 35 U.S.C. § 112.

Claims 1-64 fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention for at least the following reasons.

- Claims 1-64 all require, *inter alia*, "at least 98% [or 99%] of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography." The 865 patent does not offer any disclosure or description of the steps needed to obtain a "vial," "pre-filled syringe," and/or "formulation" comprising a VEGF antagonist fusion protein meeting that limitation. The 865 patent further fails to inform persons of ordinary skill in the art of the SEC parameters required to test a "vial," "pre-filled syringe," and/or "formulation" for VEGF antagonist in "native conformation."

- The preamble claim terms "vial," "pre-filled syringe," and "formulation," to the extent they are determined to be limiting, are undefined and do not convey the scope of the claimed invention(s).

Accordingly, claims 1-64 of the 865 patent are invalid for at least indefiniteness because they fail to inform, with reasonable certainty, those of ordinary skill in the art about the scope of the invention

6. Unpatentable Subject Matter.

The language of claims 1-64 of the 865 patent are set forth above.

Claims 1-64 of the 865 patent are invalid for failure to claim patent eligible subject matter. Claims 1-64 are all directed toward a "vial," "pre-filled syringe," or "formulation" comprising a VEGF antagonist in "native conformation." Consequently, the claims are drawn to nothing more than the observation of a natural law in a prior art composition.

Accordingly, claims 1-64 of the 865 patent are invalid for failure to claim patent eligible subject matter pursuant to 35 U.S.C. § 101.

D. Unenforceability.

For at least the following reasons, claims 1-64 of the 865 patent are unenforceable due to Regeneron's inequitable conduct during prosecution of the application(s) that led to the 865 patent issuance.

The applicant failed to disclose to the United States Patent and Trademark Office (U.S.P.T.O.") all information it knew to be material to patentability. 37 C.F.R. § 1.56(a). For example, while arguing to the U.S.P.T.O during prosecution of the 269 application that the disclosures supported the patentability of the pending claims, the applicant knew of at least the prior art Wulff, Papadopoulos, Dix, Holash and/or Liu references, which were withheld from the U.S.P.T.O. The applicant was also aware of the materiality of these references, which disclose the manufacture of formulations comprising VEGF antagonist fusion proteins at greater than 98% native conformation. Moreover, Regeneron has engaged in a pattern of deception wherein, during prosecution of its applications, Regeneron intentionally obscures references it knows to be relevant to the subject matter of the pending claims by submitting numerous other references to the PTO, effectively burying those that contain invalidating disclosures. (*See, e.g.*, 865 patent at pp. 1-2).

Further, in prosecuting the 610 application,[18] Regeneron included in the original application Table 7 and the data therein, and presented said data as corresponding to the formulation set forth in Example 4 at 10:27-38. Upon information and belief, the data in Table 7 does not correspond to the formulation set forth in Example 4 at 10:27-38. (*See* Exhibit 3001, PGR2021-00117 ("[B]ased on very recently discovered information, Patent Owner has reason to question whether the data presented in Table 7 of the Dix '231 Patent corresponds to the formulation described in Example 4 at column 10, lines 27-38."); Exhibit 2048, PGR2021-00117 (copy of Regeneron's disclaimer of the 231 patent); Paper 16, PGR2021-00117 (order denying institution of Post-Grant Review based on Regeneron's disclaiming all claims of the 231 patent)). In addition, during prosecution of the 610 application, the applicantstated in an interview summary that the "invention is a formulation which comprises the VEGF antagonist and exhibits less than a 3% degradation after 15 months of storage at 5° C." (231 patent PH, 10/7/2020 Applicant Summary of Interview with Examiner at 1). As amended, all the claims at issue required, *inter alia*, a buffer comprising histidine and 10-50 mg/ml of a VEGF antagonist fusion protein. There

[18] U.S. Patent No. 10,857,231, issued on December 8, 2020, from U.S. Patent Application No. 16/535,610 ("the 610 application"), filed on August 8, 2019. The 610 application was filed as a purported continuation of U.S. Patent Application No. 15/692,893 filed on August 31, 2017 (now U.S. Patent No. 10,406,226).

is no support for such a genera of formulations in the 231 patent specification. For those formulations that contain a buffer comprising histidine, as required by all claims of the 231 patent, the 231 patent specification discloses only one formulation containing "100 mg/ml VEGF trap protein" (231 patent at 10:56-66), and another that contains "50-100 mg/ml VEGF trap protein" (231 patent at 10:27-54)—the stability results of the latter formulation are in doubt. (*See* Exhibit 3001, PGR2021-00117). After amending the claims to include that the buffer must comprise histidine, the Patent Owner misrepresented that "[a]s discussed during the interview of October 6, 2020, in view of the amendments and the recited formulation components, at a minimum, the amended claims meet the written description requirement." (231 patent FH, 10/12/2020 Applicant Arguments/Remarks Made in an Amendment at 15). As such, during prosecution of the 610 application, Regeneron made material, and upon information and belief, intentional misrepresentations that the claims met the written description requirement, and, upon information and belief, relied on incorrect information relevant to the subject matter of the pending claims. Shortly after these claim amendments were made and after the misrepresentations about the claim amendments were made, the pending claims were allowed. (231 patent PH, 11/2/2020 Notice of Allowability at 3 ("Applicant amended the claims so that the reasons for the Double patenting rejection no longer apply."). In addition, the most reasonable inference to be drawn from Regeneron's failures to comply with its duties of candor, good faith and disclosure (e.g., Regeneron's intentional withholding of the above-mentioned references from the U.S.P.T.O.), is that the actions were done with the intent to deceive.

For at least these reasons, claims 1-64 of the 865 patent are unenforceable for inequitable conduct.

* * *

Mylan expressly reserves all rights to raise any additional defenses relating to invalidity, unenforceability, and non-infringement, based, *inter alia*, on the facts and information revealed through discovery (including based upon the patentee's asserted claim construction and/or based upon any third party discovery that results in additional defenses to any asserted claims). Mylan also reserves the right to raise any defenses relating to invalidity, unenforceability, and non-infringement in any prior, future, and/or ongoing litigations.

Exhibit J

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA
AT CLARKSBURG

REGENERON PHARMACEUTICALS, INC., Plaintiff, v. MYLAN PHARMACEUTICALS INC., Defendant.	Case No.: 1:22-cv-00061-TSK **CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER**

MYLAN PHARMACEUTICALS INC.'S FIRST SET OF INTERROGATORIES TO REGENERON PHARMACEUTICALS, INC. (NOS. 1-17)

Pursuant to Federal Rule of Civil Procedure 33, Defendant Mylan Pharmaceuticals Inc. ("Mylan") directs the following First Set of Interrogatories to Plaintiff Regeneron Pharmaceuticals, Inc. ("Regeneron"). Responses to these interrogatories shall be served upon Mylan's undersigned counsel. Pursuant to Federal Rule of Civil Procedure 26(e), these interrogatories are continuing and require supplemental answers.

INSTRUCTIONS AND DEFINITIONS

1. Mylan incorporates herein the Definitions and Instructions set forth in Mylan Pharmaceuticals Inc.'s First Requests for the Production of Documents and Things to Regeneron (Nos. 1-120), dated and served October 3, 2022; Mylan Pharmaceuticals Inc.'s Second Requests for the Production of Documents and Things to Regeneron (Nos. 121-155), dated December 13, 2022, and concurrently served with these Interrogatories; and Mylan Pharmaceuticals Inc.'s First Set of Requests for Admission to Regeneron (Nos. 1-35), dated December 13, 2022, and concurrently served with these Interrogatories.

invention disclosures, protocols, and reports), including by bates number, that concern the contribution of the Named Inventor(s) and other person(s).

INTERROGATORY NO. 4

Explain the facts concerning and/or underlying the application leading to Regeneron's BLA No. 125387, including but not limited to who decided to apply for a BLA, when and why the decision to apply for a BLA was made, who liaised with FDA during the pendency of Regeneron's BLA No. 125387, and who decided what prior art to provide FDA in connection with securing FDA approval of Regeneron's BLA No. 125387.

INTERROGATORY NO. 5

Describe the circumstances, including the dates, locations, business strategies, and product marking and labeling efforts, under which the subject matter claimed in each of the Initial Patents was: first offered for sale and/or sold (regardless of whether the purchaser was contractually obligated to keep the sale or offer for sale confidential, or whether the sale or offer of sale made an invention available to the public (*see Helsinn Healthcare S.A. v. Teva Pharms. USA, Inc.*, 139 S. Ct. 628 (2019)), first described in a printed publication anywhere in the world, and/or first publicly used in the United States, and list the identities of persons with knowledge of the information requested in this Interrogatory.

INTERROGATORY NO. 6

If Regeneron contends that any reference identified as prior art in Mylan's Detailed Statements provided pursuant to 42 U.S.C. § 262(*l*)(3)(B) and/or § 262(*l*)(7)(B) does not qualify as prior art under 35 U.S.C. § 102 or 35 U.S.C. § 103 with respect to any asserted claim of the Initial Patents, based on the date and/or public availability of such reference (or any other reason),

identify each such reference for each such claim and provide each basis for Regeneron's contention.

INTERROGATORY NO. 7

For each example that appears in each of the Initial Patents, identify with particularity (including but not limited to production number) all documents and communications that Regeneron contends provides data, support, and/or bases for each particular example including but not limited to, laboratory notebooks or other documentation where the experimental work associated with the example was recorded or otherwise described, analytical testing associated with any product that is the subject of the example, or its components and technical reports, without regard to whether such documents evidence successful or failed attempts to arrive at any product.

INTERROGATORY NO. 8

Identify each witness that Regeneron will or may call at trial of this case, including fact witnesses, expert witnesses, adverse witnesses, and witnesses who will testify by deposition, and for each such witness, identify the subject matter and documents about which the witness will offer testimony.

INTERROGATORY NO. 9

If Regeneron intends to rely on any secondary considerations for any Asserted Claim, identify each secondary consideration that Regeneron intends to rely upon with respect to each Asserted Claim, provide the basis for asserting each purported secondary consideration, and identify, by Bates number, each piece of evidence that Regeneron contends support each said secondary consideration (including, but not limited to, proof of nexus).

INTERROGATORY NO. 10

For each claim of each of the Initial Patents, identify (a) the date that the claimed subject matter was first conceived and the date it was reduced to practice, and (b) the diligence leading to such reduction to practice, and for each such date and diligence, identify with particularity the documentary evidence supporting that date or diligence and at least three persons with any knowledge relating to that date or diligence.

INTERROGATORY NO. 11

For the '715 patent, the '280 patent and the '532 patent, identify each product that is, or has been, commercially available that Regeneron contends is covered by one or more claims of the '715 patent, the '280 patent, and the '532 patent; identify each specific claim of each of said patents that Regeneron contends covers each said product; identify the exact dates that each said product first became commercially available; and identify with particularity the documentary evidence that Regeneron contends supports its contentions.

INTERROGATORY NO. 12

INTERROGATORY NO. 13

Describe in detail the decision(s) that led to the investigation of each dosing regimen employed in the VIEW, DAVINCI, VIVID and VISTA clinical trials, including the decision-making regarding each arm that involved dosing every 8 weeks, and the decision-making regarding the number of loading doses used in each arm of each said clinical trial, and identify with

sales, total prescriptions, new prescriptions, profit/loss, unit sales, market share (in units, prescriptions, and dollars), price charged per unit, research and development costs, and cost of goods sold, for the United States market, from the product's launch to present.

INTERROGATORY NO. 17

If Regeneron asserts that sales of Eylea® are driven by, or are due to, one or more patented features of that product, identify each and every such patented feature, including by reference to the limitation(s) of each claim of each of the Initial Patents, and identify all evidence (including any documents produced by Regeneron) that Regeneron contends support such assertions.

Date: December 13, 2022

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Attorneys for Defendant Mylan Pharmaceuticals Inc.

Exhibit K

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA
CLARKSBURG DIVISION

REGENERON PHARMACEUTICALS, INC., Plaintiff, v. MYLAN PHARMACEUTICALS INC., Defendant.	Case No. 1:22-cv-00061-TSK **CONFIDENTIAL – SUBJECT TO PROTECTIVE ORDER**

REGENERON PHARMACEUTICALS, INC.'S OBJECTIONS AND RESPONSES TO DEFENDANT'S FIRST SET OF INTERROGATORIES (NOS. 1–17)

Pursuant to Rules 33 of the Federal Rules of Civil Procedure and Rule 33.01 of the Local Rules of Civil Procedure, Plaintiff Regeneron Pharmaceuticals, Inc. ("Plaintiff" and/or "Regeneron"), by and through its counsel, hereby submits the following objections and responses to Defendant Mylan Pharmaceuticals Inc.'s ("Defendant" and/or "Mylan") First Set of Interrogatories (Nos. 1–17) ("Interrogatories").

These objections and responses are based on information currently available and without prejudice to Regeneron's right to produce evidence of any subsequently discovered fact or information, to add, modify, or otherwise change, amend, or supplement its responses as appropriate or to correct any inadvertent errors, mistakes, or omissions.

GENERAL OBJECTIONS

1. Regeneron incorporates by reference these General Objections into each and every specific response below. A specific response may repeat a General Objection for emphasis or for other reasons. The omission of any General Objection in any specific response to an Interrogatory is not intended to be and should not be construed as a waiver or limitation of any

first publicly used upon the launch of Eylea following the first FDA approval on November 18, 2011.

With respect to U.S. Patent No. 11,104,715, Regeneron Protected Material The first publication of the patent family specification occurred when U.S. 2021/0171570 was published on June 10, 2021.

INTERROGATORY NO. 6

If Regeneron contends that any reference identified as prior art in Mylan's Detailed Statements provided pursuant to 42 U.S.C. § 262(l)(3)(B) and/or § 262(l)(7)(B) does not qualify as prior art under 35 U.S.C. § 102 or 35 U.S.C. § 103 with respect to any asserted claim of the Initial Patents, based on the date and/or public availability of such reference (or any other reason), identify each such reference for each such claim and provide each basis for Regeneron's contention.

RESPONSE TO INTERROGATORY NO. 6:

Regeneron incorporates each of its General Objections as if fully set forth herein.

Regeneron objects to this Interrogatory to the extent that it seeks documents and things protected by the attorney-client privilege, the work-product doctrine, the common-interest privilege, or any other applicable privilege.

Subject to the foregoing general and specific objections, Regeneron states as follows:

With respect to U.S. Patent No. 11,084,865:

- U.S. Patent No. 7,608,261 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- U.S. Patent No. 8,110,546 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- U.S. Patent No. 8,647,842 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- U.S. Patent No. 9,340,594 is not prior art under either 35 U.S.C. § 102 or 35

U.S.C. § 103.

- U.S. Patent No. 9,580,489 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- U.S. Patent No. 9,914,763 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- U.S. Patent No. 10,406,226 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- U.S. Patent No. 10,464,992 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The '959 patent Petition for Patent Term Extension is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- U.S. Patent No. 9,340,594 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 11/22/11 Response to 7/13/11 Office Action regarding U.S. Patent No. 8,110,546 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- U.S. Patent Application Publication No. 2016/0144025 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The LUCENTIS® Prescribing Information (2006) is not prior art under 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The EYLEA Prescribing Information (2011) is not prior art under 35 U.S.C. § 102 or 35 U.S.C. § 103.

With respect to the Yancopoulos Patents:

- The '959 patent Petition for Patent Term Extension is not prior art under either 35

U.S.C. § 102 or 35 U.S.C. § 103.

- The '757 patent Petition for Patent Term Extension The '959 patent Petition for Patent Term Extension is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 9-11-2015 338 Patent Applicant Remarks is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 1-30-2017 069 Patent Applicant Remarks is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 3-28-2017 281 Patent Applicant Remarks is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 3-28-2017 681 Patent Notice of Allowability is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 10-12-2018 345 Patent Applicant Remarks is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 4-29-2019 601 Patent Disclosure Statement is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 758 FH, 12/22/2011 PTE is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 2-18-2010 Bayer Press Release is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 11-22-2010 Bayer Press Release is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 12-20-2010 Bayer Press Release is not prior art under either 35 U.S.C. § 102

or 35 U.S.C. § 103.

- The 2-18-2010 Regeneron Press Release is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 11-22-2010 Regeneron Press Release is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 12-20-2010 Regeneron Press Release is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 1-18-2011 Regeneron Press Release is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 2-17-2011 Regeneron Press Release is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 4-27-2011 Regeneron Press Release is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 5-3-2011 Regeneron Press Release is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 12-5-2011 Regeneron Press Release is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 3-31-2010 Regeneron 10-Q is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 6-30-2010 Regeneron 10-Q is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 9-30-2010 Regeneron 10-Q is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.

- The 8-22-2011 Regeneron 8-K is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 12-31-2010 Regeneron 10-K is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- The 2010 Regeneron 10-K is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Anderson 2011 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Barbazetto 2011 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Boyer 2011 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Brown 2011 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Brown 2013A is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Brown 2015 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Cai 2018 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Campochiaro 2010 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Campochiaro 2011 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Dhoot 2018 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Do 2011 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Do 2012 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Engelbert 2010 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Engelbert 2010A is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.

- Eylea Medical Review is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Eylea DME/DR Medical Review is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Eylea Label 10/2014 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Eylea Label 3/2015 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Eylea Label 5/2016 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Haller is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Hansen 2010 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Heier 2011 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Heier 2012 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Heier 2016 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Keating 2015 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Korobelnik 2014 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Larsen 2015 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Major 2010 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Margolis 2010 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Massin 2010 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Mitchell 2010 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.

- Mitchell 2011 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Mitra is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Mousa 2010 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- NCT 072 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- NCT 377 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- NCT 423 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- NCT 477 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- NCT 594 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- NCT 623 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- NCT 775 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- NCT 788 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- NCT 795 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- NCT 814 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- NCT 836 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- NCT 973 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- NCT01512966 (Japanese VIVID) is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- NCT01512966 (Japanese VIVID) is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- NCT01331681 (US VIVID) is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- NCT01363440 (US VISTA) is not prior art under either 35 U.S.C. § 102 or 35

U.S.C. § 103.

- Nguyen 2011 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Olivera is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Pai is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Reichert is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Retinal Physician 2010 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Schachat 2010 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Schmidt-Erfuth Proceedings is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Schmidt-Erfuth is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Sharma 2010 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Slakter 2010 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Sophie is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Stewart & Grippon is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Stewart 2012 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Tolentino 2011 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Waisbourd 2011 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Wykoff 2017a is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Wykoff 2017b is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Yancopoulos 2010 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. §

103.

- Zarbin is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Ziemssen 2016 is not prior art under either 35 U.S.C. § 102 or 35 U.S.C. § 103.

With respect to U.S. Patent No. 11,104,715:

- U.S. Patent No. 10,927,342 is not prior art under 35 U.S.C. § 102 or 35 U.S.C. § 103.
- Krattenmacher is not prior art under 35 U.S.C. § 102 or 35 U.S.C. § 103.

INTERROGATORY NO. 7

For each example that appears in each of the Initial Patents, identify with particularity (including but not limited to production number) all documents and communications that Regeneron contends provides data, support, and/or bases for each particular example including but not limited to, laboratory notebooks or other documentation where the experimental work associated with the example was recorded or otherwise described, analytical testing associated with any product that is the subject of the example, or its components and technical reports, without regard to whether such documents evidence successful or failed attempts to arrive at any product.

RESPONSE TO INTERROGATORY NO. 7:

Regeneron incorporates each of its General Objections as if fully set forth herein.

Regeneron objects to this Interrogatory to the extent that it seeks documents and things protected by the attorney-client privilege, the work-product doctrine, the common-interest privilege, or any other applicable privilege. Regeneron further objects to this Interrogatory on the ground that it is unduly burdensome, overly broad, and not proportionate to the needs of the case, including because it seeks "all documents and communications that Regeneron contends provides data, support, and/or bases for each particular example," from an unlimited number of custodians and is not limited to a particular time period. Regeneron further objects to this Interrogatory as vague and ambiguous, including the phrase "associated with." Regeneron objects that this Interrogatory seeks information not relevant to any party's claim or defense.

through RGN-EYLEA-MYLAN-00706751, materials relied upon in IPR2021-00881 (*see, e.g.*, Ex. 2052), and further evidence adduced as part of expert discovery. Regeneron further intends to adduce evidence of unexpected results. For example, the formulations disclosed in the Furfine Patent exhibited unexpected stability with concentrations of aflibercept of 40 mg/ml or higher and low amounts of an organic co-solvent, *see, e.g.*, RGN-EYLEA-MYLAN-00476242, and exhibited unexpected syringeability, *see* RGN-EYLEA-MYLAN-00556524, and unexpectedly low turbidity, *see, e.g.*, RGN-EYLEA-MYLAN-00476244. Regeneron further intends to adduce evidence of Regeneron's failure to develop its first formulation, *see* RGN-EYLEA-MYLAN-00556528. Regeneron further intends to adduce evidence of industry skepticism, including its development partner's decision not to support an ophthalmology indication for aflibercept. *See* RGN-EYLEA-MYLAN-00666432, at -434.

With respect to U.S. Patent No. 11,104,715, Regeneron intends to adduce evidence of unexpected results, including that the claimed inventions were unexpectedly successful at reducing color without a substantial negative impact on other properties, such as titer, viable cell concentration, viability, ammonia, and/or osmolality. *See, e.g.*, '715 patent, Examples 5 and 9; RGN-EYLEA-MYLAN-00653424; RGN-EYLEA-MYLAN-00654379; RGN-EYLEA-MYLAN-00654488; RGN-EYLEA-MYLAN-00654580; RGN-EYLEA-MYLAN-00654668; RGN-EYLEA-MYLAN-00654761; RGN-EYLEA-MYLAN-00654865; RGN-EYLEA-MYLAN-00686117; RGN-EYLEA-MYLAN-00686215.

INTERROGATORY NO. 10

For each claim of each of the Initial Patents, identify (a) the date that the claimed subject matter was first conceived and the date it was reduced to practice, and (b) the diligence leading to such reduction to practice, and for each such date and diligence, identify with particularity the documentary evidence supporting that date or diligence and at least three persons with any knowledge relating to that date or diligence.

RESPONSE TO INTERROGATORY NO. 10:

Regeneron incorporates each of its General Objections as if fully set forth herein.

Regeneron objects to this Interrogatory to the extent that it seeks documents and things protected by the attorney-client privilege, the work-product doctrine, the common-interest privilege, or any other applicable privilege. Regeneron further objects to this Interrogatory on the ground that it is unduly burdensome, overly broad, and not proportionate to the needs of the case, including because it requests a response as to "each claim of each of the Initial Patents." Regeneron will respond with respect to the Initial Patents. Regeneron objects that this Interrogatory seeks information not relevant to any party's claim or defense. Regeneron objects that this Interrogatory is premature because it seeks facts subject to discovery.

Subject to the foregoing general and specific objections, Regeneron states as follows:

With respect to U.S. Patent No. 11,084,865, the inventors conceived the inventions in the asserted claims of the '865 patent no later than March 21, 2006, the date on which samples from stability study 207 were analyzed after two months incubation, *see* RGN-EYLEA-MYLAN-00475679.

With respect to the Yancopoulos Patents, Dr. Yancopoulos conceived of the inventions in the asserted claims of the '572 and '601 patents and began diligent reduction to practice no later than January 13, 2010, or in the alternative no later than November 2010, or in the alternative no later than December 2010, or in the alternative no later than January 2011, or in the alternative no later than November 21, 2011. Documents evidencing conception and diligent reduction to practice of the inventions of the asserted claims include but are not limited to: RGN-EYLEA-MYLAN-00634608; RGN-EYLEA-MYLAN-00634629; RGN-EYLEA-MYLAN-00553399; RGN-EYLEA-MYLAN-00523361 RGN-EYLEA-MYLAN-00523363; RGN-EYLEA-MYLAN-

00523302; RGN-EYLEA-MYLAN-00631170; RGN-EYLEA-MYLAN-00526135; RGN-EYLEA-MYLAN-00526216; RGN-EYLEA-MYLAN-00526317; RGN-EYLEA-MYLAN-00526316; RGN-EYLEA-MYLAN-00526220; RGN-EYLEA-MYLAN-00526328; RGN-EYLEA-MYLAN-00526335; RGN-EYLEA-MYLAN-00495781; RGN-EYLEA-MYLAN-00495782; RGN-EYLEA-MYLAN-00614216; RGN-EYLEA-MYLAN-00614217; RGN-EYLEA-MYLAN-00616825; RGN-EYLEA-MYLAN-00616827; RGN-EYLEA-MYLAN-00617044; RGN-EYLEA-MYLAN-00617045; RGN-EYLEA-MYLAN-00617046; RGN-EYLEA-MYLAN-00617123; RGN-EYLEA-MYLAN-00617450; RGN-EYLEA-MYLAN-00617466; RGN-EYLEA-MYLAN-00617469; RGN-EYLEA-MYLAN-00617496; RGN-EYLEA-MYLAN-00617559; RGN-EYLEA-MYLAN-00495950; RGN-EYLEA-MYLAN-00495951; RGN-EYLEA-MYLAN-00585571; RGN-EYLEA-MYLAN-00585572; RGN-EYLEA-MYLAN-00495476; RGN-EYLEA-MYLAN-00495691; RGN-EYLEA-MYLAN-00495621; RGN-EYLEA-MYLAN-00613972; RGN-EYLEA-MYLAN-00495191; RGN-EYLEA-MYLAN-00617686; RGN-EYLEA-MYLAN-00619224; RGN-EYLEA-MYLAN-00513418; RGN-EYLEA-MYLAN-00497802; RGN-EYLEA-MYLAN-00613038; RGN-EYLEA-MYLAN-00613040; RGN-EYLEA-MYLAN-00617594; RGN-EYLEA-MYLAN-00617595; RGN-EYLEA-MYLAN-00495389; RGN-EYLEA-MYLAN-00495390; RGN-EYLEA-MYLAN-00635373; RGN-EYLEA-MYLAN-00635808; RGN-EYLEA-MYLAN-00635812; RGN-EYLEA-MYLAN-00635480; RGN-EYLEA-MYLAN-00635759; RGN-EYLEA-MYLAN-00635808; RGN-EYLEA-MYLAN-00534406; RGN-EYLEA-MYLAN-00548820.

INTERROGATORY NO. 11

For the '715 patent, the '280 patent and the '532 patent, identify each product that is, or has been, commercially available that Regeneron contends is covered by one or more claims of the '715 patent, the '280 patent, and the '532 patent; identify each specific claim of each of said

protected by the attorney-client privilege, the work-product doctrine, the common-interest privilege, or any other applicable privilege. Regeneron objects that this Interrogatory is premature because it seeks facts subject to expert discovery.

Subject to the foregoing general and specific objections, Regeneron states that the commercial success of EYLEA is driven by the dosing regimen set forth in the asserted claims of the Yancopoulos Patents, *see* IPR2021-00881, Ex. 2052, as well as the stability of the EYLEA formulation as set forth in the asserted claims of U.S. Patent No. 11,084,865, including that 98% of aflibercept is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography, and that the formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C. The evidence of commercial success Regeneron intends to adduce includes materials produced in RGN-EYLEA-MYLAN-00686453 through RGN-EYLEA-MYLAN-00706751, materials relied upon in IPR2021-00881 (*see, e.g.*, Ex. 2052), and further evidence adduced as part of expert discovery.

Date: January 12, 2023

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Exhibit L

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA
At Clarksburg

REGENERON PHARMACEUTICALS, INC., Plaintiff, v. MYLAN PHARMACEUTICALS INC., Defendant.	Case No. 1:22-cv-00061-TSK **CONFIDENTIAL**

DEFENDANT MYLAN PHARMACEUTICALS INC.'S INVALIDITY CONTENTIONS REGARDING U.S. PATENT NOS. 10,888,601, 11,084,865, 11,104,715, and 11,253,572

TABLE OF CONTENTS

I. INTRODUCTION.

Pursuant to the Court's Scheduling Order entered October 25, 2022 (Dkt. No. 87), Defendant and Counterclaimant Mylan Pharmaceuticals Inc. ("Mylan") sets forth its Contentions relating to the invalidity of U.S. Patent Nos. 10,888,601 ("601 patent"), 11,084,865 ("865 patent"), 11,104,715 ("715 patent"), and 11,253,572 ("572 patent") (collectively, "the Patents-in-Suit").

In particular, these Invalidity Contentions address claims 1-2, 5-12, 15-19, 21, 23-28, 31-39, 41-43, and 45-47 of the 601 patent ("601 patent Asserted Claims"); claims 1-5, 7-11, and 14-18 of the 865 patent ("865 patent Asserted Claims"); claims 1-6 and 12-16 of the 715 patent ("715 patent Asserted Claims"); and claims 1-23 and 25-30 of the 572 patent ("572 patent Asserted Claims"), which are the claims currently asserted against Mylan in this litigation. (12/16/2022 Fletcher Letter; *see also* Dkt. No. 88, Regeneron's Narrowing Stipulation).[1]

II. RESERVATION OF RIGHTS AND OBJECTIONS.

These Contentions are based on information reasonably available to Mylan at this time; thus, these Contentions are necessarily preliminary and may require subsequent amendment, alteration, or supplementation. By providing these Contentions, Mylan does not waive any claim or defense in this litigation. Further, these Contentions should not be interpreted as a statement of Mylan's positions with regard to the proper construction of any claim term. Instead, Mylan has made certain assumptions, to the extent necessary and appropriate, with respect to the meaning of claim terms for the purpose of these Contentions only in the preparation of this statement. To the extent Mylan determines that a different meaning is appropriate for any claim term, Mylan will assert that meaning in connection with any claim construction proceedings, and further reserves

[1] From the four Patents-in-Suit, Regeneron is currently asserting 92 claims against Mylan. By continuing to assert 92 claims, Regeneron unduly burdens Mylan with, *inter alia*, having to address each limitation of each of the Asserted Claims in these Invalidity Contentions.

the right to update these Contentions as a result of any *Markman* proceedings, or any other disclosure or alteration of the meaning of claim terms.

In addition, Mylan specifically reserves its rights to identify and produce additional documents, including prior art, and/or to amend, alter, or supplement these Contentions at any time based on the following non-limiting examples:

- Further investigation;
- Any fact or expert discovery materials, including, but not limited to, documents, laboratory notebooks, testing of samples or products, reports, communications, and deposition testimony, that have not yet been obtained by, produced, or provided to Mylan, and/or with respect to which Mylan has not yet had adequate opportunity to review and analyze;
- Any further evaluation of the scope and content of the prior art, or as prior art is discovered;
- If Plaintiff asserts, or attempts to assert, an interpretation of the prior art different from that used herein;
- Revision, amendment, supplementation, and/or clarification of Plaintiff's Asserted Claims and infringement contentions;
- Any claim construction proceedings, including any claim contentions/constructions that Plaintiff may assert that are different from any assumptions that Mylan made herein; any constructions or additional or different infringement allegations that Plaintiff discloses or asserts at a later date; claim construction rulings and/or any *Markman* decision in this case or in any other litigation (including matters initiated in the PTAB) involving any of the Patents-in-Suit;
- During the expert discovery phase of the litigation, including in response to any opinions offered by any one or more experts on Plaintiff's behalf;
- In light of any positions Plaintiff takes in response to any allegations of invalidity in any other proceeding (including matters initiated in the PTAB) involving any of the Patents-in-Suit or related patents;
- Based on any discovery materials that have not yet been produced or provided to Mylan (whether by Plaintiff, by a party to another action (including matters initiated in the PTAB) involving any of the Patents-in-Suit, or by a third party to this action), including deposition testimony, and/or with respect to which Mylan has not yet had adequate opportunity to review and analyze;
- Plaintiff's response(s) to Mylan's Invalidity Contentions and/or defenses;

- As necessary and appropriate, including, but not limited to, as discovery proceeds;[2] and/or
- Any other grounds otherwise provided for under any applicable Rules or statutes, by order of any court, or upon leave of the Court, or for any other good cause or reason.

In addition to the reservations of rights expressly set forth above, Mylan reserves the right to supplement and/or amend these Contentions at any time and for any reason as the case proceeds, and as otherwise provided under, or in accordance with, any applicable Rules or statutes, and/or by order of the Court.

These Contentions may be asserted in the alternative and do not constitute any concession by Mylan for purposes of, *inter alia*, claim construction or infringement. *See* FED. R. CIV. P. 8(d).

Mylan further incorporates in these Contentions, in full, all documents and prior art references cited in the Patents-in-Suit, as well as any related patents and applications, including their respective prosecution histories, including those filed in the United States or in a foreign country. Mylan further reserves the right to rely upon any and all information from the petitions, briefs, decisions, or any other papers submitted or cited in the *inter partes* review proceedings, including: IPR2021-00880, IPR2021-00881, IPR2022-01225, IPR2022-01226, IPR2022-01524, IPR2023-00099, and IPR2023-00442.

Mylan also incorporates in these Contentions and refers to the following as part of the prior art: any and all teachings and disclosures in the specifications and prosecution histories of the Patents-in-Suit, as well any other documents the Patents-in-Suit may attempt to claim priority to, that reflect the state of the art at the time of the alleged invention and/or constitute prior art by admission.

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[2] Mylan notes, for instance, that as of service of these Invalidity Contentions, fact discovery is ongoing; Plaintiff have not yet provided responses to all of the written discovery requests that Mylan has propounded to date; fact depositions are ongoing; and the Court has not issued a claim construction ruling.

Mylan reserves the right to rely on any portion of any prior art (as defined in the preceding paragraph) reference cited herein and/or in Appendices A-C, attached hereto.

These Contentions are provided without prejudice to Mylan's right to introduce at trial any subsequently-discovered or generated evidence or expert opinions relating to currently-known facts and to produce and introduce at trial all evidence, whenever discovered, relating to the proof of subsequently-discovered facts. Furthermore, nothing in these Contentions limits any of Mylan's experts from relying upon any information in this litigation, in support of any defense, and from providing opinions and testimony in support of any defense. Moreover, facts, documents, and things now known may be imperfectly understood and, accordingly, such facts, documents, and things may not have been included in this statement. Mylan reserves its rights to refer to, conduct discovery with reference to, or offer into evidence at the time of trial, any and all facts, expert opinion testimony, documents, and things notwithstanding this statement of Mylan's Invalidity Contentions. Mylan further reserves its right to refer to, conduct discovery with reference to, or offer into evidence at the time of trial, any and all facts, documents, and things that are not currently recalled but might be recalled at some time in the future. Mylan objects to the disclosure of information that is protected by the attorney-client privilege, the work-product doctrine, and/or other applicable privileges and/or immunities. To the extent Mylan inadvertently discloses information that may be protected from discovery under the attorney-client privilege, work product immunity, and/or any other applicable privileges and/or immunities, such inadvertent disclosure does not constitute a waiver of any such privilege or immunity.

The information set forth below is provided, without in any manner waiving: (1) the right to object to the use of any statement for any purpose, in this litigation or any other litigation, on the grounds of privilege, relevance, materiality, or any other appropriate ground; (2) the right to

object to any request involving or relating to the subject matter of these statements; or (3) the right to revise, correct, supplement, or clarify any of the statements provided below at any time.

Mylan provides its Invalidity Contentions subject to, and without waiving, its reservation of rights and objections.

III. THE PATENTS-IN-SUIT.

A. 601 Patent.

The 601 patent, titled *Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*, issued on January 12, 2021, from U.S. Patent Application No. 16/397,267 ("267 application"), filed on April 29, 2019, as a purported continuation of U.S. Patent Application No. 16/159,282, filed on October 12, 2018, as a purported continuation of U.S. Patent Application No. 15/471,506, filed on March 28, 2017, as a purported continuation of U.S. Patent Application No. 14/972,560, filed on December 17, 2015, as a purported continuation of U.S. Patent Application No. 13/940,370, filed on July 12, 2013, as a purported continuation-in-part of International Application No. PCT/US2012/020855, filed on January 11, 2012. The 601 patent also purports to claim priority to U.S. Provisional Patent Application Nos. 61/432,245 ("245 application"), filed on January 13, 2011; 61/434,836 ("836 application"), filed on January 21, 2011, and 61/561,957 ("957 application), filed on November 21, 2011. The face of the 601 patent identifies George D. Yancopoulos as the sole purported inventor and Regeneron Pharmaceuticals, Inc. as the purported assignee.

1. The Priority Date for the 601 Patent.

The content of the prior art is dictated by the priority date for the claimed invention. Here, the earliest priority date to which the 601 patent is purportedly entitled is January 13, 2011.[3]

[3] Fact discovery in this case is ongoing; Mylan reserves the right to challenge the purported priority date of any Patent-in-Suit based on any fact or expert discovery materials, including, but not

Therefore, without conceding that the 601 patent properly claims priority to any earlier-filed application, which priority claims Mylan reserves all rights to challenge, any teachings known to those of ordinary skill in the art as of January 13, 2011, at the earliest, make up the content of the prior art under at least 35 U.S.C. § 102 (AIA and/or pre-AIA).

2. The Issued Claims.

The 601 patent issued with 47 claims, which recite as follows:

What is claimed is:

1. A method for treating age related macular degeneration in a patient in need thereof, comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 3 months, followed by 2 mg approximately once every 8 weeks or once every 2 months.

2. The method of claim **1**, wherein the age-related macular degeneration is neovascular (wet).

3. The method of claim **2** wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

4. The method of claim **3** wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

5. The method of claim **2** wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

6. The method of claim **5** wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

7. The method of claim **1**, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

8. The method of claim **7**, wherein the age-related macular degeneration is neovascular (wet).

9. The method of claim **8** wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

10. A method for treating diabetic macular edema in a patient in need thereof, comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months.

11. The method of claim **10**, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

12. The method of claim **10**, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

13. The method of claim **10** wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

14. The method of claim **13** wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

15. The method of claim **10** wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

16. The method of claim **15** wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

17. The method of claim **10** wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

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limited to, documents, laboratory notebooks, testing of samples or products, reports, communications, and deposition testimony, that have not yet been obtained by, produced, or provided to Mylan, and/or with respect to which Mylan has not yet had adequate opportunity to review and analyze. Indeed, it appears Regeneron's document production is not yet complete as evidenced by, *inter alia*, Regeneron's production of additional documents on the eve of the deadline for serving these contentions. (*See, e.g.*, 1/11/2023 A. Argall production email).

18. A method for treating diabetic retinopathy in a patient in need thereof, comprising, intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or 2 months.

19. The method of claim 18, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

20. The method of claim 19 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

21. The method of claim 18, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

22. The method of claim 18 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

23. The method of claim 18 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

24. The method of claim 23 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

25. The method of claim 18 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

26. A method for treating diabetic retinopathy in a patient with diabetic macular edema, who is in need of such treatment, comprising intravitreally administering, to said patient, an effective amount of aflibercept which is 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or 2 months.

27. The method of claim 26, wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly.

28. The method of claim 26, further comprising, after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks.

29. The method of claim 26 wherein the patient loses less than 15 letters of Best Corrected Visual Acuity (BCVA) score.

30. The method of claim 29 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

31. The method of claim 26 wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score.

32. The method of claim 31 wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

33. The method of claim 26 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

34. A method for treating an angiogenic eye disorder in a patient in need thereof, said method comprising administering to the patient an effective sequential dosing regimen of a single initial dose of a VEGF antagonist, followed by one or more secondary doses of the VEGF antagonist, followed by one or more tertiary doses of the VEGF antagonist;

wherein each secondary dose is administered 4 weeks after the immediately preceding dose; and

wherein each tertiary dose is administered 8 weeks after the immediately preceding dose;

wherein the VEGF antagonist is a receptor-based chimeric molecule comprising

an immunoglobin-like (Ig) domain 2 of a first VEGF receptor which is VEGFR1 and an Ig domain 3 of a second VEGF receptor which is VEGFR2, and a multimerizing component.

35. The method of claim 34 wherein the VEGF antagonist is aflibercept.

36. The method of claim 35 wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection.

37. The method of claim 34, wherein all doses of the VEGF antagonist are administered to the patient by intraocular administration.

38. The method of claim 37, wherein the intraocular administration is intravitreal administration.

39. The method of claim 38, wherein all doses of the VEGF antagonist comprise from about 0.5 mg to about 2 mg of the VEGF antagonist.

40. The method of claim 39, wherein all doses of the VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

41. The method of claim 39, wherein all doses of the VEGF antagonist comprise 2 mg of the VEGF antagonist.

42. The method of claim 34, wherein the angiogenic eye disorder is selected from the group consisting of: age related macular degeneration, diabetic retinopathy, diabetic macular edema, central retinal vein occlusion, branch retinal vein occlusion, and corneal neovascularization.

43. The method of claim 34 wherein the angiogenic eye disorder is age related macular degeneration.

44. The method of claim 43 wherein all doses of VEGF antagonist comprise 0.5 mg of the VEGF antagonist.

45. The method of claim 43 wherein all doses of VEGF antagonist comprise 2.0 mg of the VEGF antagonist.

46. The method of claim 34 wherein the angiogenic eye disorder is diabetic retinopathy.

47. The method of claim 34, wherein the angiogenic eye disorder is diabetic macular edema.

* * * * *

(601 patent at 21:41 – 24:51). Pursuant to a Disclaimer in Patent Under 37 CFR 1.321(a), dated July 11, 2022, Regeneron disclaimed the following claims in the 601 patent: claims 3, 4, 13, 14, **22,** 29, and 30. (601 patent FH, 7/11/2022 Disclaimer).

B. The 865 Patent.

The 865 patent, titled *VEGF Antagonist Formulations Suitable for Intravitreal Administration*, issued on August 10, 2021, from U.S. Patent Application No. 16/739,559 ("the 559 application"), filed on January 10, 2020. The 559 application was filed as a purported continuation application of U.S. Patent Application No. 16/582,486, filed on September 25, 2019 (now U.S. Patent No. 11,066,458), which is a purported continuation of application No. 16/159,269, filed on October 12, 2018 (now U.S. Patent No. 10,464,992), which is a purported continuation of application No. 15/879,294, filed on January 24, 2018 (now U.S. Patent No. 10,400,025), which is a purported continuation of application No. 15/095,606, filed on April 11, 2016 (now U.S. Patent No. 9,914,763), which is a purported continuation of application No. 14/330,096, filed on July 14, 2014 (now U.S. Patent No. 9,340,594), which is a purported continuation of application No. 13/914,996, filed on June 11, 2013 (now U.S. Patent No. 8,802,107), which is a purported continuation of application No. 13/329,770, filed on December 19, 2011 (now U.S. Patent No. 8,481,046), which is a purported continuation of application No. 12/833,417, filed on July 9, 2010 (now U.S. Patent No. 8,092,803), which is a purported continuation of application No. 12/560,885, filed on September 16, 2009 (now U.S. Patent No. 7,807,164), which is a purported division of application No. 11/818,463, filed on June 14, 2007 (now U.S. Patent No. 7,608,261), and which purports to claim priority to U.S. Provisional Application No. 60/814,484, filed on June 16, 2006. The face of the 865 patent identifies Eric Furfine, Daniel Dix, Kenneth Graham, and Kelly Frye as the purported inventors and Regeneron Pharmaceuticals, Inc. as the purported assignee.

1. The Priority Date for the 865 Patent.

The content of the prior art is dictated by the priority date for the claimed invention. Here, the earliest priority date to which the 865 patent is purportedly entitled is June 16, 2006.[4]

Therefore, without conceding that the 865 patent properly claims priority to any earlier-filed application, which priority claims Mylan reserves all rights to challenge, any teachings known to those of ordinary skill in the art as of June 16, 2006, at the earliest, make up the content of the prior art under at least 35 U.S.C. § 102 (AIA and/or pre-AIA).

2. The Issued Claims.

The 865 patent issued with 64 claims:

[4] Fact discovery in this case is ongoing; Mylan reserves the right to challenge the purported priority date of any Patent-in-Suit based on any fact or expert discovery materials, including, but not limited to, documents, laboratory notebooks, testing of samples or products, reports, communications, and deposition testimony, that have not yet been obtained by, produced, or provided to Mylan, and/or with respect to which Mylan has not yet had adequate opportunity to review and analyze. Indeed, it appears Regeneron's document production is not yet complete as evidenced by, *inter alia*, Regeneron's production of additional documents on the eve of the deadline for serving these contentions. (*See, e.g.*, 1/11/2023 A. Argall production email).

We claim:

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/ml, and wherein said organic co-solvent comprises polysorbate.

3. The vial of claim 2, wherein said organic co-solvent comprises 0.01% to 3% polysorbate.

4. The vial of claim 2, wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20.

5. The vial of claim 2, wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20.

6. The vial of claim 5, wherein said buffer comprises a phosphate buffer.

7. The vial of claim 5, wherein said buffer comprises 5-25 mM buffer.

8. The vial of claim 5, wherein said buffer comprises a pH between about 5.8-7.0.

9. The vial of claim 5, wherein said buffer comprises a pH about 6.2-6.3.

10. The vial of claim 5, wherein said stabilizing agent comprises a sugar.

11. The vial of claim 10, wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.

12. The vial of claim 5, wherein said stabilizing agent comprises 1.0-7.5% of sucrose.

13. The vial of claim 5, wherein said formulation further comprises a tonicity agent.

14. The vial of claim 5, 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.

15. The vial of claim 5, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C.

16. The vial of claim 5, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography.

17. The vial of claim 5, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography.

18. The vial of claim 5, wherein said formulation does not contain phosphate.

19. The vial of claim 5, wherein said formulation does not contain trehalose.

20. The vial of claim 5, wherein said stabilizing agent comprises 1.0-10% of sucrose.

21. The vial of claim 20, wherein said formulation further comprises a tonicity agent.

22. The vial of claim 20, 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.

23. The vial of claim 20, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C.

24. The vial of claim 20, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography.

25. The vial of claim 20, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography.

26. A pre-filled syringe comprising an ophthalmic formulation suitable for intravitreal administration comprising:

a vascular endothelial growth factor (VEGF) antagonist fusion protein,

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 said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography.

27. The pre-filled syringe of claim **26**, wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate.

28. The pre-filled syringe of claim **27**, wherein said organic co-solvent comprises 0.01% to 3% polysorbate.

29. The pre-filled syringe of claim **27**, wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20.

30. The pre-filled syringe of claim **27**, wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20.

31. The pre-filled syringe of claim **30**, wherein said buffer comprises a phosphate buffer.

32. The pre-filled syringe of claim **30**, wherein said buffer comprises 5-25 mM buffer.

33. The pre-filled syringe of claim **30**, wherein said buffer comprises a pH between about 5.8-7.0.

34. The pre-filled syringe of claim **30**, wherein said buffer comprises a pH about 6.2-6.3.

35. The pre-filled syringe of claim **30**, wherein said stabilizing agent comprises a sugar.

36. The pre-filled syringe of claim **35**, wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.

37. The pre-filled syringe of claim **30**, wherein said stabilizing agent comprises 1.0-7.5% of sucrose.

38. The pre-filled syringe of claim **30**, wherein said formulation further comprises a tonicity agent.

39. The pre-filled syringe of claim **30**, 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.

40. The pre-filled syringe of claim **30**, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C.

41. The pre-filled syringe of claim **30**, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography.

42. The pre-filled syringe of claim **30**, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography.

43. The pre-filled syringe of claim **30**, wherein said formulation does not contain phosphate.

44. The pre-filled syringe of claim **30**, wherein said formulation does not contain trehalose.

45. The pre-filled syringe of claim **30**, wherein said stabilizing agent comprises 1.0-10% of sucrose.

46. The pre-filled syringe of claim **45**, wherein said formulation further comprises a tonicity agent.

47. The pre-filled syringe of claim **45**, 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.

48. The pre-filled syringe of claim **45**, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C.

49. The pre-filled syringe of claim **45**, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography.

50. The pre-filled syringe of claim **45**, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography.

51. An ophthalmic formulation comprising:

(a) 40 mg/ml of a glycosylated VEGF antagonist fusion protein comprising amino acids 27-457 of SEQ ID NO:4;

(b) 0.03% to 0.1% polysorbate;

(c) 5-40 mM of sodium phosphate buffer, pH between 5.8-7.0; and

(d) sucrose;

wherein the ophthalmic formulation is suitable for intravitreal administration; and

wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for 2 months as measured by size exclusion chromatography.

52. The formulation of claim **51**, wherein said formulation comprises at least 5% sucrose.

53. The formulation of claim **51**, wherein said formulation comprises 1-10% sucrose.

54. A pre-filled syringe suitable for intravitreal administration comprising the formulation of claim **51**.

55. A vial suitable for intravitreal administration comprising the formulation of claim **51**.

56. The formulation of claim **51**, wherein said formulation comprises 10 mM sodium phosphate buffer, 0.03% polysorbate, 5% sucrose, and a pH between 6.2-6.3.

57. A pre-filled syringe suitable for intravitreal administration comprising the formulation of claim **56**.

58. A vial suitable for intravitreal administration comprising the formulation of claim **56**.

59. The formulation of claim **56**, wherein said formulation further comprises 40 mM NaCl.

60. A pre-filled syringe suitable for intravitreal administration comprising the formulation of claim **59**.

61. A vial suitable for intravitreal administration comprising the formulation of claim **59**.

62. The formulation of claim **59**, 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.

63. A pre-filled syringe suitable for intravitreal administration comprising the formulation of claim **62**.

64. A vial suitable for intravitreal administration comprising the formulation of claim **62**.

* * * * *

(865 patent at 19:29 – 22:60).

C. The 715 Patent.

The 715 patent, titled "*Methods for Producing Aflibercept in Chemically Defined Media Having Reduced Aflibercept Variants*," issued on August 31, 2021, from U.S. Patent Application No. 16/996,030 ("030 application"), filed on August 18, 2020. The 715 patent also purports to claim the benefit of U.S. Provisional Patent Application No. 63/065,012, filed on August 13, 2020, and U.S. Provisional Patent Application No. 62/944,635 ("635 application"), filed on December 6, 2019. The face of the 715 patent identifies Shawn Lawrence, Amy Johnson, Meghan Casey, Jamie Mastrogiacomo, Shunhai Wang, and Ning Li as the purported inventors and Regeneron Pharmaceuticals, Inc. as the purported assignee.

1. The Priority Date for the 715 Patent.

The content of the prior art is dictated by the priority date for the claimed invention. Here, the earliest priority date to which the 715 patent is purportedly entitled is December 6, 2019.[5]

Therefore, without conceding that the 715 patent properly claims priority to any earlier-filed application, which priority claims Mylan reserves all rights to challenge, any teachings known

[5] However, Regeneron has articulated a theory under which the 715 patent is not entitled to the priority date of the 635 application. (*See, e.g.*, Dkt. No. 124 at 25-26; Dkt. No. 174-2 at 25-26). Accordingly, and because fact discovery in this case is ongoing, Mylan reserves the right to challenge the purported priority date of any Patent-in-Suit based on any fact or expert discovery materials, including, but not limited to, documents, laboratory notebooks, testing of samples or products, reports, communications, and deposition testimony, that have not yet been obtained by, produced, or provided to Mylan, and/or with respect to which Mylan has not yet had adequate opportunity to review and analyze. Indeed, it appears Regeneron's document production is not yet complete as evidenced by, *inter alia*, Regeneron's production of additional documents on the eve of the deadline for serving these contentions. (*See, e.g.*, 1/11/2023 A. Argall production email).

Regeneron Protected Material

to those of ordinary skill in the art as of December 6, 2019, at the earliest, make up the content of the prior art under at least 35 U.S.C. § 102 (AIA and/or pre-AIA).

2. The Issued Claims.

The 715 patent issued with 16 claims:

What is claimed is:

1. A method of producing aflibercept harvested from a host cell cultured in a chemically defined medium (CDM), comprising:

(a) providing a host cell genetically engineered to express aflibercept;

(b) culturing said host cell in said CDM under conditions suitable in which said host cell expresses said aflibercept wherein the cumulative concentration of nickel in said CDM is less than or equal to 0.4 μM or about 0.4 μM and one or more of the following:

i. the cumulative concentration of iron in said CDM is less than or equal to 55.0 μM;

ii. the cumulative concentration of copper in said CDM is less than or equal to 0.8 μM;

iii. the cumulative concentration of zinc in said CDM is less than or equal to 56.0 μM;

iv. the cumulative concentration of cysteine in said CDM is less than or equal to 10.0 mM, and

v. said CDM includes anti-oxidants where the cumulative concentration of an antioxidant is about 0.001 mM to about 10.0 mM for any single anti-oxidant; and

(c) harvesting aflibercept produced by said host cell.

2. The method of claim 1, wherein said harvest has a color no more yellow-brown than European Color Standard BY2, wherein the aflibercept concentration is 5.0 g/L.

3. The method of claim 2, wherein said anti-oxidants are taurine, hypotaurine, glycine, thioctic acid, glutathione, choline, hydrocortisone, Vitamin C, Vitamin E or combinations thereof.

4. The method of claim 2, wherein said cumulative concentration of an anti-oxidant in said CDM is about 0.001 mM to about 10.0 mM for any single anti-oxidant and the cumulative concentration of all anti-oxidants is about 30.0 mM or less than 30.0 mM.

5. The method of claim 1, wherein aflibercept titer, viable cell concentration, viability, ammonia or osmolality is substantially unchanged.

6. The method of claim 1, wherein said host cell is selected from the group consisting of CHO, NS0, Sp2/0, embryonic kidney cell and BHK.

7. The method of claim 1, wherein said harvest comprises one or more aflibercept variants, wherein said variants have at least one oxidized amino acid residue.

8. The method of claim 7, wherein said oxidized amino acid residue is selected from the group consisting of methionine, tryptophan, histidine, phenylalanine, tyrosine and a combination thereof.

9. The method of claim 8, wherein said oxidized amino acid residue is histidine.

10. The method of claim 8, wherein said oxidized amino acid residue is tryptophan.

11. The method of claim 7, wherein said aflibercept variant comprises a polypeptide having an amino acid sequence selected from the group consisting of: SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19, SEQ ID NO: 20, SEQ ID NO: 21, SEQ ID NO: 22, SEQ ID NO: 23, SEQ ID NO: 62, SEQ ID NO: 63, SEQ ID NO: 64, SEQ ID NO: 65, SEQ ID NO: 66, SEQ ID NO: 67, SEQ ID NO: 68, SEQ ID NO: 69, SEQ ID NO: 70, SEQ ID NO: 71 and combinations thereof.

12. The method of claim 1, wherein said anti-oxidants are taurine, hypotaurine, glycine, thioctic acid, glutathione, choline, hydrocortisone, Vitamin C, Vitamin E or combinations thereof.

13. The method of claim 1, wherein the harvest has a color that is:

a. no more yellow-brown than European Color Standard BY2;

b. no more yellow-brown than European Color Standard BY3;

c. no more yellow-brown than European Color Standard BY4;

d. no more yellow-brown than European Color Standard BY5;

e. between European Color Standard BY2 and BY3; or

f. between European Color Standard BY2 and BY4, and wherein the aflibercept concentration in the harvest is 5.0 g/L.

14. The method of claim 13, wherein the color of harvest is characterized in the CIE L*, a*, b* color space, where L* is about 70 to about 99, a* is about 0 and b* is about 20 or less than 20 when the concentration of aflibercept is 5.0 g/L.

15. A method of producing aflibercept harvested from a host cell cultured in a chemically defined medium (CDM), comprising:

(a) providing a host cell genetically engineered to express aflibercept;

(b) culturing said host cell in said CDM under conditions suitable in which said host cell expresses said aflibercept wherein the cumulative concentration of nickel in said CDM is about 0.4 μM and one or more of the following:

i. the cumulative concentration of iron in said CDM is less than or equal to 55.0 μM;

ii. the cumulative concentration of copper in said CDM is less than or equal to 0.8 μM;

iii. the cumulative concentration of zinc in said CDM is less than or equal to 56.0 μM;

iv. the cumulative concentration of cysteine in said CDM is less than or equal to 10.0 mM; and

v. said CDM includes anti-oxidants where the cumulative concentration of an antioxidant is about 0.001 mM to about 10.0 mM for any single anti-oxidant; and

(c) harvesting aflibercept produced by said host cell, wherein the color of said harvest is:

a. no more yellow-brown than European Color Standard BY2;

b. no more yellow-brown than European Color Standard BY3;

c. no more yellow-brown than European Color Standard BY4;

d. no more yellow-brown than European Color Standard BY5;

e. between European Color Standard BY2 and BY3; or

f. between European Color Standard BY2 and BY4,

wherein the aflibercept concentration is 5.0 g/L.

16. A method of producing aflibercept harvested from a host cell cultured in a chemically defined medium (CDM), comprising:

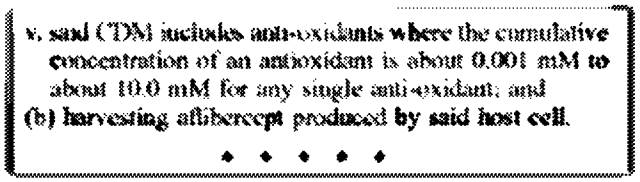
(a) culturing said host cell in said CDM under conditions suitable in which said host cell expresses said aflibercept wherein the cumulative concentration of nickel in said CDM is less than or equal to 0.4 μM or about 0.4 μM and one or more of the following:

i. the cumulative concentration of iron in said CDM is less than or equal to 55.0 μM;

ii. the cumulative concentration of copper in said CDM is less than or equal to 0.8 μM;

iii the cumulative concentration of zinc in said CDM is less than or equal to 56.0 μM;

iv. the cumulative concentration of cysteine in said CDM is less than or equal to 10.0 mM; and



v. said CDM includes anti-oxidants where the cumulative concentration of an antioxidant is about 0.001 mM to about 10.0 mM for any single anti-oxidant; and
(b) harvesting aflibercept produced by said host cell.

* * * * *

(715 patent at 261:1 – 263:4).

D. The 572 Patent.

The 572 patent, titled *Use of a VEGF Antagonist to Treat Angiogenic Eye Disorders*, issued on February 22, 2022, from U.S. Patent Application No. 17/352,892, filed on June 21, 2021, as a purported continuation of U.S. Patent Application No. 17/350,958, filed on June 17, 2021, as a purported continuation of U.S. Patent Application No. 17/112,404, filed on December 4, 2020, as a purported continuation of U.S. Patent Application No. 17/072,417, filed on October 16, 2020, as a purported continuation of U.S. Patent Application No. 16/055,847, filed on August 6, 2018, as a purported continuation of U.S. Patent Application No. 16/397,267, filed on April 29, 2019, as a purported continuation of U.S. Patent Application No. 16/159,282, filed on October 12, 2018, as a purported continuation of U.S. Patent Application No. 15/471,506, filed on March 28, 2017, as a purported continuation of U.S. Patent Application No. 14/972,560, filed on December 17, 2015, as a purported continuation of U.S. Patent Application No. 13/940,370, filed on July 12, 2013, as a purported continuation-in-part of International Application No. PCT/US2012/020855, filed on January 11, 2012. The 572 patent also purports to claim priority to the 245 application, filed on January 13, 2011; the 836 application, filed on January 21, 2011; and the 957 application, filed on November 21, 2011. The face of the 572 patent identifies George D. Yancopoulos as the sole purported inventor and Regeneron Pharmaceuticals, Inc. as the purported assignee.

1. The Priority Date for the 572 Patent.

The content of the prior art is dictated by the priority date for the claimed invention. Here, the earliest priority date to which the 572 patent is purportedly entitled is January 13, 2011.[6]

Therefore, without conceding that the 572 patent properly claims priority to any earlier-filed application, which priority claims Mylan reserves all rights to challenge, any teachings known to those of ordinary skill in the art as of January 13, 2011, at the earliest, make up the content of the prior art under at least 35 U.S.C. § 102 (AIA and/or pre-AIA).

2. The Issued Claims.

The 572 patent issued with 30 claims:

[6] Fact discovery in this case is ongoing; Mylan reserves the right to challenge the purported priority date of any Patent-in-Suit based on any fact or expert discovery materials, including, but not limited to, documents, laboratory notebooks, testing of samples or products, reports, communications, and deposition testimony, that have not yet been obtained by, produced, or provided to Mylan, and/or with respect to which Mylan has not yet had adequate opportunity to review and analyze. Indeed, it appears Regeneron's document production is not yet complete as evidenced by, *inter alia*, Regeneron's production of additional documents on the eve of the deadline for serving these contentions. (*See, e.g.*, 1/11/2023 A. Argall production email).

What is claimed is:

1. A method of treating an angiogenic eye disorder in a patient in need thereof comprising sequentially administering to the patient by intravitreal injection a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;

wherein each secondary dose is administered approximately 4 weeks following the immediately preceding dose; and

wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose;

wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.

2. The method of claim 1 wherein the patient achieves a gain in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

3. The method of claim 2 wherein the patient gains at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

4. The method of claim 3 wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.

5. The method of claim 3 wherein only two secondary doses are administered to the patient.

6. The method of claim 3 wherein the aflibercept is formulated as an isotonic solution.

7. The method of claim 3 wherein the aflibercept is formulated with a nonionic surfactant.

8. The method of claim 2 wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

9. The method of claim 8 wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose.

10. The method of claim 2 wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

11. The method of claim 10 wherein only two secondary doses are administered to the patient.

12. The method of claim 10 wherein the aflibercept is formulated as an isotonic solution.

13. The method of claim 10 wherein the aflibercept is formulated with a nonionic surfactant.

14. The method of claim 1 wherein exclusion criteria for the patient include both of:

(1) active ocular inflammation; and

(2) active ocular or periocular infection.

15. A method of treating diabetic macular edema in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;

wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and

wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose.

16. The method of claim 15 wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose.

17. The method of claim 16 wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

18. The method of claim 17 wherein the aflibercept is formulated as an isotonic solution.

19. The method of claim 17 wherein the aflibercept is formulated with a non-ionic surfactant.

20. The method of claim 17 wherein the patient achieves a gain in visual acuity within 24 weeks following the initial dose.

21. The method of claim 16 wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

22. The method of claim 21 wherein the aflibercept is formulated as an isotonic solution.

23. The method of claim 21 wherein the aflibercept is formulated with a nonionic surfactant.

24. The method of claim 15 wherein only two secondary doses are administered to the patient.

25. The method of claim 15 wherein four secondary doses are administered to the patient.

26. A method of treating age related macular degeneration in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;

wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and

wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose;

wherein the method is as effective in achieving a gain in visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose.

27. The method of claim 26 wherein only two secondary doses are administered to the patient.

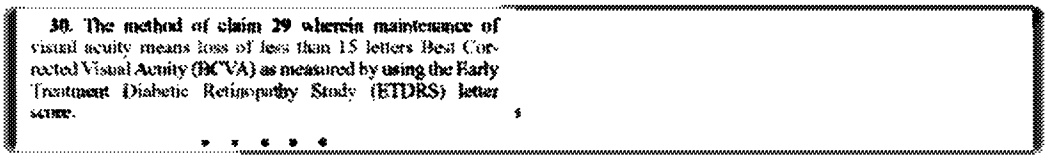
28. The method of claim 26 wherein the gain in visual acuity is measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

29. A method of treating age-related macular degeneration in a patient in need thereof comprising sequentially administering to the patient a single initial dose of 2 mg of aflibercept, followed by one or more secondary doses of 2 mg of aflibercept, followed by one or more tertiary doses of 2 mg of aflibercept;

wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and

wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose;

wherein the method is as effective in maintaining visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose.



30. The method of claim 29 wherein maintenance of visual acuity means loss of less than 15 letters Best Corrected Visual Acuity (BCVA) as measured by using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score.

* * * * *

(572 patent at 23:1 – 25:5).

IV. LEGAL.

Patent invalidity is a complete defense to a charge of infringement. *See TypeRight Keyboard Corp. v. Microsoft Corp.*, 374 F.3d 1151, 1157 (Fed. Cir. 2004) (holding that a finding of invalidity is a complete defense to infringement); *Viskase Corp. v. Am. Nat'l Can Co.*, 261 F.3d 1316, 1323 (Fed. Cir. 2001) (same); *Weatherchem Corp. v. J.L. Clark, Inc.*, 163 F.3d 1326, 1335 (Fed. Cir. 1998) ("[I]nvalidity operates as a complete defense to infringement for any product, forever[.]"). A patent is invalid if it fails to satisfy any of the conditions for patentability found in 35 U.S.C. §§ 101 *et seq.* Furthermore, a patent claim may be invalid for being an obvious variation of a prior patented claim under the judicially-created doctrine of obviousness-type double patenting. *See Georgia-Pacific Corp. v. U.S. Gypsum Co.*, 195 F.3d 1322, 1326 (Fed. Cir. 1999).

The statutory presumption of validity merely assumes the U.S.P.T.O. properly did its job by considering all prior art or other evidence material to patentability. *See Lannom Mfg. Co. v. U.S. Int'l Trade Comm'n*, 799 F.2d 1572, 1575 (Fed. Cir. 1986). "[W]here the PTO has not considered facts relevant to an issue in suit, there is no reason to give deference to its action in issuing the patent and a court may find those facts controlling in determining whether the burden of proof has been sustained." *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 773 n.3 (Fed. Cir. 1983), *overruled in part on other grounds by SRI Int'l v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107, 1125 (Fed. Cir. 1985) (en banc). Thus, "[t]he courts are the final arbiter of patent validity and, although courts may take cognizance of, and benefit from, the proceedings before the patent examiner, the question is ultimately for the courts to decide, without deference to the rulings of

the patent examiner." *Quad Env't Techs. Corp. v. Union Sanitary Dist.*, 946 F.2d 870, 876 (Fed. Cir. 1991).

A. 35 U.S.C. § 101—Lack of Utility.

35 U.S.C. § 101 provides that "[w]hoever invents . . . any new and useful process . . . or composition of matter . . . may obtain a patent therefor." A patent claim is invalid if no substantial or practical utility for the invention claimed is disclosed. *Cross v. Iizuka*, 753 F.2d 1040, 1044 (Fed. Cir. 1985). As noted by the Supreme Court:

> The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point—where specific benefit exists in currently available form—there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.

Brenner v. Manson, 383 U.S. 519, 534-35 (1966). Utility generally goes hand in hand with the enablement inquiry. "If a patent claim fails to meet the utility requirement because it is not useful or operative, then it also fails to meet the how-to-use aspect of the enablement requirement." *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1324 (Fed. Cir. 2009) (quoting *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1358 (Fed. Cir. 1999)). The utility requirement thus serves as a gatekeeper to ensure that mere ideas are not patented. "The utility requirement also prevents the patenting of a mere research proposal or an invention that is simply an object of research." *Id.* In other words, an invention that is simply an object of further research, without assurance that anything useful will result, does not meet the utility requirement. *See id.*

B. 35 U.S.C. § 101—Unpatentable Subject Matter.

Patentable subject matter is limited to "any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof." 35 U.S.C. § 101. "[L]aws of nature, physical phenomena, and abstract ideas" are not patentable subject matter under 35

U.S.C. § 101. *Bilski v. Kappos*, 561 U.S. 593, 601 (2010); *see also INO Therapeutics LLC v. Praxair Distribution Inc.*, 782 F. App'x 1001, 1006 (Fed. Cir. 2019) (holding "claim . . . directed to detecting the presence of [an adverse event] in a patient and then doing nothing" claims a natural phenomenon). As set forth in *Alice Corp. v. CLS Bank International*, "distinguishing patents that claim laws of nature, natural phenomena, and abstract ideas from those that claim patent-eligible applications of those concepts" is accomplished via a two-step analysis. 573 U.S. 208, 217-18 (2014). The first step requires "determin[ing] whether the claims at issue are directed to one of those patent-ineligible concepts" (i.e., laws of nature, natural phenomena, and abstract ideas). *Id.* at 217. If the claims at issue are directed to patent-ineligible concepts, then the second step involves an analysis of "the elements of each claim both individually and 'as an ordered combination' to determine whether the additional elements 'transform the nature of the claim' into a patent-eligible application." *Id.* (quoting *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66, 78-79 (2012)). That is, "[a] claim that recites an abstract idea must include 'additional features' to ensure 'that the [claim] is more than a drafting effort designed to monopolize the [abstract idea].'" *Id* at 221 (alterations in original) (quoting *Mayo*, 566 U.S. at 77); *see also INO Therapeutics*, 782 F. App'x at 1010-11 (finding additional prior art limitations of claimed method "routine and conventional" and unable to transform the "naturally occurring phenomena into a patent-eligible application").

C. 35 U.S.C. § 101—Statutory Double Patenting.

Only one patent, i.e., "a patent," can issue for each patentable invention. *See Miller v. Eagle Mfg. Co.*, 151 U.S. 186, 197 (1894). "The double patenting doctrine generally prevents a patentee from receiving two patents for the same invention." *Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1372 (Fed. Cir. 2005). The double patenting doctrine prevents "the extension of the statutory period of monopoly that would occur if successive patents were allowed on the same

basic concept" and reduces the potential for harassment by multiple assignees. 3A DONALD S. CHISUM, CHISUM ON PATENTS § 9.01 (2020); *In re Robeson*, 331 F.2d 610, 615 (C.C.P.A. 1964). Furthermore, the filing of a terminal disclaimer does not cure invalidity due to double patenting under 35 U.S.C. § 101. *In re Vogel*, 422 F.2d 438, 441 (C.C.P.A. 1970).

D. 35 U.S.C. § 102—Anticipation.

Under current 35 U.S.C. § 102 (i.e., AIA 35 U.S.C. § 102), a person shall be entitled to a patent unless "the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention," AIA 35 U.S.C. § 102(a)(1), or "the claimed invention was described in a patent . . . or in an application for a patent published or deemed published . . . in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention," *id.*, AIA § 102(a)(2).[7]

Under pre-AIA 35 U.S.C. § 102, a person shall be entitled to a patent unless "the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent," 35 U.S.C. § 102(a), or "the invention was patented or described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States," *id.* § 102(b).

A patent claim is said to be anticipated (i.e., not novel) if a comparison of the claim with a prior art reference reveals that every element of the claim is described, either expressly or inherently, in the prior art reference. *See Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373,

[7] AIA 35 U.S.C. § 102 is applicable to any patent or patent application "that contains or contained at any time" a claim that has an effective filing date on or after March 16, 2013. *See* 35 U.S.C. § 100 (note).

1377 (Fed. Cir. 2003); *Rockwell Int'l Corp. v. United States*, 147 F.3d 1358, 1363 (Fed. Cir. 1998); *In re King*, 801 F.2d 1324, 1326 (Fed. Cir. 1986); *In re Mousa*, 479 F. App'x 348, 352 (Fed. Cir. 2012). "Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates." *MEHL/Biophile Int'l Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999); *see also In re Omeprazole Patent Litig.*, 483 F.3d 1364, 1373 (Fed. Cir. 2007) (citing *Bristol-Myers Squibb Co. v. Ben Venue Labs., Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) ("newly discovered results of known processes are not patentable because those results are inherent in the known processes"); *In re Montgomery*, 677 F.3d 1375, 1381 (Fed. Cir. 2012). In addition, where a specific numerical claim limitation is encompassed by a numerical range in the prior art, the claim is anticipated absent a showing of criticality of the specific numerical claim limitation. *ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1344-45 (Fed. Cir. 2012).

Application of the on-sale bar under 35 U.S.C. § 102(b) requires that (1) "the product must be the subject of a commercial offer for sale" and (2) "the invention must be ready for patenting." *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 67 (1998). To determine if there was an offer for sale, courts generally apply the law of contracts and "focus on those activities that would be understood to be commercial sales and offers for sale 'in the commercial community.'" *Meds. Co. v. Hospira, Inc.*, 827 F.3d 1363, 1373 (Fed. Cir. 2016) (en banc) (quoting *Grp. One, Ltd. v. Hallmark Cards, Inc.*, 254 F.3d 1041, 1047 (Fed. Cir. 2001)). "A sale occurs when there is a 'contract between parties to give and to pass rights of property for consideration which the buyer pays or promises to pay the seller for the thing bought or sold.'" *Helsinn Healthcare S.A. v. Teva Pharm. USA, Inc.*, 855 F.3d 1356, 1364 (Fed. Cir. 2017) (quoting *Trading Techs. Int'l, Inc. v. eSpeed, Inc.*, 595 F.3d 1340, 1361 (Fed. Cir. 2010)).

Regarding invalidity due to prior public use, "[t]he proper test . . . is whether the purported use: (1) was accessible to the public; or (2) was commercially exploited." *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 424 F.3d 1374, 1380 (Fed. Cir. 2005). In evaluating a purported public use, a court will consider such factors as "evidence relevant to experimentation, . . . the nature of the activity that occurred in public; public access to the use; confidentiality obligations imposed on members of the public who observed the use; and commercial exploitation." *Id.*; *Pronova Biopharma Norge AS v. Teva Pharms. USA, Inc.*, 549 F. App'x 934, 939 (Fed. Cir. 2013) (finding shipment and testing of product samples disclosing all aspects of the claimed invention and unprotected by confidentiality restrictions triggered public use bar).

Under pre-AIA 35 U.S.C. § 102(f), a person shall be entitled to a patent unless "he did not himself invent the subject matter sought to be patented." 35 U.S.C. § 102(f). In other words, if the conception of an invention is derived from another source rather than the named inventors, the patent is said to be invalid under § 102(f). *Price v. Symsek*, 988 F.2d 1187, 1190 (Fed. Cir. 1993). In order to demonstrate derivation under § 102(f), both prior conception of an invention by another and communication of that conception to the patentee must be established. *Id.*

E. 35 U.S.C. § 103(a)—Obviousness.

Under AIA 35 U.S.C. § 103:

> A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains.[8]

[8] AIA 35 U.S.C. § 103 is applicable to any patent or patent application "that contains or contained at any time" a claim that has an effective filing date on or after March 16, 2013. *See* AIA 35 U.S.C. § 100 (note).

AIA 35 U.S.C. § 103.

Under pre-AIA 35 U.S.C. § 103(a):

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

35 U.S.C. § 103(a); *see KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

Obviousness is ultimately a legal conclusion, based upon underlying factual inquiries. *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1368 (Fed. Cir. 2003). The required factual inquiry considers: (1) the level of ordinary skill in the pertinent art; (2) the scope and content of the prior art; and (3) the differences between the prior art and the asserted claims. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). Objective evidence of nonobviousness, i.e., so-called "secondary considerations," if any, is considered where relevant. *See id.* at 17-18; *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538-39 (Fed. Cir. 1983).

Additionally, it is well settled "that objective evidence [of] non-obviousness must be commensurate in scope with the claims which the evidence is offered to support." *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983) (quoting *In re Tiffin*, 448 F.2d 791, 792 (C.C.P.A. 1971)); *see also In re Kulling*, 897 F.2d 1147, 1149 (Fed. Cir. 1990); *Hewlett-Packard Co. v. Bausch & Lomb Inc.*, 909 F.2d 1464, 1468 (Fed. Cir. 1990). A patentee offering objective evidence of non-obviousness bears the burden of demonstrating this "nexus." *See In re Paulsen*, 30 F.3d 1475, 1482 (Fed. Cir. 1994). That is, the patentee must demonstrate "a legally and factually sufficient connection" between the evidence and the patented invention to demonstrate that the evidence does in fact corroborate the invention's non-obviousness. *See id.*; *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1327-

28 (Fed. Cir. 2008), *abrogated on other grounds by Travel Sentry, Inc. v. Tropp*, 877 F.3d 1370 (Fed. Cir. 2017).

When, from the perspective of a person of ordinary skill in the art, the differences between the prior art and the claimed invention as a whole would be obvious, a *prima facie* case of obviousness is established under § 103, thus rendering the subject claim invalid. *See In re Dillon*, 919 F.2d 688, 692-93 (Fed. Cir. 1990) (en banc).

Obviousness may be based on one or more references. However, either the prior art as a whole, or knowledge generally available to one of ordinary skill in the art, should suggest the desirability, and thus the obviousness of combining and modifying the prior art to arrive at the claimed invention. *See SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1356 (Fed. Cir. 2000). This requirement for a showing of motivation to combine references ensures that a combination is not improperly made in hindsight. *See In re Gartside*, 203 F.3d 1305, 1318-19 (Fed. Cir. 2000). However, it is not necessary that the references be combined for the same reasons as the inventor. *In re Beattie*, 974 F.2d 1309, 1312 (Fed. Cir. 1992) ("As long as some motivation or suggestion to combine the references is provided by the prior art taken as a whole, the law does not require that the references be combined for the reasons contemplated by the inventor."). Moreover, a "combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416. More specifically, "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *Id.* at 417. Further, "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *E.I. DuPont de Nemours & Co. v. Synvina C.V.*,

904 F.3d 996, 1006 (Fed. Cir. 2018) (quoting *In re Aller*, 220 F.2d 454, 456 (C.C.P.A. 1955). Further, "[i]t is long settled that in the context of obviousness, the 'mere recitation of a newly discovered function or property, inherently possessed by things in the prior art, does not distinguish a claim drawn to those things from the prior art.'" *Persion Pharm. LLC v. Alvogen Malta Operations Ltd.*, 945 F.3d 1184, 1190 (Fed. Cir. 2019) (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)).

Yet, the mere fact that results are not entirely predictable in advance, and must be confirmed through testing, does not mean that subject matter is nonobvious. "[A] rule of law equating unpredictability to patentability" is improper because "the expectation of success need only be reasonable, not absolute." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). That is, "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Id.*

Where "there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 550 U.S. at 421. "If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *Id.* In such instances "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.*

F. 35 U.S.C. § 112—Lack of Written Description and Enablement.

An inventor is obligated to set forth in the specification "a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention." 35 U.S.C. § 112, ¶ 1; *see also* AIA 35 U.S.C. § 112(a).

The test for satisfying the written description requirement is "whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). "Put another way, one skilled in the art, reading the original disclosure, must immediately discern the limitation at issue in the claims." *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323 (Fed. Cir. 2000); *see also id.* at 1326-27 ("[O]ne cannot disclose a forest in the original application, and then later pick a tree out of the forest and say here is my invention. In order to satisfy the written description requirement, the blaze marks directing the skilled artisan to that tree must be in the originally filed disclosure."). "[T]o satisfy the written description requirement for a claimed genus, a specification must describe the claimed invention in such a way that a person of skill in the art would understand that the genus that is being claimed has been invented, not just a species of the genus." *Carnegie Mellon Univ. v. Hoffman-La Roche Inc.*, 541 F.3d 1115, 1124 (Fed. Cir. 2008); *see also AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300-02 (Fed. Cir. 2014) (finding description of one type of structurally similar antibodies not representative of full scope of claimed genus); *Amgen Inc. v. Sanofi*, 872 F.3d 1367, 1378-79 (Fed. Cir. 2017) (finding that identifying an antigen, by itself, is not sufficient to satisfy written description requirement).

To satisfy the enablement requirement, the claimed invention must be set forth within the specification such that any person skilled in the art can make and use the full scope of the invention without undue experimentation. *In re Wands*, 858 F.2d 731, 736-37 (Fed. Cir. 1988). Thus, one of the purposes of the specification and drawings is to provide one of ordinary skill in the art with a sufficient description of the invention to enable him or her to make and use the invention without having to conduct time-consuming experimentation. *See Idenix Pharms. LLC v. Gilead Scis. Inc.*,

941 F.3d 1149, 1154, 1156-57 (Fed. Cir. 2019); *Enzo Biochem, Inc. v. Calgene, Inc.*, 188 F.3d 1362, 1371 (Fed. Cir. 1999). Whether undue experimentation is required "is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." *ALZA Corp. v. Andrx Pharm., LLC*, 603 F.3d 935, 940 (Fed. Cir. 2010) (citing *Wands*, 858 F.2d at 737). Specific factors that a court may consider when determining whether a disclosure requires undue experimentation include: (1) how much experimentation is necessary; (2) how much direction or guidance is given; (3) whether working examples are provided; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability of the art; and (8) the breadth of the claims. *Wands*, 858 F.2d at 737. No single factor is outcome-determinative. *Id.* Although illustrative, these factors are not mandatory. *See Enzo*, 188 F.3d at 1371-72 (citing *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991)). A court need not review all of the factors before making an enablement determination. *Id.* at 1371.

G. 35 U.S.C. § 112—Indefiniteness.

"The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention." 35 U.S.C. § 112, ¶ 2; *see also* AIA 35 U.S.C. § 112(b). The purpose of this section is to provide clear warning to others as to what constitutes infringement of the patent. *Honeywell Int'l, Inc. v. Int'l Trade Comm'n*, 341 F.3d 1332, 1338 (Fed. Cir. 2003) (recognizing that the definiteness requirement "focuses on whether the claims, as interpreted in view of the written description, adequately perform their function of notifying the public of the [scope of the] patentee's right to exclude") (alteration in original); *accord United Carbon Co. v. Binney & Smith Co.*, 317 U.S. 228, 232 (1942); *Ex parte Oetiker*, 23 U.S.P.Q.2d 1651 (B.P.A.I. 1990), *aff'd sub nom. In re Oetiker*, 951 F.2d 1267 (Fed. Cir. 1991) (unpublished table decision). Otherwise there would be "[a] zone of

uncertainty which enterprise and experimentation may enter only at the risk of infringement." *Nautilus, Inc. v. Biosig Instruments, Inc.*, 572 U.S. 898, 899 (2014) (quoting *United Carbon*, 317 U.S. at 236). Thus, "a patent is invalid for indefiniteness if its claims, read in light of the specification delineating the patent, and the prosecution history, fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention." *Id.* at 901. "If the court determines that a claim is not 'amenable to construction,' then the claim is invalid as indefinite under 35 U.S.C. § 112, ¶ 2." *Honeywell*, 341 F.3d at 1338. Moreover, a claim is indefinite when a given embodiment might simultaneously infringe and not infringe due to differences in the various testing methods that could be used to establish infringement. *See Geneva Pharm., Inc. v. GlaxoSmithKline PLC*, 349 F.3d 1373, 1384 (Fed. Cir. 2003); *Dow Chem. Co. v. Nova Chems. Corp.*, 803 F.3d 620, 634 (Fed. Cir. 2015); *Forest Labs., Inc. v. Teva Pharms. USA, Inc.*, 716 F. App'x 987, 994 (Fed. Cir. 2017).

H. 35 U.S.C. § 112—Improper Dependency.

A dependent claim "shall contain a reference to a claim previously set forth and then specify a further limitation of the subject matter claimed," and "shall be construed to incorporate by reference all the limitations of the claim to which it refers." 35 U.S.C. § 112, ¶ 4; *see also* AIA 35 U.S.C. § 112(d). If a dependent claim fails to further limit the claim from which it depends, that dependent claim is invalid. *Pfizer, Inc. v. Ranbaxy Labs. Ltd.*, 457 F.3d 1284, 1291-92 (Fed. Cir. 2006). Thus, improper dependency is a valid defense to an allegation of patent infringement. *Id.* at 1292.

I. Obviousness-Type Double Patenting.

"Obviousness-type double patenting is a judicially created doctrine that 'prohibit[s] a party from obtaining an extension of the right to exclude through claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent.'" *Pfizer, Inc. v. Teva Pharm.*

USA, Inc., 518 F.3d 1353, 1363 (Fed. Cir. 2008) (quoting *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 967 (Fed. Cir. 2001)). A later-issued, earlier-expiring, commonly-owned patent may be used as an invalidating obviousness-type double patenting reference. *See, e.g.*, *Gilead Scis., Inc. v. Natco Pharma Ltd.*, 753 F.3d 1208, 1216-17 (Fed. Cir. 2014). Another justification of the doctrine is the prevention of "multiple infringement suits by different assignees asserting essentially the same patented invention." *In re Hubbell*, 709 F.3d 1140, 1145 (Fed. Cir. 2013). The doctrine of obviousness-type double patenting is also known as non-statutory double patenting. *Perricone*, 432 F.3d at 1373. Under this doctrine, "'[a] later patent claim is not patentably distinct from an earlier patent claim if the later claim is obvious over, or anticipated by, the earlier claim.'" *Pfizer*, 518 F.3d at 1363 (quoting *Eli Lilly*, 251 F.3d at 968).

There are important differences between an obviousness analysis under 35 U.S.C § 103(a) and obviousness-type double patenting analysis. For example, "[o]bviousness compares claimed subject matter to the prior art; nonstatutory double patenting compares claims in an earlier patent to claims in a later patent or application." *Geneva*, 349 F.3d at 1377 n.1. Under some circumstances, an obviousness-type double patenting analysis may also compare the claims of a later patent against the specification of an earlier patent. For example, "a 'claim to a method of using a composition is not patentably distinct from an earlier claim to the identical composition in a patent disclosing the identical use.'" *Sun Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 611 F.3d 1381, 1385 (Fed. Cir. 2010) (quoting *Pfizer*, 518 F.3d at 1363; *Geneva*, 349 F.3d at 1385-86).

Obviousness-type double patenting based on anticipation does not require a motivation to modify the prior art. *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1297-98 (Fed. Cir. 2012) (construing *Geneva*, 349 F.3d at 1377 n.1), *cert. denied,* 568 U.S. 1123 (2013); *see also*

Perricone, 432 F.3d at 1374 (affirming that "the earlier species renders the later genus claims invalid under non-statutory double patenting").

35 U.S.C. § 121 "shields patents that issue on applications filed as a result of a restriction requirement from double patenting invalidation." *Amgen v. F. Hoffman-La Roche*, 580 F.3d at 1350. Because the § 121 "safe harbor provision" applies to applications filed as a result of restriction requirements (i.e., divisional applications), it "does not protect continuation applications or patents descending from only continuation applications." *Id.* at 1352-53. Moreover, even divisional applications must maintain "consonance," a judicially created concept which "specifies that the line of demarcation between the independent and distinct inventions that prompted the restriction requirement be maintained." *St. Jude Med., Inc. v. Access Closure, Inc.*, 729 F.3d 1369, 1377 (Fed. Cir. 2013) (internal quotation marks omitted). "The requirement for consonance applies to both the patent challenged for double patenting (the challenged patent) and the patent being used as a reference against the challenged patent (the reference patent)." *Id.* (citing *Boehringer Ingelheim Int'l GmbH v. Barr Labs., Inc.*, 592 F.3d 1340, 1352 (Fed. Cir. 2010)).

J. Unenforceability—Inequitable Conduct.

Those involved with prosecuting a patent application before the U.S. Patent and Trademark Office ("PTO") owe an affirmative duty of candor and good faith. *See* 37 C.F.R. § 1.56; *Manual of Patent Examining Procedures* § 2000 *et seq*. The duty of candor and good faith stems from, among other things, the fact that the patent application process is an *ex parte* process. "In light of the ex parte nature of patent prosecution, the number of applications filed, and the limited capacity of the PTO to ascertain the facts necessary to adjudge the patentable merits of each application, . . . the highest standards of honesty and candor on the part of applicants presenting such facts to the office are ... necessary elements in a working patent system." *Therasense, Inc. v. Becton, Dickinson & Co.*, 649 F.3d 1276, 1310 (Fed. Cir. 2011) (en banc) (internal quotations omitted). Indeed, the

idea that participants in the patent application process must at all times act with candor and in good faith when before the PTO is "essential" to the patent system's ability to operate properly, as the Federal Circuit's predecessor court explained long ago:

> The ex parte prosecution and examination of a patent application must not be considered as an adversary proceeding and should not be limited to the standards required in inter partes proceedings. With the seemingly ever-increasing number of applications before it, the Patent Office has a tremendous burden. While being a fact finding as well as an adjudicatory agency, it is necessarily limited in the time permitted to ascertain the facts necessary to adjudge the patentable merits of each application. In addition, it has no testing facilities of its own. Clearly, it must rely on applicants for many of the facts upon which its decisions are based. *The highest standards of honesty and candor on the part of applicants in presenting such facts to the office are thus necessary elements in a working patent system. We would go so far as to say they are essential.*

Norton v. Curtiss, 433 F.2d 779, 793-94 (C.C.P.A. 1970) (emphasis added); *see also Envtl. Designs, Ltd. v. Union Oil Co. of Cal.*, 713 F.2d 693, 698 (Fed. Cir. 1983) ("[P]rosecution of a patent application is ex parte, involving PTO reliance on the candor and good faith of a patent applicant.").

"Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the [Patent] Office." 37 C.F.R. § 1.56(a); *see also* M.P.E.P. § 2000.01. Inequitable conduct occurs when the duty of candor and good faith is breached. *See Ferring B.V. v. Barr Labs., Inc.*, 437 F.3d 1181, 1194-95 (Fed. Cir. 2006) (declaring brand patent in an ANDA case unenforceable due to inequitable conduct before the PTO). A patent obtained through inequitable conduct is unenforceable. *See, e.g.*, *id.* at 1186; *Aventis Pharma S.A. v. Hospira, Inc.*, 675 F.3d 1324, 1337 (Fed. Cir. 2012) (declaring brand patent in an ANDA case unenforceable due to inequitable conduct before the PTO); *Aventis Pharma v. Amphastar Pharm., Inc.*, 525 F.3d 1334, 1349 (Fed. Cir. 2008) (same); *Pharmacia Corp. v. Par. Pharm. Inc.*, 417 F.3d 1369, 1373-75 (Fed. Cir. 2005) (same).

"To prevail on a claim of inequitable conduct, the accused infringer must prove that the patentee acted with the specific intent to deceive the PTO. . . . In other words, the accused infringer must prove by clear and convincing evidence that the applicant knew of the reference, knew that it was material, and made a deliberate decision to withhold it." *Therasense*, 649 F.3d at 1290. "[T]he materiality required to establish inequitable conduct is but-for materiality. When an applicant fails to disclose prior art to the PTO, that prior art is but-for material if the PTO would not have allowed a claim had it been aware of the undisclosed prior art." *Id.* at 1291. The Federal Circuit, however, "recognizes an exception in cases of affirmative egregious misconduct":

> This exception to the general rule requiring but-for proof incorporates elements of the early unclean hands cases before the Supreme Court, which dealt with deliberately planned and carefully executed scheme[s] to defraud the PTO and the courts. When the patentee has engaged in affirmative acts of egregious misconduct, such as the filing of an unmistakably false affidavit, the misconduct is material.

Id. at 1292 (alteration in original) (citation and internal quotation marks omitted).

V. INVALIDITY CONTENTIONS REGARDING THE 601 PATENT.

A. The Knowledge of a Person of Ordinary Skill in the Art.

In the context of the obviousness analysis, the scope of the prior art is directed to the field of endeavor of the invention, and includes the knowledge of a person of ordinary skill in the art. Here, a person of ordinary skill in the art would have: (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in (i) developing treatments for angiogenic eye disorders (such as

AMD), including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists.[9]

B. Prior Art Relevant to the 601 Patent.

In the context of the obviousness analysis, the scope of the prior art is directed to the field of endeavor of the invention. The scope of the prior art relates, in general, to treatments for angiogenic eye disorders, including through the use of VEGF antagonists.

Mylan relies on at least the references identified in Appendix A in support of its Invalidity Contentions regarding the 601 patent based on anticipation and obviousness under 35 U.S.C. § 102 and 35 U.S.C. § 103. Unless otherwise and expressly stated, it should be presumed that Mylan intends to rely upon each reference in its entirety to the extent relevant or appropriate, including references cited in and/or referenced within the references identified in Appendix A. Similarly, the headings included in this section are for convenience only, and do not limit Mylan's right to rely on any reference to the extent relevant or appropriate.

[9] In its Decision Granting Institution of *Inter Partes* Review of the 601 patent, the Patent Trial and Appeal Board ("Board") has adopted this definition of the person of ordinary skill in the art. *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01226, Paper 22 (PTAB Jan. 11, 2023).

C. 35 U.S.C. § 102 and § 103 – The 601 Patent Claims Are Anticipated and Rendered Obvious.[10]

1. Claim 1.

a. Anticipation by the 747 Patent.[11]

The language of claim 1 of the 601 patent is set forth above.

Claim 1 of the 601 patent is anticipated by Regeneron's patents disclosing dosing regimens for the treatment of eye disorders. For example, the 747 patent discloses a method of treating eye disorders, including macular degeneration. The 747 patent further discloses treatment with the fusion polypeptide of SEQ ID NO:6 (VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). The 747 patent further discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 2-8 weeks, or 1-6 months apart, which a person of ordinary skill in the art would have immediately envisaged could encompass, e.g., "every 4 weeks for the first 3 months, followed by . . . once every 8 weeks or once every two months." (*See, e.g.*, 747 patent; 049 patent; 799 patent).

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[10] The 601 patent Asserted Claims are invalid for at least the reasons set forth in the Final Written Decisions in IPR2021-00880 (Paper 89, Nov. 9, 2022) and IPR2021-00881 (Paper 94, Nov. 9, 2022). The 601 patent Asserted Claims are also invalid for at least the reasons set forth in the Decision Granting Institution of *Inter Partes* Review in IPR2022-01226, wherein the Board found that "[Mylan] has established a reasonable likelihood of prevailing at trial in demonstrating that at least one of the challenged claims of the '601 patent is unpatentable under Dixon, and that that showing amounts to compelling evidence of unpatentability." *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01226, Paper 22, at 29 (PTAB Jan. 11, 2023); *see also Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01225, Paper 21 (PTAB Jan. 11, 2023). As noted, Mylan further incorporates by reference all grounds of invalidity set forth in IPR2021-00880, IPR2021-00881, IPR2022-01225, IPR2022-01226, IPR2022-01524, IPR2023-00099, and IPR2023-00442.

[11] The 799 patent and 049 patent are related to the 747 patent and contain the same disclosures. Claim 1 is also anticipated by the 799 patent and 049 patent.

b. Anticipation by the VIEW References.

Claim 1 of the 601 patent is anticipated by at least each of the VIEW References that disclose the dosing regimen used in the VIEW trials. For example, the VIEW References disclose a method of treating AMD, by intravitreally administering to a patient in need thereof 2 mg of VEGF Trap-Eye (i.e., aflibercept), using three monthly doses, followed by every-8-week dosing. (*See, e.g.*, Dixon; Adis; NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release). In addition, it was well known among those of ordinary skill in the art that aflibercept and VEGF Trap-Eye were different terms for the same molecule, and were often used interchangeably, and also that aflibercept was the molecule used in the VIEW trials. (*See, e.g.*, Dixon; Adis; 9-30-2009 Regeneron 10-Q; 757 patent Petition for Patent Term Extension; 758 patent Petition for Patent Term Extension; 959 patent Petition for Patent Term Extension; Nguyen 2009a; Dix; 095 patent). As a result, each of the references disclosing the every-8-week dosing regimen used in the VIEW clinical trials, including Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release anticipates claim 1 of the 601 patent.

Further, the aflibercept dosing regimen recited in claim 1 of the 601 patent claims the same every-8-week dosing regimen claimed by an earlier patent in the same family, U.S. Patent No. 9,254,338 ("338 patent"). In a Final Written Decision relating to the 338 patent, the Board determined that the Dixon reference anticipates the aflibercept dosing regimen claimed by the 338 patent and repeated in claim 1 of the 601 patent. *See Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2021-00881 ("338 IPR"), Paper 94 ("338 FWD"); *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01226, Paper 22, at 28-29 (PTAB Jan. 11, 2023) ("[Mylan] has established a reasonable likelihood of prevailing at trial in demonstrating that at least one of the challenged claims of the '601 patent is unpatentable under Dixon, and that that showing amounts to compelling evidence of unpatentability."). Given that the Board already found the substantively identical dosing regimen is disclosed in Dixon, claim 1 of the 601 patent is likewise anticipated by Dixon for the same reasons articulated by the Board in the 338 IPR. *See Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01226, Paper 22, at 28-29 (PTAB Jan. 11, 2023) ("We conclude that it was material error on the part of the Examiner to fail to reject the claims of the '267 application [which application ultimately issued as the 601 patent] over Dixon because, as we explained in the -00881 Decision, the claims of the '338 patent, which are substantially identical to those of the '267 application, were anticipated by Dixon.").

Claim 1 does not contain efficacy limitations.[12] To the extent that Regeneron later argues that one or more claim limitations carry efficacy limitations,[13] or that the prior art disclosures of

[12] To the extent Regeneron argues that the "method for treating" preamble of claim 1 requires a "high level of efficacy" or any particular level of efficacy, Mylan relies on and incorporates the Board's findings rejecting this argument in the related 338 IPR, (*see, e.g.*, 338 FWD at 18), as well as Mylan's IPR briefing on the issue, all of which is expressly incorporated by reference herein.

[13] Mylan does not concede that any term in claim 1 carries specific efficacy limitations, and reserves the right to contest any effort to read such limitations into the claims, including, but not limited to, in connection with district court claim construction proceedings and any appeals related

VEGF Trap-Eye do not expressly disclose "aflibercept," claim 1 of the 601 patent is inherently anticipated by at least each of the VIEW References that disclose the dosing regimen and VEGF Trap-Eye/aflibercept used in the VIEW trials. First, claim 1 expressly defines "an effective amount" as 2 mg, an acknowledgement that effectiveness is a natural result flowing from the administration of 2 mg of aflibercept, which was disclosed in the prior art references disclosing the VIEW clinical trial dosing regimens. Second, inherency is evidenced by, among other things, the CLEAR-IT-2 Phase 2 trials and the results of the VIEW Phase 3 trials. For example, the CLEAR-IT-2 data demonstrate success at treating patients with AMD using even fewer doses, on average, than in the VIEW every-8-week dosing regimen. (*See, e.g.*, Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-3-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). The VIEW data confirm that any therapeutic effect was a natural result flowing from the operation of the VIEW regimen. (*See, e.g.*, 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release; Heier 2012). In addition, it was well known among those of ordinary skill in the art that aflibercept and VEGF Trap-Eye were different terms for the same molecule, and were often used interchangeably, and also that aflibercept was the molecule used in the VIEW trials. (*See, e.g.*, Dixon; Adis; 9-30-2009 Regeneron 10-Q; 757 patent Petition for

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thereto. Mylan also incorporates herein arguments made and evidence presented, by Mylan, in IPR2021-00880 and IPR2021-00881, relating to the meaning of terms in the related 338 and 069 patents.

Patent Term Extension; 758 patent Petition for Patent Term Extension; 959 patent Petition for Patent Term Extension). As a result, each of the references cited above disclosing the VIEW dosing regimen inherently anticipates claim 1 of the 601 patent for at least these additional reasons.

c. Anticipation by Public Use.

Claim 1 of the 601 patent is invalid for being in public use, including in this country, or otherwise available to the public, more than one year before the filing of the 601 patent's earliest priority application. The public use of the claimed invention is evidenced by at least the VIEW References discussed above. (*See, e.g.*, Dixon; Adis; NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; Retina Society Meeting Presentation).

d. Obviousness over the 747 Patent.[14]

Claim 1 of the 601 patent is obvious in view of Regeneron's patents disclosing dosing regimens for the treatment of eye disorders. For example, the 747 patent discloses a method of treating eye disorders, including macular degeneration. The 747 patent further discloses treatment with the fusion polypeptide of SEQ ID NO:6 (VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). The 747 patent further discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment

[14] The 799 patent and 049 patent are related to the 747 patent and contain the same disclosures. Claim 1 is also rendered obvious by the 799 patent and 049 patent.

followed by subsequent treatments between 2-8 weeks, or 1-6 months apart, which a person of ordinary skill in the art would have immediately envisaged could encompass, e.g., "every 4 weeks for the first 3 months, followed by . . . once every 8 weeks or once every two months." (*See, e.g.*, 747 patent; 049 patent; 799 patent). A person of ordinary skill in the art would have been motivated to refine the regimens disclosed in the above references to arrive at the claimed regimen in view of the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration. A person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed regimens. First, there are no efficacy limitations in the claims. Second, positive results from a variety of regimens, including single intravitreal injections, had been reported for VEGF Trap-Eye/aflibercept. (*See, e.g.*, Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-3-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). Accordingly, claim 1 of the 601 patent is obvious in view of at least each of the 747, 049, and 799 patents, and, if necessary, in combination with one or more of the references disclosing the Phase 1 and Phase 2 clinical trial results.

e. Obviousness over the VIEW References.

Claim 1 of the 601 patent is obvious in view of the VIEW references, either alone or in combination. For the reasons discussed above, that discussion incorporated herein, each VIEW reference discloses expressly or inherently each and every claim element. (*See, e.g.*, Dixon; Adis;

NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release). Further, the motivation to adopt the claimed dosing regimens for VEGF Trap-Eye comes from the references themselves, which persons of ordinary skill in the art would have appreciated set forth dosing regimens that allowed for dosing less frequently than monthly, as well as the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration.

Also, a person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed VIEW dosing regimens at least because of the Phase 1 and/or CLEAR-IT-2 Phase 2 results, which were obtained using single injections and extended dosing regimens of VEGF Trap-Eye. (*See, e.g.*, Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-3-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q).

Accordingly, claim 1 of the 601 patent is obvious in view of at least each of the VIEW references cited above, and, if necessary, in combination with one or more of the references cited above disclosing the Phase 1 and Phase 2 CLEAR-IT-2 results.

Claim 1 of the 601 patent is obvious in view of the VIEW references, either alone or in combination. For the reasons discussed above, that discussion incorporated herein, each VIEW reference discloses expressly or inherently each and every claim element. (*See, e.g.*, Dixon; Adis; NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release). Further, the motivation to adopt the claimed dosing regimens for VEGF Trap-Eye comes from the references themselves, which persons of ordinary skill in the art would have appreciated set forth dosing regimens that allowed for dosing less frequently than monthly, as well as the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration.

In addition, a person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed VIEW dosing regimens at least because of the widely publicized results of the VIEW trials, which were made available to the public before the earliest filing date listed on the face of the 601 patent. (*See, e.g.*, 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release).

Accordingly, claim 1 of the 601 patent is obvious in view of at least each of the VIEW references cited above, and, if necessary, in combination with one or more of the references cited above disclosing the VIEW trial results.

2. Claim 2.

The language of claim 2 of the 601 patent is set forth above.

Claim 2 of the 601 patent depends from claim 1 and thus incorporates the elements of claim 1. The reasons why claim 1 is obvious and/or anticipated are incorporated by reference.

The additional element "wherein the age-related macular degeneration is neovascular (wet)" does not distinguish the claim from the prior art. Specifically, the VIEW References, alone and in the combinations set forth above, and/or further in combination with the knowledge of a person of ordinary skill in the art, disclosed that the AMD being treated in the VIEW trials was neovascular (wet). (*See, e.g.*, Dixon; Adis; NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release).

Accordingly, claim 2 of the 601 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claim 1, in view of the knowledge of a person of ordinary skill in the art.

3. Claim 5.

The language of claim 5 of the 601 patent is set forth above.

Claim 5 of the 601 patent depends from claim 2 and thus incorporates the elements of claim 2. The reasons why claim 2 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score" is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *In Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1023-24 (Fed. Cir. 2018). Since the method steps are "performed in the same way regardless whether or not the patient experiences" a clinical change, the additional element of claim 5 is non-limiting. *Bristol-Myers*, 246 F.3d at 1375; *see also Prometheus Lab'ys Inc. v. Roxane Lab'ys, Inc.*, Nos. 11-230 (FSH), 11-1241 (FSH), 2013 WL 5333033, at *5-6 (D.N.J. Sept. 23, 2013 (phrase that merely "expresses the intended result of a process step positively recited" is non-limiting); *Minton v. Nat'l Ass'n of Sec. Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003).[15]

Separately, this element represents nothing more than the natural result flowing from the prior art method of administration disclosed in the VIEW References, using a measure (BCVA) which had already been disclosed in the prior art as a clinical trial measurement and/or endpoint, including in the VEGF Trap-Eye Phase 1, Phase 2, and Phase 3 AMD trials. In addition, the prior art disclosures of the results of those trials provide further support for the inherency of the subject matter of claim 5. For example, 29% of the patients receiving monthly 2.0 mg doses for three months, followed by as-needed dosing in the VEGF Trap-Eye Phase 2 AMD trial exhibited an increase in BCVA of ≥ 15 letters; and 30.6% of the patients receiving three monthly doses followed by every-8-week dosing in the Phase 3 VIEW1 trial gained ≥ 15 letters. (*See, e.g.*, Dixon; Retina Society Meeting Presentation; 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release; Heier 2012). Accordingly, claim 5 is anticipated at least by each of the references disclosing the VIEW dosing regimen, including, but not limited to,

[15] Mylan incorporates fully herein the arguments set forth in its claim construction briefs, served on November 29, 2022 and December 15, 2022.

Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release.

To the extent this element is limiting, the element is expressly set forth in the prior art. For example, the VIEW References identify improvement by > 15 letters as a metric in assessing AMD treatment, including as a secondary outcome measure for the VIEW trials. (*See, e.g.*, Dixon; NCT-795; NCT-377; 5-8-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 5-8-2008 Bayer Press Release). Therefore, a person of ordinary skill in the art reading each of the VIEW References would have understood and been aware of the secondary endpoint identified for those trials.

Further, a person of ordinary skill in the art would have understood from the prior art that the BCVA letter measure is an obvious choice to use when assessing patients in clinical trials relating to AMD treatments. (*See, e.g.*, Nguyen 2009a; Dixon; Adis; NCT-795; NCT-377; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; Heier 2009; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-3-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; Brown 2006; Rosenfeld 2006;

Lucentis Medical Review; Fung 2007; Lalwani 2009; Avila 2009; Bashshur 2008; Wu 2009). Further a person of ordinary skill in the art would have had a reasonable expectation of success at meeting the BCVA criteria set forth in claim 5 when using the recited regimen, in light of the positive Phase 1 and Phase 2 results discussed above and reported in the prior art. (*See, e.g.*, Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-3-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). Further, the results from the VIEW trials provide further evidence of the reasonable expectation of success that a person of ordinary skill in the art would have had in meeting the criteria set forth in claim 5 when using the recited regimen. (*See, e.g.*, 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release).

Accordingly, claim 5 of the 601 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claim 1, including combinations incorporating one or more references disclosing the use of BCVA in assessing AMD, and/or results of the Phase 1, Phase 2, or Phase 3 trials, in view of the knowledge of a person of ordinary skill in the art.

4. Claim 6.

The language of claim 6 of the 601 patent is set forth above.

Claim 6 of the 601 patent depends from claim 5 and thus incorporates the elements of claim 5. The reasons why claim 5 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" does not distinguish the claim from the prior art, as disclosed above with respect to claim 5.

A person of ordinary skill in the art would have known, from their background knowledge, and from the prior art cited above, that BCVA scores were assessed using an ETDRS letter score. (*See, e.g.*, Nguyen 2009a; Dixon; Adis; NCT-795; NCT-377; 5-8-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; Lucentis Medical Review; Brown 2006; Rosenfeld 2006; Lalwani 2009; Avila 2009; Bashshur 2008; Wu 2009; 5-8-2008 Bayer Press Release).

Accordingly, claim 6 of the 601 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claim 1, including combinations incorporating one or more references disclosing the use of BCVA (ETDRS) in assessing AMD, and/or results of the Phase 1, Phase 2, or Phase 3 trials, in view of the knowledge of a person of ordinary skill in the art.

5. Claim 7.

The language of claim 7 of the 601 patent is set forth above.

Claim 7 of the 601 patent depends from claim 1 and thus incorporates the elements of claim 1. The reasons why claim 1 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly" does not distinguish the claim from the prior art, as disclosed above with respect to claim 1.

A person of ordinary skill in the art would have understood approximately every 4 weeks to be equivalent to approximately 28 days or approximately monthly, and, moreover, would often

use the terms interchangeably in the prior art. (*See, e.g.*, Dixon at 1576 ("Two groups received monthly doses of either 0.5 or 2.0 mg for 12 weeks (at weeks 0, 4, 8 and 12)"; *see also, e.g.*, Adis; 4-28-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 8-19-2008 Bayer Press Release).

Accordingly, claim 7 of the 601 patent is anticipated and rendered obvious by each of the references disclosing the VIEW dosing regimen, and obvious in view of each of the prior art combinations set forth above for claim 1.

6. Claim 8.

The language of claim 8 of the 601 patent is set forth above.

Claim 8 of the 601 patent depends from claim 7 and thus incorporates the elements of claim 7. The reasons why claim 7 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein the age-related macular degeneration is neovascular (wet)" does not distinguish the claim from the prior art. For example, the references disclosing the VIEW dosing regimen also disclose that the VIEW trials were to evaluate wet/neovascular age-related macular degeneration, and/or disclose that the VIEW acronym itself specifies wet AMD (VEGF Trap: Investigation of Efficacy and safety in Wet age-related macular degeneration). (*See, e.g.*, Dixon; Adis; NCT-795; NCT-377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron

10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regencron 10-Q; 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release).

Accordingly, claim 8 of the 601 patent is anticipated and rendered obvious by each of the references disclosing the VIEW dosing regimen, and obvious in view of each of the prior art combinations set forth above for claim 1.

7. Claim 9.

The language of claim 9 of the 601 patent is set forth above.

Claim 9 of the 601 patent depends from claim 8 and thus incorporates the elements of claim 8. The reasons why claim 8 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection" does not distinguish the claim from the prior art. For example, the claimed exclusion criteria elements constitute mental steps and/or written material, and thus are not entitled to patentable weight. Relevantly, the Board has found that the exclusion criteria are not limiting upon claim 9 of the 601 patent under the printed matter doctrine. *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01226, Paper 22, at 11-15 (PTAB Jan. 11, 2023); *id.* at 15 ("[T]he information provided by the exclusionary criteria can be considered to be optional information, in that there is no direction to the practitioner to perform, or not perform, any specific step based upon the provided criteria. Thus, the exclusionary criteria are strictly informational, without requiring the practitioner to act, or refrain from acting, in a specified manner, and not functionally related to the practice of the claimed method.").

To the extent the exclusion criteria claim element is entitled to patentable weight, claim 9 of the 601 patent is inherently anticipated by at least each of the VIEW References that disclose the dosing regimen used in the VIEW trials. For example, the Eylea® Medical Review shows that

a list of 37 non-confidential exclusion criteria, including the "exclusion criteria" listed in claim 9, were necessarily and inevitably applied in connection with practicing the claimed, and publicly disclosed, VIEW dosing regimen. (Eylea® Medical Review at 112-114; *see also, e.g.*, Heier 2012 at Appendix 2). The application of the claimed exclusion criteria thus was a natural result flowing from the application of the VIEW trial study protocol. As a result, each of the VIEW References, including Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release inherently anticipates claim 9 of the 601 patent.

Claim 9 of the 601 patent is obvious in view of the VIEW References and combinations presented above, further in combination with references disclosing the exclusion criteria employed in the Lucentis ANCHOR and MARINA trials. For the reasons discussed above, that discussion incorporated herein, each VIEW reference discloses expressly or inherently each and every claim element, and as discussed above, the recited exclusion criteria are not entitled to patentable weight and/or are inherent aspects of the VIEW study protocols. In addition to not being entitled to patentable weight, the claimed exclusion criteria also were disclosed in the prior art. For example, the Lucentis AMD MARINA and ANCHOR trials, involving monthly intravitreal administration of the VEGF antagonist Lucentis® (ranibizumab), employed exclusion criteria that included, among other relevant criteria, active intraocular inflammation in the study eye; history of idiopathic or autoimmune-associated uveitis in either eye; and infectious conjunctivitis, keratitis,

scleritis, or endophthalmitis in either eye. (*See, e.g.*, Lucentis Medical Review; Rosenfeld 2006; Brown 2006; NCT 836; NCT 594). The Lucentis Medical Review further disclosed that dose-holding criteria included intraocular inflammation and local or systemic infection, including infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye. (Lucentis Medical Review at 66-67). Accordingly, it would have been obvious to adopt such exclusion criteria for the VEGF Trap-Eye clinical trials, particularly in light of the inclusion of monthly ranibizumab as a comparator arm in the VIEW clinical trials.

For at least these reasons, claim 9 of the 601 patent is obvious in view of at least each of the VIEW References and combinations cited above, in combination with one or more of the references cited above disclosing the ranibizumab MARINA and ANCHOR clinical trial exclusion criteria.

Claim 9 of the 601 patent is obvious in view of the references disclosing the VIEW regimens, and combinations presented above, further in combination with references disclosing exclusion criteria employed in the context of Macugen® (pegaptanib). For the reasons discussed above, that discussion incorporated herein, each VIEW reference discloses expressly or inherently each and every claim element, and as discussed above, the recited exclusion criteria are not entitled to patentable weight and/or are inherent aspects of the VIEW study protocols. In addition to not being entitled to patentable weight, the claimed exclusion criteria also were disclosed in the prior art. For example, the pegaptanib trials involving intravitreal administration in treating AMD employed exclusion criteria that included, among other relevant criteria, choroiditis, and acute ocular or periocular infection. (*See, e.g.*, Macugen Medical Review; Macugen Study Group; Gragoudas 2004). Accordingly, it would have been obvious to adopt such exclusion criteria for

the VEGF Trap-Eye clinical trials, which also involved intravitreal administration to patients with angiogenic eye disorders.

For at least these reasons, claim 9 of the 601 patent is obvious in view of at least each of the VIEW References and combinations cited above, in combination with one or more of the references cited above disclosing the pegaptanib clinical trial exclusion criteria.

Claim 9 of the 601 patent is obvious in view of the VIEW References and combinations presented above, further in combination with references disclosing general guidelines, precautions, and general potential complications of intravitreal administration. For the reasons discussed above, that discussion incorporated herein, each VIEW reference discloses expressly or inherently each and every claim element, and as discussed above, the recited exclusion criteria are not entitled to patentable weight and/or are inherent aspects of the VIEW study protocols. In addition to not being entitled to patentable weight, the claimed exclusion criteria also were obvious from the prior art. For example, it was known among those of ordinary skill in the art that intravitreal administration could be associated with serious side effects if proper, aseptic technique is not adhered to. Consequently, persons of ordinary skill in the art recognized, and reported on, the need to avoid injecting eyes that are infected or show signs of infection (i.e., inflammation). (*See, e.g.*, Aiello 2004; Jager 2004; Donahue; De Caro; Heimann). Accordingly, it would have been obvious to adopt exclusion criteria for the VEGF Trap-Eye clinical trials that included active intraocular inflammation or active ocular or periocular infection.

For at least these reasons, claim 9 of the 601 patent is obvious in view of at least each of the VIEW References and combinations cited above, in combination with one or more of the references cited above disclosing general guidelines and precautions for intravitreal injections.

Additionally, claim 9 of the 601 patent is obvious because the claimed exclusion criteria were well known in the art for treatments involving intravitreal injections of VEGF antagonists. For example, with respect to the first claimed exclusion criterion, "active intraocular inflammation," the CATT, MACTEL, and PIER studies describe the exclusion criteria for clinical trials of the leading prior art anti-VEGF treatments—bevacizumab (Avastin) and ranibizumab (Lucentis). (*See, e.g.*, CATT Study, Exclusion Criteria (disclosing the criterion verbatim: "[a]ctive or recent (within 4 weeks) intraocular inflammation"); Regillo 2008, Supplemental Table A (disclosing the criterion verbatim: "[a]ctive intraocular inflammation (grade trace or above) in the study eye"); MACTEL Study). With respect to the second claimed exclusion criterion, "active ocular or periocular infection," the prior art again includes nearly verbatim exclusion criteria. (*See* MACTEL Study, Exclusion Criteria; CATT Study, Exclusion Criteria; Regillo 2008, Supplemental Table A). The person of ordinary skill in the art understood that the exclusion criteria disclosed in the CATT, MACTEL, and PIER studies reflected basic safety precautions designed to minimize the known risks, and the person of ordinary skill in the art would have been motivated to adopt the exclusion criteria from these studies in order to mitigate potential complications for intravitreal injections of aflibercept, which posed the same potential risks as prior anti-VEGF agents that were administered intravitreally. (*See, e.g.*, Jaffe; Lucentis PI 2006; Regillo 2008; Retinal Physician II; Dixon; Jager 2004). Indeed, the person of ordinary skill in the art would have had a strong motivation to look to exclusion criteria from prior studies involving anti-VEGF intravitreal injections such as those disclosed by the CATT, MACTEL, and PIER studies, and to apply them to the aflibercept dosing regimen recited by Dixon. Further, because the known risks associated with intravitreal injections are common to all intravitreal injections, including injections of VEGF antagonists, the person of ordinary skill in the art would reasonably

expect that the exclusion criteria developed for prior art VEGF antagonists could be successfully applied to aflibercept. Accordingly, it would have been obvious to adopt exclusion criteria for the VEGF Trap-Eye clinical trials that included active intraocular inflammation or active ocular or periocular infection.

For at least these reasons, claim 9 of the 601 patent is obvious in view of Dixon, in combination with one or more of the references cited above disclosing the exclusion criteria from the CATT, MACTEL, and PIER studies.

Accordingly, claim 9 of the 601 patent is invalid under 35 U.S.C. §§ 102 and 103 for at least these additional reasons.

8. Claim 10.

a. Anticipation by the 747 Patent.[16]

The language of claim 10 of the 601 patent is set forth above.

Claim 10 of the 601 patent is anticipated by Regeneron's patents disclosing dosing regimens for the treatment of eye disorders. For example, the 747 patent discloses a method of treating eye disorders, including diabetic retinopathy ("DR"), and one of its complications, retinal edema (i.e., diabetic macular edema ("DME")). The 747 patent further discloses treatment with the fusion polypeptide of SEQ ID NO:6 (VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). The 747 patent further discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 1-6 months apart, which a person of ordinary skill in

[16] The 799 patent and 049 patent are related to the 747 patent and contain the same disclosures. Claim 10 is also anticipated by the 799 patent and 049 patent.

the art would have immediately envisaged could encompass, e.g., "every 4 weeks for the first 5 injections followed by . . . once every 8 weeks or once every two months." (*See, e.g.*, 747 patent; 049 patent; 799 patent). Further, claim 12 reveals that the patentee intended claim 10 to cover monthly dosing, which was taught by the 747 patent, 049 patent, and 799 patent.

b. Anticipation by the Phase 2 DME References.

Claim 10 also is anticipated by prior art disclosing Regeneron's Phase 2 VEGF Trap-Eye clinical trial in DME. For example, the 9-14-2009 Regeneron Press Release disclosed VEGF Trap-Eye (aflibercept), a drug for intravitreal administration, being administered to patients in 2 mg doses every eight weeks after three loading doses or on an as-needed (PRN) basis after three monthly loading doses. A possible dosing schedule falling within the Phase 2 PRN dosing regimen and immediately envisaged by a person of ordinary skill in the art would have been "every 4 weeks for the first 5 injections," followed by doses administered "approximately once every eight weeks or once every two months." (9-14-2009 Regeneron Press Release; *see also, e.g.*, 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release). Further, claim 12 reveals that the patentee intended claim 10 to cover monthly dosing, which was taught by the prior art references cited above.

To the extent that Regeneron later argues that one or more claim limitations carry efficacy limitations,[17] claim 10 of the 601 patent is inherently anticipated by at least each of the references disclosed above. First, claim 10 expressly defines "an effective amount" as 2 mg, an

[17] Mylan does not concede that any term in claim 1 carries specific efficacy limitations, and reserves the right to contest any effort to read such limitations into the claims, including, but not limited to, in connection with district court claim construction proceedings and any appeals related thereto. Mylan also incorporates herein arguments made and evidence presented, by Mylan, in IPR2021-00880 and IPR2021-00881, relating to the meaning of terms in the related 338 and 069 patents.

acknowledgement that effectiveness is a natural result flowing from the administration of 2 mg of aflibercept, which was in the prior art. Second, inherency is evidenced by, among other things, the Phase 2 and Phase 3 DME clinical trials, which showed efficacious treatment of DME using regimens that fall within the scope of the prior art cited above. (*See, e.g.*, 2-18-2010 Bayer Press Release, 12-20-2010 Bayer Press Release; Do 2011; Do 2012; Brown 2015; Korobelnik 2014; Heier 2016; Larsen 2015). Thus, the Phase 2 and Phase 3 results illustrate that any therapeutic effect was a natural result flowing from the operation of dosing regimens disclosed in the prior art, including at least 747 patent, 049 patent, 799 patent, 9-14-2009 Regeneron Press Release, 2-18-2010 Regeneron Press Release, and 12-20-2010 Regeneron Press Release. As a result, each of these references also inherently anticipates claim 10 of the 601 patent for at least these additional reasons.

In addition, to the extent claim 10 is found to have a later priority date, then claim 10 also is anticipated by references disclosing the dosing regimen used in the VEGF Trap-Eye VIVID and VISTA clinical trials. (*See, e.g.*, Korobelnik 2014; Brown 2015; Keating 2015; Heier 2016; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01512966 (Japanese VIVID); NCT01331681 (US VIVID); NCT01363440 (US VISTA)). The VISTA and VIVID trials employed a regimen of 2 mg aflibercept administered intravitreally every 8 weeks after 5 initial monthly doses (i.e., 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every 8 weeks or once every 2 months.) Further, to the extent that Regeneron later argues that one or more claim limitations carry efficacy limitations,[18] claim 10 of the 601 patent is anticipated by at

[18] Mylan does not concede that any term in claim 10 carries specific efficacy limitations, and reserves the right to contest any effort to read such limitations into the claims, including, but not limited to, in connection with district court claim construction proceedings and any appeals related

least each of the references disclosed above. First, claim 10 expressly defines "an effective amount" as 2 mg, an acknowledgement that effectiveness is a natural result flowing from the administration of 2 mg of aflibercept, which was in the above prior art references. Second, efficacy is evidenced by, among other things, the results reported for the VIVID and VISTA clinical trials, including reductions in retinal thickness and improvements in BCVA. (*See, e.g.*, Korobelnik 2014; Brown 2015; Keating 2015; Heier 2016; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01512966 (Japanese VIVID); NCT01331681 (US VIVID); NCT01363440 (US VISTA)). As a result, each of the references disclosing the dosing regimen used in the VEGF Trap-Eye VIVID and VISTA clinical trials anticipates claim 10 of the 601 patent for at least these additional reasons.

c. Anticipation by Public Use.

Claim 10 of the 601 patent is invalid for being in public use, including in this country, or otherwise available to the public, more than one year before the filing of the 601 patent's earliest priority application and/or more than one year before the earliest priority date to which claim 10 is entitled. The public use of the claimed invention is evidenced by at least the references discussed above disclosing the VEGF Trap-Eye DME clinical trials. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Korobelnik 2014; Brown 2015; Keating 2015; Heier 2016; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01512966 (Japanese VIVID); NCT01331681 (US VIVID); NCT01363440 (US VISTA)).

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thereto. Mylan also incorporates herein arguments made and evidence presented, by Mylan, in IPR2021-00880 and IPR2021-00881, relating to the meaning of terms in the related 338 and 069 patents.

d. Obviousness over the 747 Patent.[19]

Claim 10 of the 601 patent is obvious in view of Regeneron's patents disclosing dosing regimens for the treatment of eye disorders. For example, the 747 patent discloses a method of treating eye disorders, including DR, and one of its complications, retinal edema (i.e., DME). The 747 patent further discloses treatment with the fusion polypeptide of SEQ ID NO:6 (VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). The 747 patent further discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 2-8 weeks, or 1-6 months apart, which a person of ordinary skill in the art would have immediately envisaged could encompass, e.g., "every 4 weeks for the first 5 injections, followed by . . . once every 8 weeks or once every two months." (*See, e.g.*, 747 patent; 049 patent; 799 patent). A person of ordinary skill in the art would have been motivated to refine the regimens disclosed in the above references to arrive at the claimed regimen in view of the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration. A person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed regimens. First, there are no efficacy limitations in the claims. Second, positive results from single intravitreal injections, had been reported for VEGF Trap-Eye/aflibercept. (*See, e.g.*, Do 2007; Do 2009). Accordingly, claim 10 of the 601 patent is obvious in view of at least each of the 747, 049, and 799 patents, and, if

[19] The 799 patent and 049 patent are related to the 747 patent and contain the same disclosures. Claim 10 is also rendered obvious by the 799 patent and 049 patent.

necessary, in combination with one or more of the references disclosing the Phase 1 DME clinical trial results.

e. Obviousness over the Phase 2 DME References.

Claim 10 of the 601 patent is obvious in view of the references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the results of the VEGF Trap-Eye DME Phase 1 clinical trial. For the reasons discussed above, that discussion incorporated herein, each reference disclosing the VEGF Trap-Eye Phase 2 DME clinical trial regimen expressly or inherently discloses each and every claim element. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; and 12-20-2010 Regeneron Press Release). In addition, these references render claim 10 obvious, because the claimed regimen is nothing more than an obvious embodiment of the disclosed regimens. For example, a person of ordinary skill in the art would have assessed the outcomes of the Phase 2 trial using three monthly loading doses followed by PRN or every-eight-week dosing, and would have been motivated to make routine adjustments to the number of loading doses in order to achieve, or come close to achieving, the results obtained with every-month dosing.

In addition, the person of ordinary skill in the art would have had a reasonable expectation of success in view of the results observed in the Phase 1 VEGF Trap-Eye DME trial, in which patients receiving a single intravitreal injection of VEGF Trap-Eye experienced improvements in BCVA and retinal thickness. (*See, e.g.*, Do 2007; Do 2009).

Accordingly, for at least these reasons, claim 10 is rendered obvious by references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the results of the VEGF Trap-Eye Phase 1 DME clinical trial.

Claim 10 of the 601 patent is obvious in view of the references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the results of

the VEGF Trap-Eye Phase 2 DME clinical trial. For the reasons discussed above, that discussion incorporated herein, each reference disclosing the VEGF Trap-Eye Phase 2 DME clinical trial regimen expressly or inherently discloses each and every claim element. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012). In addition, these references render claim 10 obvious, because the claimed regimen is nothing more than an obvious embodiment of the disclosed regimens. For example, 5 monthly injections followed by injections every 8 weeks is an obvious variation of the PRN regimen disclosed in the references describing the VEGF Trap-Eye Phase 2 DME clinical trial. In addition, a person of ordinary skill in the art would have assessed the outcomes of the Phase 2 trial using three monthly loading doses followed by PRN or every-eight-week dosing, and would have been motivated to make routine adjustments to the number of loading doses in order to achieve, or come close to achieving, the results obtained with every-month dosing.

The person of ordinary skill in the art would have had a reasonable expectation of success in view of the results observed in the Phase 2 VEGF Trap-Eye DME trial, in which patients experienced improvements in BCVA and retinal thickness. (*See, e.g.*, 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Tolentino 2011; Boyer 2011; Do 2012).

Accordingly, for at least these reasons, claim 10 is rendered obvious by references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the results of the VEGF Trap-Eye Phase 2 DME clinical trial.

Claim 10 of the 601 patent is obvious in view of the references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the use of ranibizumab in treating DME. For the reasons discussed above, that discussion incorporated herein, each reference disclosing the VEGF Trap-Eye Phase 2 DME clinical trial regimen

expressly or inherently discloses each and every claim element. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; and 12-20-2010 Regeneron Press Release; Do 2011; Do 2012). In addition, these references render claim 10 obvious, because the claimed regimen is nothing more than an obvious embodiment of the disclosed regimens. For example, 5 monthly injections followed by injections every 8 weeks is an obvious variation of the PRN regimen disclosed in the references describing the VEGF Trap-Eye Phase 2 DME clinical trial. In addition, a person of ordinary skill in the art would have assessed the outcomes of the Phase 2 trial using three monthly loading doses followed by PRN or every-eight-week dosing, and would have been motivated to make routine adjustments to the number of loading doses in order to achieve, or come close to achieving, the results obtained with every-month dosing.

Further, the person of ordinary skill in the art would have had a reasonable expectation of success in view of the results observed in the ranibizumab DME clinical trials, in which patients being treated with dosing regimens that included every other month dosing after a series of loading doses, experienced improvements in BCVA and retinal thickness, similar to the BCVA and retinal thickness results observed in the use of ranibizumab to treat AMD. (*See, e.g.*, Chun 2006; Nguyen 2006b; Campochiaro 2006; Nguyen 2009b; Querques 2009; Rodriguez-Fontal 2009; Schwartz 2009; Hansen 2010; Schachat 2010; Waisbourd 2011).

Accordingly, for at least these reasons, claim 10 is rendered obvious by references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the results of the ranibizumab DME clinical trials.[20]

[20] To the extent that any specific limitation is found not to be explicitly or inherently disclosed in these references, it would have been achieved through routine optimization by one of ordinary skill in the art.

Accordingly, for at least the reasons set forth herein, claim 10 of the 601 patent is anticipated and rendered obvious by each of the references and combinations set forth above.

9. Claim 11.

The language of claim 11 of the 601 patent is set forth above.

Claim 11 of the 601 patent depends from claim 10 and thus incorporates the elements of claim 10. The reasons why claim 10 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly" does not distinguish the claim from the prior art.

A person of ordinary skill in the art would have understood approximately every 4 weeks to be equivalent to approximately 28 days or approximately monthly, and, moreover, would often use the terms interchangeably in the prior art. (*See, e.g.*, 9-14-2009 Regeneron Press Release at 1 ("2 mg every eight weeks after three monthly loading doses"); 2-18-2010 Regeneron Press Release at 1 ("2 mg every other month, following 3 monthly injections"); Dixon at 1576 ("Two groups received monthly doses of either 0.5 or 2.0 mg for 12 weeks (at weeks 0, 4, 8 and 12)").

Accordingly, for at least these additional reasons, claim 11 of the 601 patent is anticipated and rendered obvious by each of the references and combinations set forth above for claim 10.

10. Claim 12.

The language of claim 12 of the 601 patent is set forth above.

Claim 12 of the 601 patent depends from claim 10 and thus incorporates the elements of claim 10. The reasons why claim 10 is anticipated and/or obvious are incorporated by reference.

The additional element "after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks" does not distinguish the claim from the prior art.

The references disclosing the dosing regimens for the VEGF Trap-Eye Phase 2 DME clinical trial disclosed that one of the dosing regimens being used was 2 mg monthly. (*See, e.g.*,

9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012). In addition, Regeneron has stated to the U.S.P.T.O. that "at the time of the invention" monthly administration of anti-VEGF therapy for angiogenic eye disorders was the "well-accepted standard of care," further underscoring the obviousness and lack of novelty of the claimed subject matter. (*See, e.g.*, 338 patent PH, 9-11-2015 Applicant Remarks at 6-9; 069 patent PH, 1-30-2017 Applicants Remarks at 5-8; 681 patent PH, 6-25-2018 Applicant Remarks at 6-11).

Accordingly, for at least these additional reasons, claim 12 of the 601 patent is anticipated and rendered obvious by each of the references and combinations set forth above for claim 10.

11. Claim 15.

The language of claim 15 of the 601 patent is set forth above.

Claim 15 of the 601 patent depends from claim 10 and thus incorporates the elements of claim 10. The reasons why claim 10 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score" is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Since the method steps are "performed in the same way regardless whether or not the patient experiences" a clinical change, the additional element of claim 15 is non-limiting. *Bristol-Myers*, 246 F.3d at 1375; *see also Prometheus*, 2013 WL 5333033, at *5-6 (phrase that merely "expresses the intended result of a process step positively recited" is non-limiting); *Minton*, 336 F.3d at 1381.[21]

[21] Mylan incorporates fully herein the arguments set forth in its claim construction briefs, served on November 29, 2022 and December 15, 2022.

Separately, this element represents nothing more than the natural result flowing from the prior art method of administration disclosed in the anticipatory references described above for claim 10, using a measure (BCVA) which had already been disclosed in the prior art as a clinical trial measurement and/or endpoint, including in the VEGF Trap-Eye AMD, RVO, and DME clinical trials. In addition, the prior art disclosures of the results of the Phase 1 and Phase 2 DME trials provide further support for the inherency of the subject matter of claim 15. For example, patients receiving a single intravitreal dose of 4 mg of VEGF Trap-Eye in the Phase 1 trial exhibited a mean increase in ETDRS BCVA. (*See, e.g.*, Do 2007; Do 2009). In addition, patients in the Phase 2 DME clinical trial treated with monthly, PRN, or every-other-month dosing exhibited mean increases in ETDRS BCVA. (*See, e.g.*, 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012).

To the extent this element is limiting, the element is expressly set forth in the prior art. For example, references disclosing the results of the VEGF Trap-Eye Phase 3 VISTA and VIVID trials disclose that patients in those trials gained at least 15 letters of ETDRS BCVA score. (*See, e.g.*, Korobelnik 2014; Brown 2015; Keating 2015; Heier 2016; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01331681 (US VIVID); NCT01363440 (US VISTA)).

Accordingly, claim 15 is anticipated by references disclosing the regimen and results of the VEGF Trap-Eye VIVID and VISTA clinical trials.

Further, a person of ordinary skill in the art would have understood from the prior art that the BCVA letter measure is an obvious choice to use when assessing clinical trials relating to anti-VEGF therapies in treating angiogenic eye disorders. (*See, e.g.*, Do 2007; Do 2009; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Chun 2006;

Nguyen 2006b; Campochiaro 2006; Nguyen 2009b; Querques 2009; Hansen 2010). Further a person of ordinary skill in the art would have had a reasonable expectation of success at meeting the BCVA criteria set forth in claim 15 when using the recited regimen, at least in light of the positive Phase 1 and Phase 2 results discussed above and reported in the prior art. (*See, e.g.*, Do 2007; Do 2009; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012). Further, the results from the VIVID and VISTA trials provide further evidence of the reasonable expectation of success that a person of ordinary skill in the art would have had in meeting the criteria set forth in claim 15 when using the recited regimen. (*See, e.g.*, Korobelnik 2014; Brown 2015; Keating 2015; Heier 2016; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01512966 (Japanese VIVID); NCT01331681 (US VIVID); NCT01363440 (US VISTA)).

Accordingly, claim 15 is obvious in view of the prior art combinations presented above for claim 10, either alone, or in further combination with one or more references disclosing patients gaining at least 15 letters of BCVA score, and/or one or more references disclosing the positive results reported in clinical trials assessing VEGF Trap-Eye in treating DME.

Accordingly, for at least these additional reasons, claim 15 of the 601 patent is anticipated and rendered obvious by each of the references and combinations set forth above for claim 10.

12. Claim 16.

The language of claim 16 of the 601 patent is set forth above.

Claim 16 of the 601 patent depends from claim 15 and thus incorporates the elements of claim 15. The reasons why claim 15 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" does not distinguish the claim from the prior art.

A person of ordinary skill in the art would have known, from their background knowledge, and from the prior art cited above, that BCVA scores were assessed using an ETDRS letter score. (*See, e.g.*, Do 2007; Do 2009; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Chun 2006; Nguyen 2006b; Campochiaro 2006; Nguyen 2009b; Querques 2009; Hansen 2010).

Accordingly, for at least these additional reasons, claim 16 of the 601 patent is anticipated and rendered obvious by each of the references and combinations set forth above for claim 10.

13. Claim 17.

The language of claim 17 of the 601 patent is set forth above.

Claim 17 of the 601 patent depends from claim 10 and thus incorporates the elements of claim 10. The reasons why claim 10 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection" does not distinguish the claim from the prior art. For example, the claimed exclusion criteria elements constitute mental steps and/or written material, and thus are not entitled to patentable weight. *See, e.g.*, *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01226, Paper 22, at 11-15 (PTAB Jan. 11, 2023); *id.* at 15 ("[T]he information provided by the exclusionary criteria can be considered to be optional information, in that there is no direction to the practitioner to perform, or not perform, any specific step based upon the provided criteria. Thus, the exclusionary criteria are strictly informational, without requiring the practitioner to act, or refrain from acting, in a specified manner, and not functionally related to the practice of the claimed method.").

To the extent the exclusion criteria claim element is entitled to patentable weight, claim 17 of the 601 patent is anticipated, either expressly or inherently, by at least the references that disclose the dosing regimen used in the VEGF Trap-Eye Phase 2 DME clinical trial. For example,

exclusion criteria for the Phase 2 DME clinical trial included ocular inflammation, and infectious blepharitis, keratitis, scleritis, or conjunctivitis. (*See, e.g.*, Do 2011). These exclusion criteria were necessarily and inevitably applied in connection with practicing the publicly disclosed, Phase 2 DME dosing regimen. The application of the claimed exclusion criteria thus was a natural result flowing from the application of the Phase 2 DME trial study protocol. As a result, in addition to those references that expressly disclose the Phase 2 DME exclusion criteria, each of the references disclosing the Phase 2 DME clinical trial inherently disclosed the subject matter of claim 17. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012).

Claim 17 of the 601 patent is anticipated either expressly or inherently, by at least the references disclosing the dosing regimen used in the VISTA and VIVID Phase 3 clinical trials. For example, the Eylea® DME/DR Medical Review shows that a list of non-confidential exclusion criteria were necessarily and inevitably applied in connection with practicing the claimed, and publicly disclosed, VISTA and VIVID dosing regimens. (Eylea® DME/DR Medical Review at 84-86, 91). The application of the claimed exclusion criteria thus was a natural result flowing from the application of the VISTA and/or VIVID clinical trial study protocol. As a result, each of the references disclosing the VISTA and/or VIVID clinical trial anticipates the subject matter of claim 17. (*See, e.g.*, Korobelnik 2014; Brown 2015; Keating 2015; Heier 2016; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01512966 (Japanese VIVID); NCT01331681 (US VIVID); NCT01363440 (US VISTA)).

Claim 17 of the 601 patent is obvious in view of the VEGF Trap-Eye Phase 2 DME references and combinations presented above, further in combination with references disclosing

the exclusion criteria employed in the VEGF Trap-Eye AMD VIEW Phase 3 clinical trials and/or Lucentis ANCHOR and MARINA trials. For the reasons discussed above, that discussion incorporated herein, each reference disclosing the Phase 2 DME regimen discloses expressly or inherently each and every claim element, and as discussed above, the recited exclusion criteria are not entitled to patentable weight and/or are inherent aspects of the Phase 2 study protocols. In addition to not being entitled to patentable weight, the claimed exclusion criteria also were disclosed in the prior art. For example, the VEGF Trap-Eye VIEW AMD clinical trials employed the claimed exclusion criteria. (Eylea® Medical Review at 112-114; Heier 2012 at Appendix 2). In addition, the Lucentis DME clinical trials included the claimed exclusion criteria. (*See, e.g.*, Chun 2006). Further, the Lucentis AMD MARINA and ANCHOR trials, involving monthly intravitreal administration of the VEGF antagonist Lucentis® (ranibizumab), employed exclusion criteria that included, among other relevant criteria, active intraocular inflammation in the study eye; history of idiopathic or autoimmune-associated uveitis in either eye; and infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye. (*See, e.g.*, Lucentis Medical Review; Rosenfeld 2006; Brown 2006; NCT 836; NCT 594). The Lucentis Medical Review further disclosed that dose-holding criteria included intraocular inflammation and local or systemic infection, including infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye. (Lucentis Medical Review at 66-67).

In addition, the pegaptanib trials involving intravitreal administration in treating AMD employed exclusion criteria that included, among other relevant criteria, choroiditis, and acute ocular or periocular infection. (*See, e.g.*, Macugen Medical Review; Macugen Study Group; Gragoudas 2004).

Also, it was known among those of ordinary skill in the art that intravitreal administration could be associated with serious side effects if proper, aseptic technique is not adhered to. Consequently, persons of ordinary skill in the art recognized, and reported on, the need to avoid injecting eyes that are infected or show signs of infection (i.e., inflammation). (*See, e.g.*, Aiello 2004; Jager 2004; Donahue; De Caro; Heimann; CATT Study; Regillo 2008; MACTEL Study; Jaffe; Lucentis PI 2006; Retinal Physician II; Dixon).

Accordingly, it would have been obvious to adopt such exclusion criteria for the VEGF Trap-Eye DME clinical trials.

For at least these reasons, claim 17 of the 601 patent is obvious in view of at least each of the references, and combinations cited above further in combination with one or more of the references cited above disclosing the exclusion criteria or precautions used in the context of intravitreal administration, including in the intravitreal administration of VEGF antagonists.

Accordingly, claim 17 of the 601 patent is invalid under 35 U.S.C. §§ 102 and 103 for at least these additional reasons.

14. Claim 18.

The language of claim 18 of the 601 patent is set forth above.

The dosing regimen disclosed in claim 18 is identical to that claimed in claim 10. Thus, the reasons why claim 10 is anticipated and/or obvious are incorporated by reference.

The fact that claim 18 is drawn to a method for treating DR rather than a method for treating DME does not distinguish the claim from the prior art presented above.

For example, it was widely understood among those of ordinary skill in the art that DME was a common complication or manifestation of DR. (*See, e.g.*, Do 2009; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release Do 2011; Do 2012; Korobelnik 2014; Brown 2015; Wykoff 2017a; Wykoff 2017b; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; Chun

2006; Nguyen 2006b; Nguyen 2009b; Querques 2009; Schwartz 2009). As a result, a person of ordinary skill in the art would have understood that when one is treating DME, one is treating one of the complications or manifestations of DR, and thus is treating DR. This is evident based on the same criteria being used in the 601 patent claims to assess both DME and DR. (*Compare, e.g.*, 601 patent, claims 13 and 15, *with* claims 22 and 23). This also is evident from the FDA approvals of the DME and DR indications for aflibercept, which were based on the same VIVID and VISTA clinical trials. (*See, e.g.*, Eylea Label 3/2015; Eylea Label 5/2016). As a result, the treatment of DR is expressly, or at least inherently, disclosed in each of the anticipation grounds presented for claim 10, and is obvious in view of each of the combinations presented above for claim 10.

Accordingly, claim 18 of the 601 patent is invalid under 35 U.S.C. §§ 102 and 103 for at least these additional reasons.

15. Claim 19.

The language of claim 19 of the 601 patent is set forth above.

Claim 19 of the 601 patent depends from claim 18 and thus incorporates the elements of claim 18. The reasons why claim 18 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly" does not distinguish the claim from the prior art.

A person of ordinary skill in the art would have understood approximately every 4 weeks to be equivalent to approximately 28 days or approximately monthly, and, moreover, would often use the terms interchangeably in the prior art. (*See, e.g.*, 9-14-2009 Regeneron Press Release at 1 ("2 mg every eight weeks after three monthly loading doses"); 2-18-2010 Regeneron Press Release at 1 ("2 mg every other month, following 3 monthly injections"); Dixon at 1576 ("Two groups received monthly doses of either 0.5 or 2.0 mg for 12 weeks (at weeks 0, 4, 8 and 12)").

Accordingly, for at least these additional reasons, claim 19 of the 601 patent is anticipated and rendered obvious by each of the references and combinations set forth above for claims 10 and 18.

16. Claim 21.

The language of claim 21 of the 601 patent is set forth above.

Claim 21 of the 601 patent depends from claim 18 and thus incorporates the elements of claim 18. The reasons why claim 18 is anticipated and/or obvious are incorporated by reference.

The additional element "after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks" does not distinguish the claim from the prior art.

The references disclosing the dosing regimens for the VEGF Trap-Eye Phase 2 DME clinical trial disclosed that one of the dosing regimens being used was 2 mg monthly. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012). In addition, Regeneron has stated to the U.S.P.T.O. that "at the time of the invention" monthly administration of anti-VEGF therapy for angiogenic eye disorders was the "well-accepted standard of care," further underscoring the obviousness and lack of novelty of the claimed subject matter. (*See, e.g.*, 338 patent PH, 9-11-2015 Applicant Remarks at 6-9; 069 patent PH, 1-30-2017 Applicants Remarks at 5-8; 681 patent PH, 6-25-2018 Applicant Remarks at 6-11).

Accordingly, for at least these additional reasons, claim 21 of the 601 patent is anticipated and rendered obvious by each of the references and combinations set forth above for claims 10 and 18.

17. Claim 23.

The language of claim 23 of the 601 patent is set forth above.

Claim 23 of the 601 patent depends from claim 18 and thus incorporates the elements of claim 18. The reasons why claim 18 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score" is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Since the method steps are "performed in the same way regardless whether or not the patient experiences" a clinical change, the additional element of claim 23 is non-limiting. *Bristol-Myers*, 246 F.3d at 1375; *see also Prometheus*, 2013 WL 5333033, at *5-6 (phrase that merely "expresses the intended result of a process step positively recited" is non-limiting); *Minton*, 336 F.3d at 1381.[22]

Separately, this element represents nothing more than the natural result flowing from the prior art method of administration disclosed in the anticipatory references described above for claims 10 and 18, using a measure (BCVA) which had already been disclosed in the prior art as a clinical trial measurement and/or endpoint, including in the VEGF Trap-Eye AMD, RVO, and DME clinical trials. In addition, the prior art disclosures of the results of the Phase 1 and Phase 2 DME trials provide further support for the inherency of the subject matter of claim 23. For example, patients receiving a single intravitreal dose of 4 mg of VEGF Trap-Eye in the Phase 1 trial exhibited a mean increase in ETDRS BCVA. (*See, e.g.*, Do 2007; Do 2009). In addition, patients in the Phase 2 DME clinical trial treated with monthly, PRN, or every-other-month dosing exhibited mean increases in ETDRS BCVA. (*See, e.g.*, 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012).

[22] Mylan incorporates fully herein the arguments set forth in its claim construction briefs, served on November 29, 2022 and December 15, 2022.

To the extent this element is limiting, the element is expressly set forth in the prior art. For example, references disclosing the results of the VEGF Trap-Eye Phase 3 VISTA and VIVID trials disclose that patients in those trials gained at least 15 letters of ETDRS BCVA score. (*See, e.g.*, Korobelnik 2014; Brown 2015; Keating 2015; Heier 2016; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01331681 (US VIVID); NCT01363440 (US VISTA)).

Accordingly, claim 23 is anticipated by references disclosing the regimen and results of the VEGF Trap-Eye VIVID and VISTA clinical trials.

Accordingly, claim 23 is anticipated, by at least each of the anticipatory references identified above with respect to claims 10 and 18, as evidenced by the references disclosing the results of clinical trials employing the prior art regimens.

Further, a person of ordinary skill in the art would have understood from the prior art that the BCVA letter measure is an obvious choice to use when assessing patients in clinical trials relating to anti-VEGF therapies in treating angiogenic eye disorders. (*See, e.g.*, Do 2007; Do 2009; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Chun 2006; Nguyen 2006b; Campochiaro 2006; Nguyen 2009b; Querques 2009; Hansen 2010). Further a person of ordinary skill in the art would have had a reasonable expectation of success at meeting the BCVA criteria set forth in claim 23 when using the recited regimen, at least in light of the positive Phase 1 and Phase 2 results discussed above and reported in the prior art. (*See, e.g.*, Do 2007; Do 2009; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012). Further, the results from the VIVID and VISTA trials provide further evidence of the reasonable expectation of success that a person of ordinary skill in the art would have had in meeting the criteria set forth in claim 23 when using the recited regimen. (*See, e.g.*,

Korobelnik 2014; Brown 2015; Keating 2015; Heier 2016; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01512966 (Japanese VIVID); NCT01331681 (US VIVID); NCT01363440 (US VISTA)).

Accordingly, claim 23 is obvious in view of the prior art combinations presented above for claims 10 and 18, either alone, or in further combination with one or more references disclosing patients gaining at least 15 letters of BCVA score, and/or one or more references disclosing the positive results reported in clinical trials assessing VEGF Trap-Eye in treating DME.

Accordingly, for at least these additional reasons, claim 23 of the 601 patent is anticipated and rendered obvious by each of the references and combinations set forth above for claims 10 and 18.

18. Claim 24.

The language of claim 24 of the 601 patent is set forth above.

Claim 24 of the 601 patent depends from claim 23 and thus incorporates the elements of claim 23. The reasons why claim 23 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" does not distinguish the claim from the prior art.

A person of ordinary skill in the art would have known, from their background knowledge, and from the prior art cited above, that BCVA scores were assessed using an ETDRS letter score. (*See, e.g.*, Do 2007; Do 2009; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Chun 2006; Nguyen 2006b; Campochiaro 2006; Nguyen 2009b; Querques 2009; Hansen 2010).

Accordingly, for at least these additional reasons, claim 23 of the 601 patent is anticipated and rendered obvious by each of the references and combinations set forth above for claims 10 and 18.

19. Claim 25.

The language of claim 25 of the 601 patent is set forth above.

Claim 25 of the 601 patent depends from claim 18 and thus incorporates the elements of claim 18. The reasons why claim 18 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection" does not distinguish the claim from the prior art. For example, the claimed exclusion criteria elements constitute mental steps and/or written material, and thus are not entitled to patentable weight. *See, e.g.*, *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01226, Paper 22, at 11-15 (PTAB Jan. 11, 2023); *id.* at 15 ("[T]he information provided by the exclusionary criteria can be considered to be optional information, in that there is no direction to the practitioner to perform, or not perform, any specific step based upon the provided criteria. Thus, the exclusionary criteria are strictly informational, without requiring the practitioner to act, or refrain from acting, in a specified manner, and not functionally related to the practice of the claimed method.").

To the extent that the exclusion criteria element is entitled to patentable weight, claim 25 of the 601 patent is anticipated, either expressly or inherently, by at least the references that disclose the dosing regimen used in the VEGF Trap-Eye Phase 2 DME clinical trial. For example, exclusion criteria for the Phase 2 DME clinical trial included ocular inflammation, and infectious blepharitis, keratitis, scleritis, or conjunctivitis. (*See, e.g.*, Do 2011). These exclusion criteria were necessarily and inevitably applied in connection with practicing the publicly disclosed, Phase 2 DME dosing regimen. The application of the claimed exclusion criteria thus was a natural result

flowing from the application of the Phase 2 DME trial study protocol. As a result, in addition to those references that expressly disclose the Phase 2 DME exclusion criteria, each of the references disclosing the Phase 2 DME clinical trial inherently disclosed the subject matter of claim 25. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012).

Claim 25 of the 601 patent is anticipated either expressly or inherently by at least the references disclosing the dosing regimen used in the VISTA and VIVID Phase 3 clinical trials. For example, the Eylea® DME/DR Medical Review shows that a list of non-confidential exclusion criteria were necessarily and inevitably applied in connection with practicing the claimed, and publicly disclosed, VISTA and VIVID dosing regimens. (Eylea® DME/DR Medical Review at 84-86, 91). The application of the claimed exclusion criteria thus was a natural result flowing from the application of the VISTA and/or VIVID clinical trial study protocol. As a result, each of the references disclosing the VISTA and/or VIVID clinical trial anticipate the subject matter of claim 25. (*See, e.g.*, Korobelnik 2014; Brown 2015; Keating 2015; Heier 2016; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01512966 (Japanese VIVID); NCT01331681 (US VIVID); NCT01363440 (US VISTA)).

Claim 25 of the 601 patent is obvious in view of the VEGF Trap-Eye Phase 2 DME references and combinations presented above, further in combination with references disclosing the exclusion criteria employed in the VEGF Trap-Eye AMD VIEW Phase 3 clinical trials and/or Lucentis clinical trials and/or general recommendations and precautions associated with intravitreal injections. For the reasons discussed above, that discussion incorporated herein, each reference disclosing the Phase 2 DME regimen discloses expressly or inherently each and every

claim element, and as discussed above, the recited exclusion criteria are not entitled to patentable weight and/or are inherent aspects of the Phase 2 study protocols. In addition to not being entitled to patentable weight, the claimed exclusion criteria also were disclosed in the prior art. For example, the VEGF Trap-Eye VIEW AMD clinical trials employed the claimed exclusion criteria. (Eylea® Medical Review at 112-114; Heier 2012 at Appendix 2). In addition, the Lucentis DME clinical trials included the claimed exclusion criteria. (*See, e.g.*, Chun 2006). Further, the Lucentis AMD MARINA and ANCHOR trials, involving monthly intravitreal administration of the VEGF antagonist Lucentis® (ranibizumab), employed exclusion criteria that included, among other relevant criteria, active intraocular inflammation in the study eye; history of idiopathic or autoimmune-associated uveitis in either eye; and infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye. (*See, e.g.*, Lucentis Medical Review; Rosenfeld 2006; Brown 2006; NCT 836; NCT 594). The Lucentis Medical Review further disclosed that dose-holding criteria included intraocular inflammation and local or systemic infection, including infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye. (Lucentis Medical Review at 66-67).

In addition, the pegaptanib trials involving intravitreal administration in treating AMD employed exclusion criteria that included, among other relevant criteria, choroiditis, and acute ocular or periocular infection. (*See, e.g.*, Macugen Medical Review; Macugen Study Group; Gragoudas 2004).

Also, it was known among those of ordinary skill in the art that intravitreal administration could be associated with serious side effects if proper, aseptic technique is not adhered to. Consequently, persons of ordinary skill in the art recognized, and reported on, the need to avoid injecting eyes that are infected or show signs of infection (i.e., inflammation). (*See, e.g.*, Aiello

2004; Jager 2004; Donahue; De Caro; Heimann; CATT Study; Regillo 2008; MACTEL Study; Jaffe; Lucentis PI 2006; Retinal Physician II; Dixon).

Accordingly, it would have been obvious to adopt such exclusion criteria for the VEGF Trap-Eye DME clinical trials.

For at least these reasons, claim 25 of the 601 patent is obvious in view of at least each of the references, and combinations cited above further in combination with one or more of the references cited above disclosing the exclusion criteria or precautions used in the context of intravitreal administration, including in the intravitreal administration of VEGF antagonists.

Accordingly, claim 25 of the 601 patent is invalid under 35 U.S.C. §§ 102 and 103 for at least these additional reasons.

20. Claim 26.

The language of claim 26 of the 601 patent is set forth above.

The dosing regimen disclosed in claim 26 is identical to that claimed in claims 10 and 18. Thus, the reasons why claims 10 and 18 are anticipated and/or obvious are incorporated by reference.

The fact that claim 26 is drawn to a method for treating DR in a patient with DME rather than a method for treating DME does not distinguish the claim from the prior art presented above.

For example, it was widely understood among those of ordinary skill in the art that DME was a common complication or manifestation of DR. (*See, e.g.*, Do 2009; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Korobelnik 2014; Brown 2015; Wykoff 2017a; Wykoff 2017b; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; Chun 2006; Nguyen 2006b; Nguyen 2009b; Querques 2009; Schwartz 2009). As a result, a person of ordinary skill in the art would have understood that when one is treating DME, one is treating one of the complications or manifestations of DR, and thus is treating DR in a patient with DME. This

is evident based on the same criteria being used in the 601 patent claims to assess both DME and DR. (*Compare, e.g.*, 601 patent, claims 13 and 15, *with* claims 22 and 23). This also is evident from the FDA approvals of the DME and DR indications for aflibercept, which were based on the same VIVID and VISTA clinical trials. (*See, e.g.*, Eylea Label 3/2015; Eylea Label 5/2016). As a result, the treatment of DR in a patient with DME is expressly, or at least inherently, disclosed in each of the anticipation grounds presented for claims 10 and 18, and is obvious in view of each of the combinations presented above for claims 10 and 18.

Accordingly, claim 26 of the 601 patent is invalid under 35 U.S.C. §§ 102 and 103 for at least these reasons.

21. Claim 27.

The language of claim 27 of the 601 patent is set forth above.

Claim 27 of the 601 patent depends from claim 26 and thus incorporates the elements of claim 26. The reasons why claim 26 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein approximately every 4 weeks comprises approximately every 28 days or approximately monthly" does not distinguish the claim from the prior art.

A person of ordinary skill in the art would have understood approximately every 4 weeks to be equivalent to approximately 28 days or approximately monthly, and, moreover, would often use the terms interchangeably in the prior art. (*See, e.g.*, 9-14-2009 Regeneron Press Release at 1 ("2 mg every eight weeks after three monthly loading doses"); 2-18-2010 Regeneron Press Release at 1 ("2 mg every other month, following 3 monthly injections"); Dixon at 1576 ("Two groups received monthly doses of either 0.5 or 2.0 mg for 12 weeks (at weeks 0, 4, 8 and 12)").

Accordingly, for at least these additional reasons, claim 27 of the 601 patent is anticipated and rendered obvious by each of the references and combinations set forth above for claims 10, 18, and 26.

22. Claim 28.

The language of claim 28 of the 601 patent is set forth above.

Claim 28 of the 601 patent depends from claim 26 and thus incorporates the elements of claim 26. The reasons why claim 26 is anticipated and/or obvious are incorporated by reference.

The additional element "after 20 weeks, administering, via intravitreal injection, 2 mg of aflibercept once every 4 weeks" does not distinguish the claim from the prior art.

The references disclosing the dosing regimens for the VEGF Trap-Eye Phase 2 DME clinical trial disclosed that one of the dosing regimens being used was 2 mg monthly. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012). In addition, Regeneron has stated to the U.S.P.T.O. that "at the time of the invention" monthly administration of anti-VEGF therapy for angiogenic eye disorders was the "well-accepted standard of care," further underscoring the obviousness and lack of novelty of the claimed subject matter. (*See, e.g.*, 338 patent PH, 9-11-2015 Applicant Remarks at 6-9; 069 patent PH, 1-30-2017 Applicants Remarks at 5-8; 681 patent PH, 6-25-2018 Applicant Remarks at 6-11).

Accordingly, for at least these additional reasons, claim 28 of the 601 patent is anticipated and rendered obvious by each of the references and combinations set forth above for claims 10, 18, and 26.

23. Claim 31.

The language of claim 31 of the 601 patent is set forth above.

Claim 31 of the 601 patent depends from claim 26 and thus incorporates the elements of claim 26. The reasons why claim 26 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein the patient gains at least 15 letters of Best Corrected Visual Acuity (BCVA) score" is a non-limiting statement of intended result. *See Bristol-Myers*,

246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Since the method steps are "performed in the same way regardless whether or not the patient experiences" a clinical change, the additional element of claim 31 is non-limiting. *Bristol-Myers*, 246 F.3d at 1375; *see also Prometheus*, 2013 WL 5333033, at *5-6 (phrase that merely "expresses the intended result of a process step positively recited" is non-limiting); *Minton*, 336 F.3d at 1381.[23]

Separately, this element represents nothing more than the natural result flowing from the prior art method of administration disclosed in the anticipatory references described above for claims 10 and 18, using a measure (BCVA) which had already been disclosed in the prior art as a clinical trial measurement and/or endpoint, including in the VEGF Trap-Eye AMD, RVO, and DME clinical trials. In addition, the prior art disclosures of the results of the Phase 1 and Phase 2 DME trials provide further support for the inherency of the subject matter of claim 23. For example, patients receiving a single intravitreal dose of 4 mg of VEGF Trap-Eye in the Phase 1 trial exhibited a mean increase in ETDRS BCVA. (*See, e.g.*, Do 2007; Do 2009). In addition, patients in the Phase 2 DME clinical trial treated with monthly, PRN, or every-other-month dosing exhibited mean increases in ETDRS BCVA. (*See, e.g.*, 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012).

To the extent this element is limiting, the element is expressly set forth in the prior art. For example, references disclosing the results of the VEGF Trap-Eye Phase 3 VISTA and VIVID trials disclose that patients in those trials gained at least 15 letters of ETDRS BCVA score. (*See, e.g.*, Korobelnik 2014; Brown 2015; Keating 2015; Heier 2016; Ziemssen 2016; Wykoff 2017a;

[23] Mylan incorporates fully herein the arguments set forth in its claim construction briefs, served on November 29, 2022 and December 15, 2022.

Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01331681 (US VIVID); NCT01363440 (US VISTA)).

Accordingly, claim 31 is anticipated, by at least each of the anticipatory references identified above with respect to claims 10, 18, and 26, as evidenced by the references disclosing the results of clinical trials employing the prior art regimens.

Further, a person of ordinary skill in the art would have understood from the prior art that the BCVA letter measure is an obvious choice to use when assessing clinical trials relating to anti-VEGF therapies in treating angiogenic eye disorders. (*See, e.g.*, Do 2007; Do 2009; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Chun 2006; Nguyen 2006b; Campochiaro 2006; Nguyen 2009b; Querques 2009; Hansen 2010). Further a person of ordinary skill in the art would have had a reasonable expectation of success at meeting the BCVA criteria set forth in claim 31 when using the recited regimen, at least in light of the positive Phase 1 and Phase 2 results discussed above and reported in the prior art. (*See, e.g.*, Do 2007; Do 2009; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012). Further, the results from the VIVID and VISTA trials provide further evidence of the reasonable expectation of success that a person of ordinary skill in the art would have had in meeting the criteria set forth in claim 31 when using the recited regimen. (*See, e.g.*, Korobelnik 2014; Brown 2015; Keating 2015; Heier 2016; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01512966 (Japanese VIVID); NCT01331681 (US VIVID); NCT01363440 (US VISTA)).

Accordingly, claim 31 is obvious in view of the prior art combinations presented above for claims 10, 18, and 26, either alone, or in further combination with one or more references

disclosing patients gaining at least 15 letters of BCVA score, and/or one or more references disclosing the positive results reported in clinical trials assessing VEGF Trap-Eye in treating DME.

Accordingly, for at least these additional reasons, claim 31 of the 601 patent is anticipated and rendered obvious by each of the references and combinations set forth above for claims 10, 18, and 26.

24. Claim 32.

The language of claim 32 of the 601 patent is set forth above.

Claim 32 of the 601 patent depends from claim 31 and thus incorporates the elements of claim 31. The reasons why claim 31 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein Best Corrected Visual Acuity (BCVA) is according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" does not distinguish the claim from the prior art.

A person of ordinary skill in the art would have known, from their background knowledge, and from the prior art cited above, that BCVA scores were assessed using an ETDRS letter score. (*See, e.g.*, Do 2007; Do 2009; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Chun 2006; Nguyen 2006b; Campochiaro 2006; Nguyen 2009b; Querques 2009; Hansen 2010).

Accordingly, for at least these additional reasons, claim 32 of the 601 patent is anticipated and rendered obvious by each of the references and combinations set forth above for claims 10, 18, and 26.

25. Claim 33.

The language of claim 33 of the 601 patent is set forth above.

Claim 33 of the 601 patent depends from claim 26 and thus incorporates the elements of claim 26. The reasons why claim 26 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection" does not distinguish the claim from the prior art. For example, the claimed exclusion criteria elements constitute mental steps and/or written material, and thus are not entitled to patentable weight. *See, e.g.*, *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01226, Paper 22, at 11-15 (PTAB Jan. 11, 2023); *id.* at 15 ("[T]he information provided by the exclusionary criteria can be considered to be optional information, in that there is no direction to the practitioner to perform, or not perform, any specific step based upon the provided criteria. Thus, the exclusionary criteria are strictly informational, without requiring the practitioner to act, or refrain from acting, in a specified manner, and not functionally related to the practice of the claimed method.").

To the extent the exclusion criteria element is entitled to patentable weight, claim 33 of the 601 patent is anticipated, either expressly or inherently, by at least the references that disclose the dosing regimen used in the VEGF Trap-Eye Phase 2 DME clinical trial. For example, exclusion criteria for the Phase 2 DME clinical trial included ocular inflammation, and infectious blepharitis, keratitis, scleritis, or conjunctivitis. (*See, e.g.*, Do 2011). These exclusion criteria were necessarily and inevitably applied in connection with practicing the publicly disclosed, Phase 2 DME dosing regimen. The application of the claimed exclusion criteria thus was a natural result flowing from the application of the Phase 2 DME trial study protocol. As a result, in addition to those references that expressly disclose the Phase 2 DME exclusion criteria, each of the references disclosing the Phase 2 DME clinical trial inherently disclosed the subject matter of claim 33. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012).

Claim 33 of the 601 patent is anticipated either expressly or inherently, by at least the references disclosing the dosing regimen used in the VISTA and VIVID Phase 3 clinical trials. For example, the Eylea® DME/DR Medical Review shows that a list of non-confidential exclusion criteria were necessarily and inevitably applied in connection with practicing the claimed, and publicly disclosed, VISTA and VIVID dosing regimens. (Eylea® DME/DR Medical Review at 84-86, 91). The application of the claimed exclusion criteria thus was a natural result flowing from the application of the VISTA and/or VIVID clinical trial study protocol. As a result, each of the references disclosing the VISTA and/or VIVID clinical trial anticipate the subject matter of claim 33. (*See, e.g.*, Korobelnik 2014; Brown 2015; Keating 2015; Heier 2016; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01512966 (Japanese VIVID); NCT01331681 (US VIVID); NCT01363440 (US VISTA)).

Claim 33 of the 601 patent is obvious in view of the VEGF Trap-Eye Phase 2 DME references and combinations presented above, further in combination with references disclosing the exclusion criteria employed in the VEGF Trap-Eye AMD VIEW Phase 3 clinical trials and/or Lucentis clinical trials and/or general recommendations and precautions associated with intravitreal injections. For the reasons discussed above, that discussion incorporated herein, each reference disclosing the Phase 2 DME regimen discloses expressly or inherently each and every claim element, and as discussed above, the recited exclusion criteria are not entitled to patentable weight and/or are inherent aspects of the Phase 2 study protocols. In addition to not being entitled to patentable weight, the claimed exclusion criteria also were disclosed in the prior art. For example, the VEGF Trap-Eye VIEW AMD clinical trials employed the claimed exclusion criteria. (Eylea® Medical Review at 112-114; Heier 2012 at Appendix 2). In addition, the Lucentis DME

clinical trials included the claimed exclusion criteria. (*See, e.g.*, Chun 2006). Further, the Lucentis AMD MARINA and ANCHOR trials, involving monthly intravitreal administration of the VEGF antagonist Lucentis® (ranibizumab), employed exclusion criteria that included, among other relevant criteria, active intraocular inflammation in the study eye; history of idiopathic or autoimmune-associated uveitis in either eye; and infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye. (*See, e.g.*, Lucentis Medical Review; Rosenfeld 2006; Brown 2006; NCT 836; NCT 594). The Lucentis Medical Review further disclosed that dose-holding criteria included intraocular inflammation and local or systemic infection, including infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye. (Lucentis Medical Review at 66-67).

In addition, the pegaptanib trials involving intravitreal administration in treating AMD employed exclusion criteria that included, among other relevant criteria, choroiditis, and acute ocular or periocular infection. (*See, e.g.*, Macugen Medical Review; Macugen Study Group; Gragoudas 2004).

Also, it was known among those of ordinary skill in the art that intravitreal administration could be associated with serious side effects if proper, aseptic technique is not adhered to. Consequently, persons of ordinary skill in the art recognized, and reported on, the need to avoid injecting eyes that are infected or show signs of infection (i.e., inflammation). (*See, e.g.*, Aiello 2004; Jager 2004; Donahue; De Caro; Heimann; CATT Study; Regillo 2008; MACTEL Study; Jaffe; Lucentis PI 2006; Retinal Physician II; Dixon).

Accordingly, it would have been obvious to adopt such exclusion criteria for the VEGF Trap-Eye DME clinical trials.

For at least these reasons, claim 33 of the 601 patent is obvious in view of at least each of the references, and combinations cited above further in combination with one or more of the references cited above disclosing the exclusion criteria or precautions used in the context of intravitreal administration, including in the intravitreal administration of VEGF antagonists.

Accordingly, claim 33 of the 601 patent is invalid under 35 U.S.C. §§ 102 and 103 for at least these additional reasons.

26. Claim 34.

a. Anticipation by the 747 Patent.[24]

The language of claim 34 of the 601 patent is set forth above.

Claim 34 of the 601 patent is anticipated by Regeneron's patents disclosing dosing regimens for the treatment of eye disorders. For example, the 747 patent discloses a method of treating eye disorders, including macular degeneration and DR. The 747 patent further discloses treatment with the fusion polypeptide of SEQ ID NO:6 (VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). The 747 patent further discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 1-6 months apart, which a person of ordinary skill in the art would have immediately envisaged could encompass, e.g., one or more secondary doses administered 4 weeks after the immediately preceding dose, followed by one or more tertiary doses administered 8 weeks after the immediately preceding dose. (*See, e.g.*, 747 patent; 049 patent; 799 patent).

[24] The 799 patent and 049 patent are related to the 747 patent and contain the same disclosures. Claim 34 is also anticipated by the 799 patent and 049 patent.

b. Anticipation by the VIEW References.

Claim 34 of the 601 patent is anticipated by at least each of the VIEW References that disclose the dosing regimen used in the VIEW trials. For example, the VIEW References disclose a method of treating AMD, an angiogenic eye disorder, with the claimed molecule, using three monthly loading doses (i.e., "a single initial dose of VEGF antagonist followed by one or more secondary doses . . . wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose"), followed by every-8-week dosing (i.e., "one or more tertiary doses . . . wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose"). (*See, e.g.*, Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release). The claim element reciting the VEGF antagonist is found in the references' disclosures of VEGF Trap-Eye and/or aflibercept, the sequence and structure of which was known and disclosed in the prior art. (*See, e.g.*, Holash 2002; Rudge; Dixon; Adis; 9-30-2009 Regeneron 10-Q; 757 patent; 758 patent; 758 patent Petition for Patent Term Extension; 959 patent; 959 patent Petition for Patent Term Extension; Nguyen 2009a; Dix; 095 patent). As a result, each of the VIEW References, including Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron

10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release anticipates claim 34 of the 601 patent.

Further, the aflibercept dosing regimen recited in claim 34 of the 601 patent claims the same every-8-week dosing regimen claimed by an earlier patent in the same family, the 338 patent. In a Final Written Decision relating to the 338 patent, the Board determined that the Dixon reference anticipates the aflibercept dosing regimen claimed by the 338 patent and repeated in claim 34 of the 601 patent. *See* 338 FWD. Given that the Board already found the substantively identical dosing regimen is disclosed in Dixon, claim 34 of the 601 patent is likewise anticipated by Dixon for the same reasons articulated by the Board in the 338 IPR.

Claim 34 does not contain efficacy limitations.[25] To the extent that Regeneron later argues that one or more claim limitations carry efficacy limitations,[26] claim 34 of the 601 patent is inherently anticipated by at least each of the VIEW References that disclose the dosing regimen used in the VIEW trials. For example, the Phase 2 CLEAR-IT-2 data demonstrate success at treating patients with angiogenic eye disorders using even fewer doses, on average, than in the VIEW every-8-week dosing regimen, thus illustrating that any claimed therapeutic effect would have been a natural result flowing from the operation of the VIEW regimen. (*See, e.g.*, Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007

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[25] To the extent Regeneron argues that the "method for treating" preamble of claim 34 requires a "high level of efficacy" or any particular level of efficacy, Mylan relies on and incorporates the Board's findings rejecting this argument in the related 338 IPR, (*see, e.g.*, 338 FWD at 18), as well as Mylan's IPR briefing on the issue, all of which is expressly incorporated by reference herein.

[26] Mylan does not concede that any term in claim 34 carries specific efficacy limitations, and reserves the right to contest any effort to read such limitations into the claims, including, but not limited to, in connection with district court claim construction proceedings and any appeals related thereto. Mylan also incorporates herein arguments made and evidence presented by Mylan, in IPR2021-00880 and IPR2021-00881, relating to the meaning of terms in the related 338 and 069 patents.

Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-3-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). In addition, the VIEW data confirm that any claimed therapeutic effect was a natural result flowing from the operation of the VIEW regimen. (*See, e.g.*, 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release; Heier 2012). As a result, each of the references cited above disclosing the VIEW dosing regimen inherently anticipates claim 34 of the 601 patent for at least these additional reasons.

c. Anticipation by the Phase 2 DME References.

Claim 34 of the 601 patent is anticipated by at least each of the references that disclose the dosing regimen used in the Phase 2 DME trials. For example, the Phase 2 DME references disclose a method of treating DME, an angiogenic eye disorder, with the claimed molecule, using three monthly loading doses (i.e., "a single initial dose of VEGF antagonist followed by one or more secondary doses . . . wherein each secondary dose is administered 2 to 4 weeks after the immediately preceding dose"), followed by every-8-week dosing (i.e., "one or more tertiary doses . . . wherein each tertiary dose is administered at least 8 weeks after the immediately preceding dose"). (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Bayer Press Release). The claim element reciting the VEGF antagonist is found in the references' disclosures of VEGF Trap-Eye and/or aflibercept, the sequence and structure of which was known and disclosed in the prior art. As a result, each of the Phase 2 DME references, including 9-14-2009 Regeneron Press Release, 2-18-2010 Regeneron Press Release, and 12-20-2010 Bayer Press Release anticipates claim 34 of the 601 patent.

Further, claim 34 of the 601 patent is inherently anticipated by at least each of the references that disclose the dosing regimen used in the Phase 2 DME trials. For example, the Phase 2 DME data demonstrate success at treating patients with an angiogenic eye disorder (DME) using three monthly loading doses, followed by every-8-week dosing. (*See, e.g.*, 2-18-2010 Bayer Press Release; 12-20-2010 Bayer Press Release; Do 2011; Do 2012). The Phase 2 DME data thus confirm that any claimed therapeutic effect would have been a natural result flowing from the operation of the Phase 2 DME regimen. As a result, each of the references cited above disclosing the Phase 2 DME clinical trial dosing regimen inherently anticipates claim 34 of the 601 patent for at least these additional reasons.

d. Anticipation by Public Use.

Claim 34 of the 601 patent is invalid for being in public use, including in this country, or otherwise available to the public, more than one year before the filing of the 601 patent's earliest priority application. The public use of the claimed invention is evidenced by at least the VIEW and Phase 2 DME references discussed above. (*See, e.g.*, Dixon; Adis; NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 9-14-2009 Regeneron Press Release; 2-18-2010 Bayer Press Release; 12-20-2010 Bayer Press Release).

e. Obviousness over the 747 Patent.[27]

Claim 34 of the 601 patent is obvious in view of Regeneron's patents disclosing dosing regimens for the treatment of eye disorders. For example, the 747 patent discloses a method of treating eye disorders, including macular degeneration and DR. The 747 patent further discloses treatment with the fusion polypeptide of SEQ ID NO:6 (VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). The 747 patent further discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 2-8 weeks, or 1-6 months apart, which a person of ordinary skill in the art would have immediately envisaged could encompass, e.g., one or more secondary doses administered 4 weeks after the immediately preceding dose, followed by one or more tertiary doses administered 8 weeks after the immediately preceding dose. (*See, e.g.*, 747 patent; 049 patent; 799 patent). A person of ordinary skill in the art would have been motivated to refine the regimens disclosed in the above references to arrive at the claimed regimen in view of the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration. A person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed regimens. First, there are no efficacy limitations in the claims. Second, positive results from single intravitreal injections and extended dosing regimens, had been reported for VEGF Trap-Eye/aflibercept. (*See, e.g.*, Do 2007; Do 2009; Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007

[27] The 799 patent and 049 patent are related to the 747 patent and contain the same disclosures. Claim 34 is also rendered obvious by the 799 patent and 049 patent.

Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-3-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). Accordingly, claim 34 of the 601 patent is obvious in view of at least each of the 747, 049, and 799 patents, and, if necessary, in combination with one or more of the references disclosing the Phase 1 DME and Phase 1 and 2 AMD clinical trial results.

f. Obviousness over the VIEW References.

Claim 34 of the 601 patent is obvious in view of the VIEW References, either alone or in combination. For the reasons discussed above, that discussion incorporated herein, each VIEW reference discloses expressly or inherently each and every claim element. (*See, e.g.*, Dixon; Adis; NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release). The motivation to adopt the claimed dosing regimens for VEGF Trap-Eye comes from the references themselves, which persons of ordinary skill in the art would have appreciated set forth dosing regimens that allowed for dosing less frequently than monthly, as well as the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration.

Also, a person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed VIEW dosing regimens at least because of the Phase 1 and CLEAR-

IT-2 Phase 2 results, which were obtained using extended dosing regimens of VEGF Trap-Eye. (*See, e.g.*, Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-3-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q).

The recitation of the structure and sequence of the VEGF antagonist in claim 34 does not distinguish the claim from the prior art. The sequence and structure of the VEGF Trap-Eye/aflibercept molecule disclosed in each of the VIEW and CLEAR-IT-2 references above was set forth in the prior art. (*See, e.g.*, 757 patent, SEQ ID NO:16, Fig.24A-C; 758 patent, SEQ ID NO:16, Fig.24A-C; 959 patent, Fig.24A-C; 758 FH, 12/22/2011 PTE, 2, 6-7; 664 patent at 1:37-41, 2:53-55; 4:18, SEQ ID NO:7, SEQ ID NO:8; Holash 2002).

Accordingly, claim 34 of the 601 patent is obvious in view of at least each of the VIEW References cited above, and, if necessary, in combination with one or more of the references cited above disclosing the Phase 2 CLEAR-IT-2 results and/or one or more of the references cited above disclosing the VEGF Trap-Eye sequences and structure.

g. Obviousness over the Phase 2 DME References.

Claim 34 of the 601 patent is obvious in view of the references disclosing the Phase 2 DME regimen, either alone or in combination. For the reasons discussed above, that discussion incorporated herein, each Phase 2 DME reference discloses expressly or inherently each and every claim element. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Bayer Press Release; and 12-20-2010 Bayer Press Release). The motivation to adopt the claimed dosing regimens for

VEGF Trap-Eye comes from the references themselves, which persons of ordinary skill in the art would have appreciated set forth dosing regimens that allowed for dosing less frequently than monthly, as well as the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration.

Also, a person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed Phase 2 DME dosing regimens at least because of the Phase 1 DME results, which were obtained using a single intravitreal injection of VEGF Trap-Eye. (*See, e.g.*, Do 2007; Do 2009; Adis; Dixon).

The recitation of the structure and sequence of the VEGF antagonist in claim 34 does not distinguish the claim from the prior art. The sequence and structure of the VEGF Trap-Eye/aflibercept molecule disclosed in each of the references cited above disclosing the Phase 2 regimen and the DME Phase 1 results was set forth in the prior art. (*See, e.g.*, 757 patent, SEQ ID NO:16, Fig.24A-C; 758 patent, SEQ ID NO:16, Fig.24A-C; 959 patent, Fig.24A-C; 758 FH, 12/22/2011 PTE, 2, 6-7; 664 patent at 1:37-41, 2:53-55; 4:18, SEQ ID NO:7, SEQ ID NO:8; Holash 2002).

Accordingly, claim 34 of the 601 patent is obvious in view of at least each of the Phase 2 DME references cited above, and, if necessary, in combination with one or more of the references cited above disclosing the Phase 1 DME results and/or one or more of the references cited above disclosing the VEGF Trap-Eye sequences and structure.

Claim 34 of the 601 patent is obvious in view of the VIEW References, either alone or in combination. For the reasons discussed above, that discussion incorporated herein, each VIEW reference discloses expressly or inherently each and every claim element. (*See, e.g.*, Dixon; Adis;

NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release). The motivation to adopt the claimed dosing regimens for VEGF Trap-Eye comes from the references themselves, which persons of ordinary skill in the art would have appreciated set forth dosing regimens that allowed for dosing less frequently than monthly, as well as the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration.

In addition, a person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed VIEW dosing regimens given the widely publicized results of the VIEW trials, which were made available to the public before the earliest filing date listed on the face of the 601 patent. (*See, e.g.*, 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release).

The recitation of the structure and sequence of the VEGF antagonist in claim 34 does not distinguish the claim from the prior art. The sequence and structure of the VEGF Trap-Eye/aflibercept molecule disclosed in each of the VIEW and CLEAR-IT-2 references above was set forth in the prior art. (*See, e.g.*, 757 patent, SEQ ID NO:16, Fig.24A-C; 758 patent, SEQ ID NO:16, Fig.24A-C; 959 patent, Fig.24A-C; 758 FH, 12/22/2011 PTE, 2, 6-7; 664 patent at 1:37-41, 2:53-55; 4:18, SEQ ID NO:7, SEQ ID NO:8; Holash 2002).

Accordingly, claim 34 of the 601 patent is obvious in view of at least each of the VIEW References cited above, and, if necessary, in combination with one or more of the references cited

above disclosing the VIEW trial results and/or one or more of the references cited above disclosing the VEGF Trap-Eye sequences and structure.

Claim 34 of the 601 patent is obvious in view of the references disclosing the Phase 2 DME regimen in combination with references disclosing the results of the Phase 2 DME trial. For the reasons discussed above, that discussion incorporated herein, each Phase 2 DME reference discloses expressly or inherently each and every claim element. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Bayer Press Release; 12-20-2010 Bayer Press Release). The motivation to adopt the claimed dosing regimens for VEGF Trap-Eye comes from the references themselves, which persons of ordinary skill in the art would have appreciated set forth dosing regimens that allowed for dosing less frequently than monthly, as well as the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration.

In addition, a person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed Phase 2 DME dosing regimens given the widely publicized results of the Phase 2 DME trials, which were made available to the public before the earliest filing date listed on the face of the 601 patent. (*See, e.g.*, 2-18-2010 Bayer Press Release; 12-20-2010 Bayer Press Release).

The recitation of the structure and sequence of the VEGF antagonist in claim 34 does not distinguish the claim from the prior art. The sequence and structure of the VEGF Trap-Eye/aflibercept molecule disclosed in each of the references cited above disclosing the Phase 2 DME regimen and results was set forth in the prior art. (*See, e.g.*, 757 patent, SEQ ID NO:16, Fig.24A-C; 758 patent, SEQ ID NO:16, Fig.24A-C; 959 patent, Fig.24A-C; 758 FH, 12/22/2011 PTE, 2, 6-7; 664 patent at 1:37-41, 2:53-55; 4:18, SEQ ID NO:7, SEQ ID NO:8; Holash 2002).

Accordingly, claim 34 of the 601 patent is obvious in view of at least each of the references cited above disclosing the Phase 2 DME trial dosing regimens, and, if necessary, in combination with one or more of the references cited above disclosing the Phase 2 DME trial results and/or one or more of the references cited above disclosing the VEGF Trap-Eye sequences and structure.

For at least each of the above reasons, claim 34 of the 601 patent is invalid.[28]

27. Claim 35.

The language of claim 35 of the 601 patent is set forth above.

Claim 35 of the 601 patent depends from claim 34 and thus incorporates the elements of claim 34. The reasons why claim 34 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein the VEGF antagonist is aflibercept" does not distinguish the claim from the prior art. For example, the references disclosing the VIEW and Phase 2 DME dosing regimens also disclose VEGF Trap-Eye, i.e., aflibercept. (*See, e.g.*, Dixon; Adis; NCT-795; NCT-377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release; 9-14-2009 Regeneron Press Release; 2-18-2010 Bayer Press Release; 12-20-2010 Bayer Press Release). It was well known to those skilled in the art that aflibercept was the VEGF antagonist molecule used in the VIEW and Phase 2 DME trials.

[28] To the extent that any specific limitation is found not to be explicitly or inherently disclosed in these references, it would have been achieved through routine optimization by one of ordinary skill in the art.

Accordingly, claim 35 of the 601 patent is anticipated and rendered obvious by each of the references cited above disclosing the VIEW and Phase 2 DME dosing regimens, and obvious in view of each of the prior art combinations set forth above for claim 34.

28. Claim 36.

The language of claim 36 of the 601 patent is set forth above.

Claim 36 of the 601 patent depends from claim 35 and thus incorporates the elements of claim 35. The reasons why claim 35 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein exclusion criteria for the patient include (1) active intraocular inflammation; or (2) active ocular or periocular infection" does not distinguish the claim from the prior art. For example, the claimed exclusion criteria elements constitute mental steps and/or written material, and thus are not entitled to patentable weight. Relevantly, the Board has found that the exclusion criteria are not limiting upon claim 9 of the 601 patent under the printed matter doctrine. *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01226, Paper 22, at 11-15 (PTAB Jan. 11, 2023); *id.* at 15 ("[T]he information provided by the exclusionary criteria can be considered to be optional information, in that there is no direction to the practitioner to perform, or not perform, any specific step based upon the provided criteria. Thus, the exclusionary criteria are strictly informational, without requiring the practitioner to act, or refrain from acting, in a specified manner, and not functionally related to the practice of the claimed method.").

To the extent the exclusion criteria element is entitled to patentable weight, claim 36 of the 601 patent is inherently anticipated by at least each of the VIEW References that disclose the dosing regimen used in the VIEW trials. For example, the Eylea® Medical Review shows that a list of 37 non-confidential exclusion criteria were necessarily and inevitably applied in connection with practicing the claimed, and publicly disclosed, VIEW dosing regimen. (Eylea® Medical

Review at 112-114; *see also, e.g.*, Heier 2012 at Appendix 2). The application of the claimed exclusion criteria thus was a natural result flowing from the application of the VIEW trial study protocol. As a result, each of the VIEW References, including Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release inherently anticipates claim 36 of the 601 patent.

Claim 36 of the 601 patent is inherently anticipated by at least each of the Phase 2 DME references that disclose the dosing regimen used in the Phase 2 DME trials. For example, Do 2011 discloses a list of exclusion criteria that were necessarily and inevitably applied in connection with practicing the claimed, and publicly disclosed, Phase 2 DME dosing regimen. (Do 2011 at 1820 (exclusion criteria include ocular inflammation; any concurrent disease that would compromise visual acuity or require medical or surgical intervention during the study period; history of idiopathic or autoimmune uveitis; and infectious blepharitis, keratitis, scleritis, or conjunctivitis)). The application of the claimed exclusion criteria thus was a natural result flowing from the application of the Phase 2 DME trial study protocol. As a result, each of the Phase 2 DME references, including 9-14-2009 Regeneron Press Release, 2-18-2010 Bayer Press Release, and 12-20-2010 Bayer Press Release inherently anticipates claim 36 of the 601 patent.

Claim 36 of the 601 patent is obvious in view of the VIEW and Phase 2 DME references and combinations presented above, further in combination with references disclosing the exclusion criteria employed in the Lucentis ANCHOR and MARINA trials. For the reasons discussed above,

that discussion incorporated herein, each VIEW and Phase 2 DME reference discloses expressly or inherently each and every claim element, and as discussed above, the recited exclusion criteria are not entitled to patentable weight and/or are inherent aspects of the VIEW and Phase 2 DME study protocols. In addition to not being entitled to patentable weight, the claimed exclusion criteria also were disclosed in the prior art. For example, the Lucentis AMD MARINA and ANCHOR trials, involving monthly intravitreal administration of the VEGF antagonist Lucentis® (ranibizumab), employed exclusion criteria that included, among other relevant criteria, active intraocular inflammation in the study eye; history of idiopathic or autoimmune-associated uveitis in either eye; and infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye. (*See, e.g.*, Lucentis Medical Review; Rosenfeld 2006; Brown 2006; NCT 836; NCT 594). The Lucentis Medical Review further disclosed that dose-holding criteria included intraocular inflammation and local or systemic infection, including infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye. (Lucentis Medical Review at 66-67). Accordingly, it would have been obvious to adopt such exclusion criteria for the VEGF Trap-Eye clinical trials, particularly in light of the inclusion of monthly ranibizumab as a comparator arm in the VIEW clinical trials.

For at least these reasons, claim 36 of the 601 patent is obvious in view of at least each of the VIEW and Phase 2 DME references and combinations cited above, in combination with one or more of the references cited above disclosing the ranibizumab MARINA and ANCHOR clinical trial exclusion criteria.

Claim 36 of the 601 patent is obvious in view of the references disclosing the VIEW and Phase 2 DME regimens, and combinations presented above, further in combination with references disclosing exclusion criteria employed in the context of Macugen® (pegaptanib). For the reasons

discussed above, that discussion incorporated herein, each VIEW and Phase 2 DME reference discloses expressly or inherently each and every claim element, and as discussed above, the recited exclusion criteria are not entitled to patentable weight and/or are inherent aspects of the VIEW and Phase 2 DME study protocols. In addition to not being entitled to patentable weight, the claimed exclusion criteria also were disclosed in the prior art. For example, the pegaptanib trials involving intravitreal administration in treating AMD employed exclusion criteria that included, among other relevant criteria, choroiditis, and acute ocular or periocular infection. (*See, e.g.*, Macugen Medical Review; Macugen Study Group; Gragoudas 2004). Accordingly, it would have been obvious to adopt such exclusion criteria for the VEGF Trap-Eye clinical trials, which also involved intravitreal administration to patients with angiogenic eye disorders.

For at least these reasons, claim 36 of the 601 patent is obvious in view of at least each of the VIEW and Phase 2 DME references and combinations cited above, in combination with one or more of the references cited above disclosing the pegaptanib clinical trial exclusion criteria.

Claim 36 of the 601 patent is obvious in view of the VIEW and Phase 2 DME references and combinations presented above, further in combination with references disclosing general guidelines, precautions, and general potential complications of intravitreal administration. For the reasons discussed above, that discussion incorporated herein, each VIEW and Phase 2 DME reference discloses expressly or inherently each and every claim element, and as discussed above, the recited exclusion criteria are not entitled to patentable weight and/or are inherent aspects of the VIEW and Phase 2 DME study protocols. Despite not being entitled to patentable weight, the claimed exclusion criteria were nevertheless obvious from the prior art. For example, it was known among those of ordinary skill in the art that intravitreal administration could be associated with serious side effects if proper, aseptic technique is not adhered to. Consequently, persons of

ordinary skill in the art recognized, and reported on, the need to avoid injecting eyes that are infected or show signs of infection (i.e., inflammation). (*See, e.g.*, Aiello 2004; Jager 2004; Donahue; De Caro; Heimann; CATT Study; Regillo 2008; MACTEL Study; Jaffe; Lucentis PI 2006; Retinal Physician II; Dixon). Accordingly, it would have been obvious to adopt exclusion criteria for the VEGF Trap-Eye clinical trials that included active intraocular inflammation or active ocular or periocular infection.

For at least these reasons, claim 36 of the 601 patent is obvious in view of at least each of the VIEW and Phase 2 DME references and combinations cited above, in combination with one or more of the references cited above disclosing general guidelines and precautions for intravitreal injections.

Accordingly, claim 36 of the 601 patent is anticipated and rendered obvious by each of the references cited above disclosing the VIEW and Phase 2 DME dosing regimens, and obvious in view of each of the prior art combinations set forth above for claim 34.

29. Claims 37 and 38.

The language of claims 37 and 38 of the 601 patent is set forth above.

Claim 37 of the 601 patent depends from claim 34 and thus incorporates the elements of claim 34. Claim 38 depends from claim 37 and thus incorporates the elements of claim 37. The reasons why claim 34 is anticipated and/or obvious are incorporated by reference.

The additional elements drawn to intraocular and intravitreal administration do not distinguish the claims from the prior art. Each of the VIEW References set forth above discloses the VIEW trials, which were widely known to involve intravitreal administration of VEGF Trap-Eye, and/or discloses VEGF Trap-Eye as an intraocular delivery product. The same is true of the references disclosing the Phase 2 DME clinical trials. (*See, e.g.*, Dixon; Adis; NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008

Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release 9-14-2009 Regeneron Press Release; 2-18-2010 Bayer Press Release; 12-20-2010 Bayer Press Release).

Accordingly, claims 37 and 38 of the 601 patent are anticipated and rendered obvious by each of the references cited above disclosing the VIEW and Phase 2 DME dosing regimens, and obvious in view of each of the prior art combinations set forth above for claim 34.

30. **Claims 39 and 41.**

The language of claims 39 and 41 of the 601 patent is set forth above.

Claim 39 of the 601 patent depends from claim 38, and thus incorporates the elements of claim 38. Claim 41 depends from claim 39 and thus incorporate the elements of claim 39. The reasons why claim 38 is anticipated and/or obvious are incorporated by reference.

The additional element pertaining to 2 mg of the VEGF antagonist does not distinguish the claim from the prior art. Each of the VIEW and Phase 2 DME references set forth above discloses the VIEW and Phase 2 DME trials, and the use of 2 mg doses in those trials. (*See, e.g.*, Dixon; Adis; NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release; 9-14-2009 Regeneron Press Release; 2-18-2010 Bayer Press Release; 12-20-2010 Bayer Press Release).

Accordingly, claims 39 and 41 of the 601 patent are anticipated and rendered obvious by each of the VIEW and Phase 2 DME references, and obvious in view of each of the prior art combinations set forth above for claim 34, and/or in view of the knowledge of a person of ordinary skill in the art.

31. Claim 42.

The language of claim 42 of the 601 patent is set forth above.

Claim 42 of the 601 patent depends from claim 34, and thus incorporates the elements of claim 34. The reasons why claim 34 is anticipated and/or obvious are incorporated by reference.

The additional element reciting wherein the angiogenic eye disorder is selected from a group of known angiogenic eye disorders does not distinguish the claims from the prior art. Each of the VIEW References set forth above discloses that the VIEW trials were to assess VEGF Trap-Eye in patients with wet AMD, an angiogenic eye disorder, and each of the Phase 2 DME references discloses that the Phase 2 DME trials were to assess VEGF Trap-Eye in patients with DME. (*See, e.g.*, Dixon; Adis; NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release; 9-14-2009 Regeneron Press Release; 2-18-2010 Bayer Press Release; 12-20-2010 Bayer Press Release).

Accordingly, claim 42 of the 601 patent is anticipated and rendered obvious by each of the VIEW and Phase 2 DME references, and obvious in view of each of the prior art combinations set forth above for claim 34, and/or in view of the knowledge of a person of ordinary skill in the art.

32. Claim 43.

The language of claim 43 of the 601 patent is set forth above.

Claim 43 of the 601 patent depends from claim 34, and thus incorporates the elements of claim 34. The reasons why claim 34 is anticipated and/or obvious are incorporated by reference.

The additional element reciting "wherein the angiogenic eye disorder is age-related macular degeneration" does not distinguish the claims from the prior art. Each of the VIEW References set forth above discloses that the VIEW trials were to assess VEGF Trap-Eye in patients with wet AMD, an angiogenic eye disorder. (*See, e.g.*, Dixon; Adis; NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q).

Accordingly, claim 43 of the 601 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claim 34, and/or in view of the knowledge of a person of ordinary skill in the art.

33. Claim 45.

The language of claim 45 of the 601 patent is set forth above.

Claim 45 of the 601 patent depends from claim 43 and thus incorporate the elements of claim 43. The reasons why claim 43 is anticipated and/or obvious are incorporated by reference.

The additional element pertaining to 2 mg of the VEGF antagonist does not distinguish the claim from the prior art. Each of the VIEW and Phase 2 DME references set forth above discloses the VIEW and Phase 2 DME trials, and the use of 0.5 mg and 2 mg doses in those trials. (*See, e.g.*, Dixon; Adis; NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron

Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 03-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release; 9-14-2009 Regeneron Press Release; 2-18-2010 Bayer Press Release; 12-20-2010 Bayer Press Release).

Accordingly, claim 45 of the 601 patent is anticipated and rendered obvious by each of the VIEW and Phase 2 DME references, and obvious in view of each of the prior art combinations set forth above for claim 34, and/or in view of the knowledge of a person of ordinary skill in the art.

34. Claims 46 and 47.

The language of claims 46 and 47 of the 601 patent is set forth above.

Claims 46 and 47 of the 601 patent depend from claim 34, and thus incorporate the elements of claim 34. The reasons why claim 34 is anticipated and/or obvious are incorporated by reference.

The additional elements reciting "wherein the angiogenic eye disorder is diabetic retinopathy" or "diabetic macular edema" do not distinguish the claims from the prior art. Each of the Phase 2 DME references set forth above discloses that the Phase 2 DME trials were to assess VEGF Trap-Eye in patients with DME. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Bayer Press Release; 12-20-2010 Bayer Press Release). Further, DME was known to be a complication of DR. (*See, e.g.*, 07-23-2009 Regeneron Press Release; Do 2009; 9-14-2009 Regeneron Press Release; 2-18-2010 Bayer Press Release; 12-20-2010 Bayer Press Release; Nguyen 2009b; Massin 2010).

Accordingly, claims 46 and 47 of the 601 patent are anticipated and rendered obvious by each of the Phase 2 DME references, and obvious in view of each of the prior art combinations set

forth above for claim 34, and, if necessary, further in combination with references disclosing the association between DME and DR, and/or in view of the knowledge of a person of ordinary skill in the art.

35. Secondary Considerations.

Mylan is unaware of any evidence of secondary considerations that would render non-obvious the particular combination of elements claimed in the 601 patent, as described above and incorporated herein by reference.

Mylan is aware that the applicant argued during prosecution of related applications that "there was a need in the art for alternative treatment protocols" and that "applicants have demonstrated improved and unexpected results." (681 patent PH, 6/25/2018 Applicant Remarks at 8). Identical arguments made by the applicant in traversing rejections during prosecution of related patent claims have been refuted. (*See, e.g.*, IPR2021-00880, Petition for *Inter Partes* Review of U.S. Patent 9,669,069 at 69-72; IPR2021-00880, Declaration of T. Albini, M.D. ¶¶ 217-24; IPR2021-00881, Petition for *Inter Partes* Review of U.S. Patent 9,254,338 at 66-69; IPR2021-00881, Declaration of T. Albini, M.D. ¶¶ 404-11). For the same reasons presented in the IPR filings, that discussion incorporated by reference herein, there are no secondary considerations that would be sufficient to render non-obvious the claimed subject matter of the 601 patent.

Additionally, the patentee must prove the required nexus before relying on any secondary considerations of alleged non-obviousness. Mylan is not aware of any evidence that would establish the required nexus for any of the claims of the 601 patent, nor has Regeneron presented any evidence that would establish the required nexus for any of the claims of the 601 patent despite Mylan's requests for such discovery.

Further, even if there were any evidence of such secondary considerations[29] and the required nexus, the *prima facie* evidence of obviousness is sufficiently strong that it cannot be rebutted by evidence relevant to secondary considerations of non-obviousness.

As a result, all claims of the 601 patent are anticipated and obvious in view of at least the references and combinations set forth above, and in view of the knowledge of a person of ordinary skill in the art.

D. Obviousness-Type Double Patenting.

The 601 patent Asserted Claims are invalid for obviousness-type double patenting ("OTDP") over at least each of U.S. Patent Nos. 7,303,746 ("746 patent"), 7,303,747 ("747 patent"), 7,306,799 ("799 patent"), and 7,521,049 ("049 patent").

1. Claim 1.

The language of claim 1 of the 601 patent is set forth above.

Claim 1 of the 601 patent is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent. Each patent discloses VEGF Trap-Eye (i.e., aflibercept), and methods of treating AMD. (*See, e.g.*, 746 patent at SEQ ID NO:16, 2:48-49, 2:53-59, 6:39-50, claims 1-5; 747 patent at SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-63; 20:15-67, 21:1 – 22:42, claims 1-6; 049 patent (same); 799 patent (same)). Further, the patents disclose dosing regimens for AMD that comprise an initial dose, and subsequent doses between 1-6 months apart. For at least these reasons, claim 1 of the 601 patent represents nothing more than an obvious species within the genus disclosed, and/or an obvious variation of the subject matter disclosed, in the 746 patent, the 747 patent, the 799 patent, and the 049 patent, and thus is not patentably distinct from

[29] Mylan reserves the right to address any evidence of secondary considerations that are raised in litigation by any entity, or entities, attempting to assert the 601 patent.

one or more claims of the 746, 747, 799, and 049 patents. Arguments made by Regeneron in contesting OTDP rejections during prosecution of related patent claims have been refuted. (*See, e.g.*, IPR2021-00880, Petition for *Inter Partes* Review of U.S. Patent 9,669,069 at 69-72; IPR2021-00880, Declaration of T. Albini, M.D. ¶¶ 217-24; IPR2021-00881, Petition for *Inter Partes* Review of U.S. Patent 9,254,338 at 66-69; IPR2021-00881, Declaration of T. Albini, M.D. ¶¶ 404-11). Accordingly, claim 1 is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

2. Claims 2 and 5-9.

The language of claims 2 and 5-9 of the 601 patent is set forth above. Claims 2 and 5-9 depend from claim 1 and thus incorporate the elements of claim 1. The reasons why claim 1 is invalid for OTDP are incorporated by reference. Claims 2 and 5-9 are invalid for OTDP for at least the additional reasons set forth below.

Claims 2 and 8 are drawn to the treatment of AMD, which was disclosed in the 746 patent, the 747 patent, the 799 patent, and the 049 patent. Thus, claim 2 is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Claims 5 and 6 contain non-limiting statements of intended result and do not require any active steps beyond those set forth in claim 1, and/or are drawn to inherent and/or obvious variations of the subject matter set forth in claim 1, and disclosed in the 746, 747, 799, and 049 patents. Thus, claims 5 and 6 are not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Claim 7 merely clarifies what would have been widely understood by those of ordinary skill in the art, and thus is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Claim 9 does not require any active steps beyond those set forth in claim 1, and/or are drawn to inherent and/or obvious variations of the subject matter set forth in claim 1, and disclosed in the 746, 747, 799, and 049 patents. Thus, claim 9 is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Accordingly, for at least these additional reasons, claims 2 and 5-9 of the 601 patent are invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

3. Claim 10.

The language of claim 10 of the 601 patent is set forth above.

Claim 10 of the 601 patent is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent. Each patent discloses VEGF Trap-Eye (i.e., aflibercept), and methods of treating AMD, as well as DR and retinal edema. (*See, e.g.*, 746 patent at SEQ ID NO:16, 2:48-49, 2:53-59, 6:39-50, claims 1-5; *see also, e.g.*, 747 patent at SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-63; 20:15-67, 21:1 – 22:42, claims 1-6; 049 patent (same); 799 patent (same)). Further, the patents disclose dosing regimens that comprise an initial dose, and subsequent doses between 1-6 months apart. For at least these reasons, claim 10 of the 601 patent represents nothing more than an obvious species within the genus disclosed, and/or an obvious variation of the subject matter disclosed, in the 746 patent, the 747 patent, the 799 patent, and the 049 patent, and thus is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents. Arguments made by Regeneron in contesting OTDP rejections during prosecution of related patent claims have been refuted. (*See, e.g.*, IPR2021-00880, Petition for *Inter Partes* Review of U.S. Patent 9,669,069 at 69-72; IPR2021-00880, Declaration of T. Albini, M.D. ¶¶ 217-24; IPR2021-00881, Petition for *Inter Partes* Review of U.S. Patent 9,254,338 at 66-69; IPR2021-00881, Declaration of T. Albini, M.D. ¶¶ 404-11). Accordingly, claim 10 is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

4. Claims 11, 12, and 15-17.

The language of claims 11, 12, and 15-17 of the 601 patent is set forth above. Claims 11, 12, and 15-17 depend from claim 10 and thus incorporate the elements of claim 10. The reasons why claim 10 is invalid for OTDP are incorporated by reference. Claims 11, 12, and 15-17 are invalid for OTDP for at least the additional reasons set forth below.

Claim 11 merely clarifies what would have been widely understood by those of ordinary skill in the art, and thus is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Claim 12 claims monthly dosing, which is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Claims 15 and 16 contain non-limiting statements of intended result and do not require any active steps beyond those set forth in claim 10, and/or are drawn to inherent and/or obvious variations of the subject matter set forth in claim 10, and disclosed in the 746, 747, 799, and 049 patents. Thus, claims 15 and 16 are not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Claim 17 does not require any active steps beyond those set forth in claim 10, and/or is drawn to inherent and/or obvious variations of the subject matter set forth in claim 10, and disclosed in the 746, 747, 799, and 049 patents. Thus, claim 17 is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Accordingly, for at least these additional reasons, claims 11, 12, and 15-17 of the 601 patent are invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

5. Claim 18.

The language of claim 18 of the 601 patent is set forth above.

Claim 18 of the 601 patent is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent. Each patent discloses VEGF Trap-Eye (i.e., aflibercept), and methods of treating AMD, as well as DR and retinal edema. (*See, e.g.*, 746 patent at SEQ ID NO:16, 2:48-49, 2:53-59, 6:39-50, claims 1-5; *see also, e.g.*, 747 patent at SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-63; 20:15-67, 21:1 – 22:42, claims 1-6; 049 patent (same); 799 patent (same)). Further, the patents disclose dosing regimens that comprise an initial dose, and subsequent doses between 1-6 months apart. For at least these reasons, claim 18 of the 601 patent represents nothing more than an obvious species within the genus disclosed, and/or an obvious variation of the subject matter disclosed, in the 746 patent, the 747 patent, the 799 patent, and the 049 patent, and thus is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents. Arguments made by Regeneron in contesting OTDP rejections during prosecution of related patent claims have been refuted. (*See, e.g.*, IPR2021-00880, Petition for *Inter Partes* Review of U.S. Patent 9,669,069 at 69-72; IPR2021-00880, Declaration of T. Albini, M.D. ¶¶ 217-24; IPR2021-00881, Petition for *Inter Partes* Review of U.S. Patent 9,254,338 at 66-69; IPR2021-00881, Declaration of T. Albini, M.D. ¶¶ 404-11). Accordingly, claim 18 is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

6. Claims 19, 21, and 23-25.

The language of claims 19, 21, and 23-25 of the 601 patent is set forth above. Claims 19, 21, and 23-25 depend from claim 18 and thus incorporate the elements of claim 18. The reasons why claim 18 is invalid for OTDP are incorporated by reference. Claims 19, 21, and 23-25 are invalid for OTDP for at least the additional reasons set forth below.

Claim 19 merely clarifies what would have been widely understood by those of ordinary skill in the art, and thus is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Claim 21 claims monthly dosing, which is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Claims 23-25 contain non-limiting statements of intended result and do not require any active steps beyond those set forth in claim 18, and/or are drawn to inherent and/or obvious variations of the subject matter set forth in claim 18, and disclosed in the 746, 747, 799, and 049 patents. Thus, claims 23-25 are not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Accordingly, for at least these additional reasons, claims 19, 21, and 23-25 of the 601 patent are invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

7. Claim 26.

The language of claim 26 of the 601 patent is set forth above.

Claim 26 of the 601 patent is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent. Each patent discloses VEGF Trap-Eye (i.e., aflibercept), and methods of treating AMD, as well as DR and retinal edema. (*See, e.g.*, 746 patent at SEQ ID NO:16, 2:48-49, 2:53-59, 6:39-50, claims 1-5; *see also, e.g.*, 747 patent at SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-63; 20:15-67, 21:1 – 22:42, claims 1-6; 049 patent (same); 799 patent (same)). Further, the patents disclose dosing regimens that comprise an initial dose, and subsequent doses between 1-6 months apart. For at least these reasons, claim 26 of the 601 patent represents nothing more than an obvious species within the genus disclosed, and/or an obvious variation of the subject matter disclosed, in the 746 patent, the 747 patent, the 799 patent, and the 049 patent, and thus is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents. Arguments made by Regeneron in contesting OTDP rejections during prosecution of related patent claims have been refuted. (*See, e.g.*, IPR2021-00880, Petition for *Inter Partes* Review of U.S. Patent 9,669,069 at 69-72; IPR2021-00880, Declaration of T. Albini, M.D. ¶¶ 217-24; IPR2021-00881,

Petition for *Inter Partes* Review of U.S. Patent 9,254,338 at 66-69; IPR2021-00881, Declaration of T. Albini, M.D. ¶¶ 404-11). Accordingly, claim 26 is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

8. Claims 27, 28, and 31-33.

The language of claims 27, 28, and 31-33 of the 601 patent is set forth above. Claims 27, 28, and 31-33 depend from claim 26 and thus incorporate the elements of claim 26. The reasons why claim 26 is invalid for OTDP are incorporated by reference. Claims 27, 28, and 31-33 are invalid for OTDP for at least the additional reasons set forth below.

Claim 27 merely clarifies what would have been widely understood by those of ordinary skill in the art, and thus is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Claim 28 claims monthly dosing, which is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Claims 31-33 contain non-limiting statements of intended result and do not require any active steps beyond those set forth in claim 26, and/or are drawn to inherent and/or obvious variations of the subject matter set forth in claim 26, and disclosed in the 746, 747, 799, and 049 patents. Thus, claims 31-33 are not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Accordingly, for at least these additional reasons, claims 27, 28, and 31-33 of the 601 patent are invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

9. Claim 34.

The language of claim 34 of the 601 patent is set forth above.

Claim 34 of the 601 patent is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent. Each patent discloses VEGF Trap-Eye (i.e., aflibercept), and

methods of treating AMD, as well as DR and retinal edema. (*See, e.g.*, 746 patent at SEQ ID NO:16, 2:48-49, 2:53-59, 6:39-50, claims 1-5; *see also, e.g.*, 747 patent at SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-63; 20:15-67, 21:1 – 22:42, claims 1-6; 049 patent (same); 799 patent (same)). Further, the patents disclose dosing regimens that comprise an initial dose, and subsequent doses between 1-6 months apart. For at least these reasons, claim 34 of the 601 patent represents nothing more than an obvious species within the genus disclosed, and/or an obvious variation of the subject matter disclosed, in the 746 patent, the 747 patent, the 799 patent, and the 049 patent, and thus is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents. Arguments made by Regeneron in contesting OTDP rejections during prosecution of related patent claims have been refuted. (*See, e.g.*, IPR2021-00880, Petition for *Inter Partes* Review of U.S. Patent 9,669,069 at 69-72; IPR2021-00880, Declaration of T. Albini, M.D. ¶¶ 217-24; IPR2021-00881, Petition for *Inter Partes* Review of U.S. Patent 9,254,338 at 66-69; IPR2021-00881, Declaration of T. Albini, M.D. ¶¶ 404-11). Accordingly, claim 34 is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

10. **Claims 35-39, 41-43, and 45-47.**

The language of claims 35-39, 41-43, and 45-47 of the 601 patent is set forth above. Claims 35-39, 41-43, and 45-47 depend from claim 34 and thus incorporate the elements of claim 34. The reasons why claim 34 is invalid for OTDP are incorporated by reference. Claims 35-39, 41-43, and 45-47 are invalid for OTDP for at least the additional reasons set forth below.

Claim 35 merely sets forth a term widely understood by persons of ordinary skill in the art to refer to a specific species of the genus of VEGF antagonists claimed in claim 34, and claimed in the 746, 747, 799, and 049 patents, and thus not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Claim 36 does not require any active steps beyond those set forth in claim 34, and/or is drawn to inherent and/or obvious variations of the subject matter set forth in claim 34, and disclosed in the 746, 747, 799, and 049 patents. Thus, claim 36 is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Claims 37 and 38 are drawn to subject matter disclosed and claimed and/or obvious variations of subject matter disclosed and claimed in the 746, 747, 799, and 049 patents. Thus, claims 37 and 38 are not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Claims 39, 41, and 45 are drawn to dosage amounts which are disclosed and claimed, and/or obvious variations of subject matter disclosed and claimed, in the 746, 747, 799, and 049 patents. Thus, claims 39, 41, and 45 are not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Claims 42, 43, 46 and 47 are drawn to angiogenic eye disorders which are disclosed and claimed, and/or obvious variations of subject matter disclosed and claimed, in the 746, 747, 799, and 049 patents. Thus, claims 42, 43, 46 and 47 are not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Accordingly, for at least these additional reasons, claims 35-39, 41-43, and 45-47 of the 601 patent are invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

* * *

For at least the reasons discussed above, the 601 patent Asserted Claims are invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

E. Enablement.

The 601 patent Asserted Claims are invalid for lack of enablement because the 601 patent fails to enable the full scope of the claims.

1. Claim 1.

The language of claim 1 of the 601 patent is set forth above.

Claim 1 of the 601 patent is invalid for lack of enablement for at least the reasons identified below.

To the extent claim 1 of the 601 patent is not anticipated or obvious, as discussed above, the 601 patent fails to provide sufficient support for the subject matter claimed in claim 1. For example, the specification does not describe or enable anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 1 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to enable a person of ordinary skill in the art to practice the claimed method without undue experimentation.

Claim 1 of the 601 patent describes administering aflibercept "once every 8 weeks or once every 2 months" without an upper limit on the number of doses. In addition, claim 1 of the 601 patent does not enable a method for treating all age-related macular degeneration. For example, the working examples in the specification are limited to neovascular AMD. Claim 1 is not limited to neovascular AMD, and thus the 601 patent specification does not include a disclosure sufficient to enable a person of ordinary skill in the art to practice the claimed method without undue experimentation.

Each of the aforementioned claim elements renders the claims open to a substantial number of inoperative embodiments, leading to the need for undue experimentation to practice the full scope of the invention.

Given the breadth of the claim, the lack of guidance in the specification, and the quantity of experimentation required, the 601 patent does not enable one skilled in the art to practice the full scope of claim 1 without undue experimentation.

Further, the 601 patent specification fails to enable a person of ordinary skill in the art to obtain the "aflibercept" formulations for the claimed method. The 601 patent provides no guidance as to the manufacturing and process steps needed to produce the "aflibercept" formulations. Regeneron's own expert, Dr. Klibanov, declared that "Sanofi is a major, sophisticated, international biopharmaceutical company; yet despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881, Expert Declaration of Alexander M. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that "Sanofi observed that the aflibercept substance made in its Vitry, France, manufacturing facility degraded faster than Regeneron's drug substance and drug product." (*Id.*). As such, the 601 patent's limited disclosure fails to enable the full scope of the claimed method.

Accordingly, for at least these reasons, claim 1 of the 601 patent is invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

2. Claims 2 and 5-9.

The language of claims 2 and 5-9 of the 601 patent is set forth above.

Claims 2 and 5-9 of the 601 patent depend either directly or indirectly from claim 1, and thus incorporate the elements of claim 1. For at least the same reasons set forth above with respect to claim 1, said discussion incorporated herein by reference, and because the limitations of claims 2 and 5-9 do not suffice to cure the failures of claim 1 to meet the requirements of § 112, the 601

patent does not enable one skilled in the art to practice the full scope of claims 2 and 5-9 without undue experimentation.

In addition, claims 5 and 6 are not enabled because the specification does not provide disclosure sufficient for a person of ordinary skill in the art to practice the full scope of the claims without undue experimentation. The specification fails to disclose AMD patients gaining at least 15 letters of BCVA, according to ETDRS letter score, and fails to identify a method to achieve said gain that was not disclosed in the prior art, and therefore does not enable one skilled in the art to practice the full scope of claims 5 and 6 without undue experimentation.

Accordingly, claims 2 and 5-9 of the 601 patent are invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

3. Claim 10.

The language of claim 10 of the 601 patent is set forth above.

Claim 10 of the 601 patent is invalid for lack of enablement for at least the reasons identified below.

To the extent claim 10 of the 601 patent is not anticipated or obvious, as discussed above, the 601 patent fails to provide sufficient support for the subject matter claimed in claim 10. For example, the specification does not describe or enable anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 10 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to enable a person of ordinary skill in the art to practice the claimed method without undue experimentation.

Further, the 601 patent specification fails to enable a person of ordinary skill in the art to obtain the "aflibercept" formulations for the claimed method. The 601 patent provides no guidance as to the manufacturing and process steps needed to produce the "aflibercept" formulations.

Regeneron's own expert, Dr. Klibanov, declared that "Sanofi is a major, sophisticated, international biopharmaceutical company; yet despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881, Expert Declaration of Alexander M. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that "Sanofi observed that the aflibercept substance made in its Vitry, France, manufacturing facility degraded faster than Regeneron's drug substance and drug product." (*Id.*). As such, the 601 patent's limited disclosure fails to enable the full scope of the claimed method.

Claim 10 of the 601 patent describes administering aflibercept "once every 8 weeks or once every 2 months" without an upper limit on the number of doses. Given the breadth of the claim, the lack of guidance in the specification, and the quantity of experimentation required, the 601 patent does not enable one skilled in the art to practice the full scope of claim 10 without undue experimentation.

Accordingly, for at least these reasons, claim 10 of the 601 patent is invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

4. Claims 11, 12, and 15-17.

The language of claims 11, 12, and 15-17 of the 601 patent is set forth above.

Claims 11, 12, and 15-17 of the 601 patent depend either directly or indirectly from claim 10, and thus incorporate the elements of claim 10. For at least the same reasons set forth above with respect to claim 10, said discussion incorporated herein by reference, and because the limitations of claims 11, 12, and 15-17 do not suffice to cure the failures of claim 10 to meet the requirements of § 112, the 601 patent does not enable one skilled in the art to practice the full scope of claims 11, 12, and 15-17 without undue experimentation.

In addition, claims 15 and 16 are not enabled because the specification does not provide disclosure sufficient for a person of ordinary skill in the art to practice the full scope of the claims without undue experimentation. The specification fails to disclose DME patients gaining at least 15 letters of BCVA, according to ETDRS letter score, and fails to identify a method to achieve said gain that was not disclosed in the prior art, and therefore does not enable one skilled in the art to practice the full scope of claims 15 and 16 without undue experimentation.

Accordingly, claims 11, 12, and 15-17 of the 601 patent are invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

5. Claim 18.

The language of claim 18 of the 601 patent is set forth above.

Claim 18 of the 601 patent is invalid for lack of enablement for at least the reasons identified below.

To the extent claim 18 of the 601 patent is not anticipated or obvious, as discussed above, the 601 patent fails to provide sufficient support for the subject matter claimed in claim 18. For example, the specification does not describe or enable anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 18 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to enable a person of ordinary skill in the art to practice the claimed method without undue experimentation.

Each of the aforementioned claim elements render the claims open to a substantial number of inoperative embodiments, leading to the need for undue experimentation to practice the full scope of the invention.

Given the breadth of the claim, the lack of guidance in the specification, and the quantity of experimentation required, the 601 patent does not enable one skilled in the art to practice the

full scope of claim 18 without undue experimentation. Claim 18 of the 601 patent describes administering aflibercept "once every 8 weeks or once every 2 months" without an upper limit on the number of doses. In addition, claim 18 of the 601 patent does not enable a method for treating DR. For example, there are no working examples provided in the specification that are directed to a method of treating DR. Further, persons of ordinary skill in the art would have been aware that there were different types of DR known as of the filing date of the 601 patent. Because claim 18 is not limited to a particular DR, the 601 patent specification does not include a disclosure sufficient to enable a person of ordinary skill in the art to practice the claimed method without undue experimentation.

Further, the 601 patent specification fails to enable a person of ordinary skill in the art to obtain the "aflibercept" formulations for the claimed method. The 601 patent provides no guidance as to the manufacturing and process steps needed to produce the "aflibercept" formulations. Regeneron's own expert, Dr. Klibanov, declared that "Sanofi is a major, sophisticated, international biopharmaceutical company; yet despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881, Expert Declaration of Alexander M. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that "Sanofi observed that the aflibercept substance made in its Vitry, France, manufacturing facility degraded faster than Regeneron's drug substance and drug product." (*Id.*). As such, the 601 patent's limited disclosure fails to enable the full scope of the claimed method.

Accordingly, for at least these reasons, claim 18 of the 601 patent is invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

6. Claims 19, 21, and 23-25.

The language of claims 19, 21, and 23-25 of the 601 patent is set forth above.

Claims 19, 21, and 23-25 of the 601 patent depend either directly or indirectly from claim 18, and thus incorporate the elements of claim 18. For at least the same reasons set forth above with respect to claim 18, said discussion incorporated herein by reference, and because the limitations of claims 19, 21, and 23-25 do not suffice to cure the failures of claim 18 to meet the requirements of § 112, the 601 patent does not enable one skilled in the art to practice the full scope of claims 19, 21, and 23-25 without undue experimentation.

In addition, claims 23 and 24 are not enabled because the specification does not provide disclosure sufficient for a person of ordinary skill in the art to practice the full scope of the claims without undue experimentation. The specification fails to disclose DR patients losing fewer than 15 letters of BCVA, or gaining at least 15 letters, according to ETDRS letter score, and fails to identify a method to achieve said outcomes that was not disclosed in the prior art, and therefore does not enable one skilled in the art to practice the full scope of claims 23 and 24 without undue experimentation.

Accordingly, claims 19, 21, and 23-25 of the 601 patent are invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

7. Claim 26.

The language of claim 26 of the 601 patent is set forth above.

Claim 26 of the 601 patent is invalid for lack of enablement for at least the reasons identified below.

To the extent claim 26 of the 601 patent is not anticipated or obvious, as discussed above, the 601 patent fails to provide sufficient support for the subject matter claimed in claim 26. For example, the specification does not describe or enable anything more than was taught in the prior

art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 26 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to enable a person of ordinary skill in the art to practice the claimed method without undue experimentation.

Claim 26 of the 601 patent describes administering aflibercept "once every 8 weeks or once every 2 months" without an upper limit on the number of doses, thus lacking enablement. In addition, claim 26 of the 601 patent does not enable a method for treating DR in a patient with macular edema. For example, there are no working examples provided in the specification that are directed to a method of treating DR. Further, persons of ordinary skill in the art would have been aware that there were different types of DR known as of the filing date of the 601 patent. Because claim 26 is not limited to a particular DR, the 601 patent specification does not include a disclosure sufficient to enable a person of ordinary skill in the art to practice the claimed method without undue experimentation.

Each of the aforementioned claim elements render the claims open to a substantial number of inoperative embodiments, leading to the need for undue experimentation to practice the full scope of the invention.

Given the breadth of the claim, the lack of guidance in the specification, and the quantity of experimentation required, the 601 patent does not enable one skilled in the art to practice the full scope of claim 26 without undue experimentation.

Further, the 601 patent specification fails to enable a person of ordinary skill in the art to obtain the "aflibercept" formulations for the claimed method. The 601 patent provides no guidance as to the manufacturing and process steps needed to produce the "aflibercept" formulations. Regeneron's own expert, Dr. Klibanov, declared that "Sanofi is a major, sophisticated,

international biopharmaceutical company; yet despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881, Expert Declaration of Alexander M. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that "Sanofi observed that the aflibercept substance made in its Vitry, France, manufacturing facility degraded faster than Regeneron's drug substance and drug product." (*Id.*). As such, the 601 patent's limited disclosure fails to enable the full scope of the claimed method.

Accordingly, for at least these reasons, claim 26 of the 601 patent is invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

8. Claims 27, 28, and 31-33.

The language of claims 27, 28, and 31-33 of the 601 patent is set forth above.

Claims 27, 28, and 31-33 of the 601 patent depend either directly or indirectly from claim 26, and thus incorporate the elements of claim 26. For at least the same reasons set forth above with respect to claim 26, said discussion incorporated herein by reference, and because the limitations of claims 27, 28, and 31-33 do not suffice to cure the failures of claim 26 to meet the requirements of § 112, the 601 patent does not enable one skilled in the art to practice the full scope of claims 27, 28, and 31-33 without undue experimentation.

In addition, claims 31 and 32 are not enabled because the specification does not provide disclosure sufficient for a person of ordinary skill in the art to practice the full scope of the claims without undue experimentation. The specification fails to disclose DR patients losing fewer than 15 letters of BCVA, or gaining at least 15 letters, according to ETDRS letter score, and fails to identify a method to achieve said outcomes that was not disclosed in the prior art, and therefore

does not enable one skilled in the art to practice the full scope of claims 31 and 32 without undue experimentation.

Accordingly, claims 27, 28, and 31-33 of the 601 patent are invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

9. Claim 34.

The language of claim 34 of the 601 patent is set forth above.

Claim 34 of the 601 patent is invalid for lack of enablement for at least the reasons identified below.

To the extent claim 34 of the 601 patent is not anticipated or obvious, as discussed above, the 601 patent fails to provide sufficient support for the subject matter claimed in claim 34. For example, the specification does not describe or enable anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 34 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to enable a person of ordinary skill in the art to practice the claimed method without undue experimentation.

Further, claim 34 is drawn to, among other things, the administration of "one or more secondary doses" without an upper limit on the number of secondary doses; the administration of "one or more tertiary doses" without an upper limit on the number of tertiary doses; administration of "doses," unbounded by any specific concentrations or even ranges of concentrations for said doses; a broad category of VEGF antagonists that comprise the recited domains but which may also comprise an untold number of additional domains and components; and a method for treating any "angiogenic eye disorder." The breadth of each of the aforementioned claim elements renders the claims open to a substantial number of inoperative embodiments and/or methods not sufficiently described in the specification, particularly in view of any Regeneron argument that the

claims require particular levels of efficacy. In addition, claim 34 is not expressly limited to any specific angiogenic eye disorders. The working examples are limited to a very narrow subset of angiogenic eye disorders, and, to the extent that Regeneron argues that the claims require particular levels of efficacy, the specification provides insufficient information and disclosures indicating how to extrapolate data and regimen design from those disorders that are disclosed in the working examples, to those that are not (e.g., branch retinal vein occlusion, choroidal neovascularization, iris neovascularization, neovascular glaucoma, etc.). (*See, e.g.*, 601 patent at 5:22-39). Accordingly, the claims would require undue experimentation to practice, and are not enabled by the specification.

The 601 patent specification also fails to enable a person of ordinary skill in the art to obtain the "VEGF antagonist" formulations for the claimed method. The 601 patent provides no guidance as to the manufacturing and process steps needed to produce the "VEGF antagonist" formulations. Regeneron's own expert, Dr. Klibanov, declared that "Sanofi is a major, sophisticated, international biopharmaceutical company; yet despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881, Expert Declaration of Alexander M. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that "Sanofi observed that the aflibercept substance made in its Vitry, France, manufacturing facility degraded faster than Regeneron's drug substance and drug product." (*Id.*). As such, the 601 patent's limited disclosure fails to enable the full scope of the claimed method.

Accordingly, for at least these reasons, claim 34 of the 601 patent is invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

10. Claims 35-39, 41-43, and 45-47.

The language of claims 35-39, 41-43, and 45-47 of the 601 patent is set forth above.

Claims 35-39, 41-43, and 45-47 of the 601 patent depend either directly or indirectly from claim 34, and thus incorporate the elements of claim 34. For at least the same reasons set forth above with respect to claim 34, said discussion incorporated herein by reference, and because the limitations of claims 35-39, 41-43, and 45-47 do not suffice to cure the failures of claim 34 to meet the requirements of § 112, the 601 patent does not enable one skilled in the art to practice the full scope of claims 35-39, 41-43, and 45-47 without undue experimentation.

Accordingly, claims 35-39, 41-43, and 45-47 of the 601 patent are invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

* * *

For at least the reasons discussed above, the 601 patent Asserted Claims are not enabled such that one of ordinary skill in the art would understand how to practice the claimed invention without undue experimentation.

F. Written Description.

The 601 patent Asserted Claims are invalid for lack of written description because the 601 patent does not convey to those skilled in the art that the named inventors were in possession of the full scope of the claims.

1. Claim 1.

The language of claim 1 of the 601 patent is set forth above.

Claim 1 of the 601 patent is invalid for lack of written description for at least the reasons identified below.

To the extent claim 1 of the 601 patent is not anticipated or obvious, as discussed above, the 601 patent fails to provide sufficient support for the subject matter claimed in claim 1. For

example, the specification does not describe or disclose anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 1 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 1.

Further, the 601 patent specification fails to disclose the "aflibercept" formulations for the claimed method. The 601 patent provides no description of the manufacturing and process steps needed to produce "aflibercept" formulations having the requisite stability, potency, and binding properties, to be administered under the claimed method. Regeneron's own expert, Dr. Klibanov, declared that "Sanofi is a major, sophisticated, international biopharmaceutical company; yet despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881, Expert Declaration of Alexander M. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that "Sanofi observed that the aflibercept substance made in its Vitry, France, manufacturing facility degraded faster than Regeneron's drug substance and drug product." (*Id.* ¶ 94). As such, the 601 patent's limited disclosure fails to describe the claimed method.

Claim 1 of the 601 patent lacks written description support at least because the specification does not disclose administering aflibercept "once every 8 weeks or once every 2 months" without an upper limit on the number of doses. In addition, claim 1 of the 601 patent lacks written description support because the specification does not disclose a method for treating all age-related macular degeneration. For example, the working examples in the specification are limited to neovascular AMD. Claim 1 is not limited to neovascular AMD, and thus the 601 patent

specification does not include a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 1.

Accordingly, claim 1 of the 601 patent is invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

2. Claims 2 and 5-9.

The language of claims 2 and 5-9 of the 601 patent is set forth above.

Claims 2 and 5-9 of the 601 patent depend either directly or indirectly from claim 1, and thus incorporate the elements of claim 1. For at least the same reasons set forth above with respect to claim 1, said discussion incorporated herein by reference, and because the limitations of claims 2 and 5-9 do not suffice to cure the failures of claim 1 to meet the requirements of § 112, the 601 patent does not provide a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claims 2 and 5-9.

In addition, the subject matter of claims 5 and 6 is not sufficiently described in the specification, because the specification fails to disclose AMD patients gaining at least 15 letters of BCVA, according to ETDRS letter score, and fails to identify a method to achieve said gain that was not disclosed in the prior art. Further, the subject matter of claim 9 is not sufficiently described in the specification, because exclusion criteria are mentioned only once in the 601 patent, and then only in the context of a Phase 3 clinical trial for AMD, along with 37 other exclusion criteria that were required to be applied. (601 patent at 10:64 – 12:18). Accordingly, there is no written description support for the application of "exclusion criteria" outside the context of an AMD clinical trial, and no written description support for applying only a subset of the 37 exclusion criteria.

Accordingly, claims 2 and 5-9 of the 601 patent are invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

3. Claim 10.

The language of claim 10 of the 601 patent is set forth above.

Claim 10 of the 601 patent is invalid for lack of written description for at least the reasons identified below.

To the extent claim 10 of the 601 patent is not anticipated or obvious, as discussed above, the 601 patent fails to provide sufficient support for the subject matter claimed in claim 10. For example, the specification does not describe or disclose anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 10 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 10.

Claim 10 of the 601 patent lacks written description support at least because the specification does not disclose administering aflibercept "once every 8 weeks or once every 2 months" without an upper limit on the number of doses. In addition, claim 10 of the 601 patent lacks written description support because the specification does not disclose a method for treating DME involving administering 2 mg aflibercept every 4 weeks for the first 5 injections. For example, Example 5 is limited to treating DME patients with 2 mg every 4 weeks for a year, or three initial doses of 2 mg, followed by doses every 8 weeks. Claim 10 is not so limited, and thus the 601 patent specification does not include a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 10.

Further, the 601 patent specification fails to disclose the "aflibercept" formulations for the claimed method. The 601 patent provides no description of the manufacturing and process steps needed to produce "aflibercept" formulations having the requisite stability, potency, and binding properties, to be administered under the claimed method. Regeneron's own expert, Dr. Klibanov,

declared that "Sanofi is a major, sophisticated, international biopharmaceutical company; yet despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881, Expert Declaration of Alexander M. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that "Sanofi observed that the aflibercept substance made in its Vitry, France, manufacturing facility degraded faster than Regeneron's drug substance and drug product." (*Id.* ¶ 94). As such, the 601 patent's limited disclosure fails to describe the claimed method.

Accordingly, for at least these reasons, claim 10 of the 601 patent is invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

4. Claims 11, 12, and 15-17.

The language of claims 11, 12, and 15-17 of the 601 patent is set forth above.

Claims 11, 12, and 15-17 of the 601 patent depend either directly or indirectly from claim 10, and thus incorporate the elements of claim 10. For at least the same reasons set forth above with respect to claim 10, said discussion incorporated herein by reference, and because the limitations of claims 11, 12, and 15-17 do not suffice to cure the failures of claim 10 to meet the requirements of § 112, the 601 patent does not provide a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claims 11, 12, and 15-17.

In addition, the subject matter of claims 15 and 16 is not sufficiently described in the specification, because the specification fails to disclose DME patients treated with the claimed regimen losing fewer than, or gaining at least, 15 letters of BCVA, according to ETDRS letter score.

Further, the subject matter of claim 17 is not sufficiently described in the specification, because the specification fails to disclose the claimed exclusion criteria being employed in connection with a method for treating DME with the claimed dosing regimen. The subject matter of claim 17 is not sufficiently described in the specification, because exclusion criteria are mentioned only once in the 601 patent, and then only in the context of a Phase 3 clinical trial for AMD, along with 37 other exclusion criteria that were required to be applied. (601 patent at 10:64 – 12:18). Accordingly, there is no written description support for the application of "exclusion criteria" outside the context of an AMD clinical trial, and no written description support for applying only a subset of the 37 exclusion criteria.

Accordingly, claims 11, 12, and 15-17 of the 601 patent are invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

5. Claim 18.

The language of claim 18 of the 601 patent is set forth above.

Claim 18 of the 601 patent is invalid for lack of written description for at least the reasons identified below.

To the extent claim 18 of the 601 patent is not anticipated or obvious, as discussed above, the 601 patent fails to provide sufficient support for the subject matter claimed in claim 18. For example, the specification does not describe or disclose anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 18 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 18.

Claim 18 of the 601 patent lacks written description support at least because the specification does not disclose administering aflibercept "once every 8 weeks or once every 2

months" without an upper limit on the number of doses. In addition, claim 18 of the 601 patent lacks written description support because the specification does not disclose a method for treating DR involving administering 2 mg aflibercept every 4 weeks for the first 5 injections. For example, none of the working examples recites treating DR, and none of the working examples recites the claimed dosing regimen. Thus, the 601 patent specification does not include a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 18.

Further, the 601 patent specification fails to disclose the "aflibercept" formulations for the claimed method. The 601 patent provides no description of the manufacturing and process steps needed to produce "aflibercept" formulations having the requisite stability, potency, and binding properties, to be administered under the claimed method. Regeneron's own expert, Dr. Klibanov, declared that "Sanofi is a major, sophisticated, international biopharmaceutical company; yet despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881, Expert Declaration of Alexander M. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that "Sanofi observed that the aflibercept substance made in its Vitry, France, manufacturing facility degraded faster than Regeneron's drug substance and drug product." (*Id.* ¶ 94). As such, the 601 patent's limited disclosure fails to describe the claimed method.

Accordingly, for at least these reasons, claim 18 of the 601 patent is invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

6. Claims 19, 21, and 23-25.

The language of claims 19, 21, and 23-25 of the 601 patent is set forth above.

Claims 19, 21, and 23-25 of the 601 patent depend either directly or indirectly from claim 18, and thus incorporate the elements of claim 18. For at least the same reasons set forth above with respect to claim 18, said discussion incorporated herein by reference, and because the limitations of claims 19, 21, and 23-25 do not suffice to cure the failures of claim 18 to meet the requirements of § 112, the 601 patent does not provide a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claims 19, 21, and 23-25.

In addition, the subject matter of claims 23 and 24 is not sufficiently described in the specification, because the specification fails to disclose DR patients treated with the claimed regimen losing fewer than, or gaining at least, 15 letters of BCVA, according to ETDRS letter score.

Further, the subject matter of claim 25 is not sufficiently described in the specification, because the specification fails to disclose the claimed exclusion criteria being employed in connection with a method for treating DR with the claimed dosing regimen. The subject matter of claim 25 is not sufficiently described in the specification, because exclusion criteria are mentioned only once in the 601 patent, and then only in the context of a Phase 3 clinical trial for AMD, along with 37 other exclusion criteria that were required to be applied. (601 patent at 10:64 – 12:18). Accordingly, there is no written description support for the application of "exclusion criteria" outside the context of an AMD clinical trial, and no written description support for applying only a subset of the 37 exclusion criteria.

Accordingly, claims 19, 21, and 23-25 of the 601 patent are invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

7. Claim 26.

The language of claim 26 of the 601 patent is set forth above.

Claim 26 of the 601 patent is invalid for lack of written description for at least the reasons identified below.

To the extent claim 26 of the 601 patent is not anticipated or obvious, as discussed above, the 601 patent fails to provide sufficient support for the subject matter claimed in claim 26. For example, the specification does not describe or disclose anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 26 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 26.

Claim 26 of the 601 patent lacks written description support at least because the specification does not disclose administering aflibercept "once every 8 weeks or once every 2 months" without an upper limit on the number of doses. In addition, claim 26 of the 601 patent lacks written description support because the specification does not disclose a method for treating DR in a patient with DME, involving administering 2 mg aflibercept every 4 weeks for the first 5 injections. For example, none of the working examples recites treating DR or DR in a patient with DME, and none of the working examples recites the claimed dosing regimen. Thus, the 601 patent specification does not include a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 26.

Further, the 601 patent specification fails to disclose the "aflibercept" formulations for the claimed method. The 601 patent provides no description of the manufacturing and process steps needed to produce "aflibercept" formulations having the requisite stability, potency, and binding properties, to be administered under the claimed method. Regeneron's own expert, Dr. Klibanov, declared that "Sanofi is a major, sophisticated, international biopharmaceutical company; yet

despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881, Expert Declaration of Alexander M. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that "Sanofi observed that the aflibercept substance made in its Vitry, France, manufacturing facility degraded faster than Regeneron's drug substance and drug product." (*Id.* ¶ 94). As such, the 601 patent's limited disclosure fails to describe the claimed method.

Accordingly, for at least these reasons, claim 26 of the 601 patent is invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

8. Claims 27, 28, and 31-33.

The language of claims 27, 28, and 31-33 of the 601 patent is set forth above.

Claims 27, 28, and 31-33 of the 601 patent depend either directly or indirectly from claim 26, and thus incorporate the elements of claim 26. For at least the same reasons set forth above with respect to claim 26, said discussion incorporated herein by reference, and because the limitations of claims 27, 28, and 31-33 do not suffice to cure the failures of claim 26 to meet the requirements of § 112, the 601 patent does not provide a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claims 27, 28, and 31-33.

In addition, the subject matter of claims 31 and 32 is not sufficiently described in the specification, because the specification fails to disclose treating DR in patients with DME, in which patients treated with the claimed regimen lost fewer than, or gained at least, 15 letters of BCVA, according to ETDRS letter score.

Further, the subject matter of claim 33 is not sufficiently described in the specification, because the specification fails to disclose the claimed exclusion criteria being employed in

connection with a method for treating DR in patients with DME with the claimed dosing regimen. The subject matter of claim 33 is not sufficiently described in the specification, because exclusion criteria are mentioned only once in the 601 patent, and then only in the context of a Phase 3 clinical trial for AMD, along with 37 other exclusion criteria that were required to be applied. (601 patent at 10:64 – 12:18). Accordingly, there is no written description support for the application of "exclusion criteria" outside the context of an AMD clinical trial, and no written description support for applying only a subset of the 37 exclusion criteria.

Accordingly, claims 27, 28 and 31-33 of the 601 patent are invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

9. Claim 34.

The language of claim 34 of the 601 patent is set forth above.

Claim 34 of the 601 patent is invalid for lack of written description for at least the reasons identified below.

To the extent claim 34 of the 601 patent is not anticipated or obvious, as discussed above, the 601 patent fails to provide sufficient support for the subject matter claimed in claim 34. For example, the specification does not describe or disclose anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 34 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 34.

In addition, claim 34 of the 601 patent lacks written description support because the specification does not disclose a method for treating all angiogenic eye disorders with the claimed dosing regimen. For example, the working examples are limited to AMD, RVO, and DME. Claim 34 is not so limited, and thus, the 601 patent specification does not include a disclosure sufficient

to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 34.

Further, claim 34 is drawn to, among other things, the administration of "one or more secondary doses" without an upper limit on the number of secondary doses; the administration of "one or more tertiary doses" without an upper limit on the number of tertiary doses; tertiary doses being administered "at least 8 weeks" apart without an upper limit on the number of weeks between tertiary doses; administration of "doses," unbounded by any specific concentrations or even ranges of concentrations for said doses; a broad category of VEGF antagonists that comprise the recited domains but which may also comprise an untold number of additional domains and components; and a method for treating any "angiogenic eye disorder." The breadth of each of the aforementioned claim elements is not sufficiently disclosed in the specification, and therefore the specification fails to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 34.

The 601 patent specification also fails to disclose the "VEGF antagonist" formulations for the claimed method. The 601 patent provides no description of the manufacturing and process steps needed to produce "VEGF antagonist" formulations having the requisite stability, potency, and binding properties, to be administered under the claimed method. Regeneron's own expert, Dr. Klibanov, declared that "Sanofi is a major, sophisticated, international biopharmaceutical company; yet despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881, Expert Declaration of Alexander M. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that "Sanofi observed that the aflibercept substance made in its Vitry, France,

manufacturing facility degraded faster than Regeneron's drug substance and drug product." (*Id.* ¶ 94). As such, the 601 patent's limited disclosure fails to describe the claimed method.

Accordingly, for at least these reasons, claim 34 of the 601 patent is invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

10. Claims 35-39, 41-43, and 45-47.

The language of claims 35-39, 41-43, and 45-47 of the 601 patent is set forth above.

Claims 35-39, 41-43, and 45-47 of the 601 patent depend either directly or indirectly from claim 34, and thus incorporate the elements of claim 34. For at least the same reasons set forth above with respect to claim 34, said discussion incorporated herein by reference, and because the limitations of claims 35-39, 41-43, and 45-47 do not suffice to cure the failures of claim 34 to meet the requirements of § 112, the 601 patent does not provide a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claims 35-39, 41-43, and 45-47.

Further, the subject matter of claim 36 is not sufficiently described in the specification, because exclusion criteria are mentioned only once in the 601 patent, and then only in the context of a Phase 3 clinical trial for AMD, along with 37 other exclusion criteria that were required to be applied. (601 patent at 10:64 – 12:18). Accordingly, there is no written description support for the application of "exclusion criteria" outside the context of an AMD clinical trial, and no written description support for applying only a subset of the 37 exclusion criteria.

Accordingly, claims 35-39, 41-43, and 45-47 of the 601 patent are invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

* * *

For at least the reasons discussed above, the 601 patent Asserted Claims are invalid for failing to satisfy the written description requirement of 35 U.S.C. § 112.

G. Indefiniteness/Improper Dependency.

The 601 patent Asserted Claims are invalid for indefiniteness pursuant to 35 U.S.C. § 112.

1. Claim 1.

The language of claim 1 of the 601 patent is set forth above.

Claim 1 of the 601 patent is indefinite for the reasons described below.

For example, the phrase "every 4 weeks for the first 3 months" does not inform, with reasonable certainty, those skilled in the art about the scope of the invention. In addition, the term "age related macular degeneration" does not inform, with reasonable certainty, those skilled in the art about the scope of the invention, because a person of ordinary skill in the art would have understood there to be different types of age-related macular degeneration.

To the extent Regeneron argues that a "method for treating" is a limitation and requires a demonstration of efficacy, then claim 1 is indefinite for failing to articulate or offer any guidance about how to assess any such efficacy, or what levels of efficacy would suffice to meet said limitation.

Accordingly, claim 1 of the 601 patent fails to inform, with reasonable certainty, a person of ordinary skill in the art about the scope of the invention, and is therefore invalid under 35 U.S.C. § 112 for being indefinite.

2. Claims 2 and 5-9.

The language of claims 2 and 5-9 of the 601 patent is set forth above.

Claims 2 and 5-9 of the 601 patent depend either directly or indirectly from claim 1, and thus incorporate the elements of claim 1. For at least the same reasons set forth above with respect to claim 1, said discussion incorporated herein by reference, and because the limitations of claims 2 and 5-9 do not suffice to cure the failures of claim 1 to meet the requirements of § 112, claims 2

and 5-9 of the 601 patent fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.

In addition, claims 5 and 6 are indefinite, because the claims fail to articulate the testing method to be used in connection with the methods of said claims. In addition, under Regeneron's proposed construction for "best corrected visual acuity," assessing BCVA letter score, according to ETDRS, could be conducted in a variety of ways, each of which could affect the outcome of the assessment. The claims also provides no guidance as to whether the BCVA letter score is to be maintained at the claimed levels, and if so, for how long, or whether, if multiple assessments are contemplated, a single result in the claimed range is sufficient to fall within the claims.

Claim 9 is indefinite, because the claim fails to specify whether the claim requires an active step of applying the claimed exclusion criteria, leaving a person of ordinary skill in the art uncertain as to what activities might or might not constitute infringement of claim 9.

Accordingly, claims 2 and 5-9 of the 601 patent fail to inform, with reasonable certainty, a person of ordinary skill in the art about the scope of the invention, and are therefore invalid under 35 U.S.C. § 112 for being indefinite.

3. Claim 10.

The language of claim 10 of the 601 patent is set forth above.

Claim 10 of the 601 patent is indefinite for the reasons described below.

To the extent Regeneron argues that a "method for treating" is a limitation and requires a demonstration of efficacy, then claim 10 is indefinite for failing to articulate or offer any guidance about how to assess any such efficacy, or what levels of efficacy would suffice to meet said limitation.

Accordingly, claim 10 of the 601 patent fails to inform, with reasonable certainty, a person of ordinary skill in the art about the scope of the invention, and is therefore invalid under 35 U.S.C. § 112 for being indefinite.

4. Claims 11, 12, and 15-17.

The language of claims 11, 12, and 15-17 of the 601 patent is set forth above.

Claims 11, 12, and 15-17 of the 601 patent depend either directly or indirectly from claim 10, and thus incorporate the elements of claim 10. For at least the same reasons set forth above with respect to claim 10, said discussion incorporated herein by reference, and because the limitations of claims 11, 12, and 15-17 do not suffice to cure the failures of claim 10 to meet the requirements of § 112, claims 11, 12, and 15-17 of the 601 patent fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.

Claim 12 is indefinite and invalid because it does not comport with the scope of claim 10, from which it depends. Claim 10 requires injections "once every 8 weeks" after "the first 5 injections." However, claim 12 requires injections every 4 weeks "after 20 weeks." Thus, claim 12 fails to include every limitation of the claim from which it depends, rendering claim 12 indefinite and invalid under § 112, fourth paragraph.

In addition, claims 15 and 16 are indefinite, because the claims fail to articulate the testing method to be used in connection with the methods of said claims. In addition, under Regeneron's proposed construction for "best corrected visual acuity," assessing BCVA letter score, according to ETDRS, could be conducted in a variety of ways, each of which could affect the outcome of the assessment. The claims also provides no guidance as to whether the BCVA letter score is to be maintained at the claimed levels, and if so, for how long, or whether, if multiple assessments are contemplated, a single result in the claimed range is sufficient to fall within the claims.

Claim 17 is indefinite, because the claim fails to specify whether the claim requires an active step of applying the claimed exclusion criteria, leaving a person of ordinary skill in the art uncertain as to what activities might or might not constitute infringement of claim 17.

Accordingly, claims 11, 12, and 15-17 of the 601 patent fail to inform, with reasonable certainty, a person of ordinary skill in the art about the scope of the invention, and are therefore invalid under 35 U.S.C. § 112 for being indefinite and/or are invalid for improper dependency under 35 U.S.C. § 112.

5. Claim 18.

The language of claim 18 of the 601 patent is set forth above.

Claim 18 of the 601 patent is indefinite for the reasons described below.

For example, the term "diabetic retinopathy" does not inform, with reasonable certainty, those skilled in the art about the scope of the invention, because a person of ordinary skill in the art would have understood there to be different types of DR.

To the extent Regeneron argues that a "method for treating" is a limitation and requires a demonstration of efficacy, then claim 18 is indefinite for failing to articulate or offer any guidance about how to assess any such efficacy, or what levels of efficacy would suffice to meet said limitation.

Accordingly, claim 18 of the 601 patent fail to inform, with reasonable certainty, a person of ordinary skill in the art about the scope of the invention, and is therefore invalid under 35 U.S.C. § 112 for being indefinite.

6. Claims 19, 21, and 23-25.

The language of claims 19, 21, and 23-25 of the 601 patent is set forth above.

Claims 19, 21, and 23-25 of the 601 patent depend either directly or indirectly from claim 18, and thus incorporate the elements of claim 18. For at least the same reasons set forth above

with respect to claim 18, said discussion incorporated herein by reference, and because the limitations of claims 19, 21, and 23-25 do not suffice to cure the failures of claim 18 to meet the requirements of § 112, claims 19, 21, and 23-25 of the 601 patent fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.

Claim 21 is indefinite and invalid because it does not comport with the scope of claim 18, from which it depends. Claim 18 requires injections "once every 8 weeks" after "the first 5 injections." However, claim 21 requires injections every 4 weeks "after 20 weeks." Thus, claim 21 fails to include every limitation of the claim from which it depends, rendering claim 21 indefinite and invalid under § 112, fourth paragraph.

In addition, claims 23 and 24 are indefinite, because the claims fail to articulate the testing method to be used in connection with the methods of said claims. In addition, under Regeneron's proposed construction for "best corrected visual acuity," assessing BCVA letter score, according to ETDRS, could be conducted in a variety of ways, each of which could affect the outcome of the assessment. The claims also provides no guidance as to whether the BCVA letter score is to be maintained at the claimed levels, and if so, for how long, or whether, if multiple assessments are contemplated, a single result in the claimed range is sufficient to fall within the claims.

Claim 25 is indefinite, because the claim fails to specify whether the claim requires an active step of applying the claimed exclusion criteria, leaving a person of ordinary skill in the art uncertain as to what activities might or might not constitute infringement of claim 25.

Accordingly, claims 19, 21, and 23-25 of the 601 patent fail to inform, with reasonable certainty, a person of ordinary skill in the art about the scope of the invention, and are therefore invalid under 35 U.S.C. § 112 for being indefinite and/or are invalid for improper dependency under 35 U.S.C. § 112.

7. Claim 26.

The language of claim 26 of the 601 patent is set forth above.

Claim 26 of the 601 patent is indefinite for the reasons described below.

For example, the term "diabetic retinopathy in a patient with diabetic macular edema" does not inform, with reasonable certainty, those skilled in the art about the scope of the invention, because a person of ordinary skill in the art would have understood there to be different types of DR.

To the extent Regeneron argues that a "method for treating" is a limitation and requires a demonstration of efficacy, then claim 26 is indefinite for failing to articulate or offer any guidance about how to assess any such efficacy, or what levels of efficacy would suffice to meet said limitation.

Accordingly, claim 26 of the 601 patent fails to inform, with reasonable certainty, a person of ordinary skill in the art about the scope of the invention, and is therefore invalid under 35 U.S.C. § 112 for being indefinite.

8. Claims 27, 28, and 31-33.

The language of claims 27, 28, and 31-33 of the 601 patent is set forth above.

Claims 27, 28, and 31-33 of the 601 patent depend either directly or indirectly from claim 26, and thus incorporate the elements of claim 26. For at least the same reasons set forth above with respect to claim 26, said discussion incorporated herein by reference, and because the limitations of claims 27, 28, and 31-33 do not suffice to cure the failures of claim 26 to meet the requirements of § 112, claims 27, 28, and 31-33 of the 601 patent fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.

Claim 28 is indefinite and invalid because it does not comport with the scope of claim 26, from which it depends. Claim 26 requires injections "once every 8 weeks" after "the first 5

injections." However, claim 28 requires injections every 4 weeks "after 20 weeks." Thus, claim 28 fails to include every limitation of the claim from which it depends, rendering claim 28 indefinite and invalid under § 112, fourth paragraph.

In addition, claims 31 and 32 are indefinite, because the claims fail to articulate the testing method to be used in connection with the methods of said claims. In addition, under Regeneron's proposed construction for "best corrected visual acuity," assessing BCVA letter score, according to ETDRS, could be conducted in a variety of ways, each of which could affect the outcome of the assessment. The claims also provides no guidance as to whether the BCVA letter score is to be maintained at the claimed levels, and if so, for how long, or whether, if multiple assessments are contemplated, a single result in the claimed range is sufficient to fall within the claims.

Claim 33 is indefinite, because the claim fails to specify whether the claim requires an active step of applying the claimed exclusion criteria, leaving a person of ordinary skill in the art uncertain as to what activities might or might not constitute infringement of claim 33.

Accordingly, claims 27, 28, and 31-33 of the 601 patent fail to inform, with reasonable certainty, a person of ordinary skill in the art about the scope of the invention, and are therefore invalid under 35 U.S.C. § 112 for being indefinite and/or are invalid for improper dependency under 35 U.S.C. § 112.

9. Claim 34.

The language of claim 34 of the 601 patent is set forth above.

Claim 34 of the 601 patent is indefinite for the reasons described below.

For example, the term "angiogenic eye disorder" does not inform, with reasonable certainty, those skilled in the art about the scope of the invention, because a person of ordinary skill in the art would have understood there to be more angiogenic eye disorders than those that find support in the specification.

To the extent Regeneron argues that a "method for treating" is a limitation and requires a demonstration of efficacy, then claim 34 is indefinite for failing to articulate or offer any guidance about how to assess any such efficacy, or what levels of efficacy would suffice to meet said limitation.

The term "one or more secondary doses" is indefinite. The term fails to place an upper limit on the number of secondary doses, placing the claim outside the scope of what is disclosed in the specification, and leaving persons of ordinary skill in the art unsure about when they may or may not be operating within the bounds of the claim. Likewise, the term "one or more tertiary doses" is indefinite for failing to place an upper limit on the number of tertiary doses.

Accordingly, claim 34 of the 601 patent is invalid for indefiniteness because it fails to inform, with reasonable certainty, those of ordinary skill in the art about the scope of the invention.

10. Claims 35-39, 41-43, and 45-47.

The language of claims 35-39, 41-43, and 45-47 of the 601 patent is set forth above.

Claims 35-39, 41-43, and 45-47 of the 601 patent depend either directly or indirectly from claim 34, and thus incorporate the elements of claim 34. For at least the same reasons set forth above with respect to claim 34, said discussion incorporated herein by reference, and because the limitations of claims 35-39, 41-43, and 45-47 do not suffice to cure the failures of claim 34 to meet the requirements of § 112, claims 35-39, 41-43, and 45-47 of the 601 patent fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.

Claim 36 is indefinite, because the claim fails to specify whether the claim requires an active step of applying the claimed exclusion criteria, leaving a person of ordinary skill in the art uncertain as to what activities might or might not constitute infringement of claim 36.

Accordingly, claims 35-39, 41-43, and 45-47 of the 601 patent fail to inform, with reasonable certainty, a person of ordinary skill in the art about the scope of the invention, and are

therefore invalid under 35 U.S.C. § 112 for being indefinite and/or are invalid for improper dependency under 35 U.S.C. § 112.

* * *

Accordingly, the 601 patent Asserted Claims are invalid for indefiniteness pursuant to 35 U.S.C. § 112.

H. Unpatentable Subject Matter.

The language of the 601 patent Asserted Claims is set forth above.

At least claims 6, 9, 15-17, 23-25, 31-33, and 36 of the 601 patent are invalid for failure to claim patent eligible subject matter pursuant to 35 U.S.C. § 101.

Claims 6, 15, 16, 23, 24, 31, and 32 of the 601 patent are directed to the mere observation of outcomes resulting from the prior art dosing regimens set forth in the independent claims. Claims 6, 15, 16, 23, 24, 31, and 32 do not require any alteration of the dosing regimens as a result of the observed BCVA/ETDRS scores, nor do the claims contain any active steps (e.g., assessment or measurement). As a result, claims 6, 15, 16, 23, 24, 31, and 32 are drawn to nothing more than the observation of a natural law.

Claims 9, 17, 25, 33, and 36 are also invalid for failure to claim patent eligible subject matter. The mere recitation of "exclusion criteria," without any instruction to alter the claimed dosing regimen, or any other active step, renders the subject matter of claims 9, 17, 25, 33, and 36 patent ineligible for being drawn to pure mental steps and/or abstract ideas.

Accordingly, claims 6, 9, 15-17, 23-25, 31-33, and 36 of the 601 patent are invalid for failure to claim patent eligible subject matter pursuant to 35 U.S.C. § 101.

I. Unenforceability.

For at least the following reasons, the 601 patent Asserted Claims are unenforceable due to Regeneron's inequitable conduct during prosecution of the application(s) that led to the 601 patent issuance and the positions that Regeneron has taken before the Board.[30]

For example, while arguing to the U.S.P.T.O. during prosecution of related applications that the disclosures of Heier 2012 supported the patentability of the pending claims, Regeneron knew that the VIEW dosing regimens were widely disclosed in the prior art, including in its own prior art press releases, (*e.g.*, 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release), 10-Q forms, and 10-K forms, which were withheld from the U.S.P.T.O. while making those arguments. Moreover, Regeneron made arguments to the U.S.P.T.O. which were, upon information and belief, intentionally misleading and inaccurate. (*See, e.g.*, 338 patent PH, 9/11/2015 Applicant Remarks; 069 patent PH, 1/30/2017 Applicant Remarks; 681 patent PH, 6/25/2018 Applicant Remarks; IPR2021-00880, Petition for *Inter Partes* Review of U.S. Patent 9,669,069 at 69-72; IPR2021-00880, Declaration of T. Albini, M.D. ¶¶ 217-24; IPR2021-00881, Petition for *Inter Partes* Review of U.S. Patent 9,254,338 at 66-69; IPR2021-00881, Declaration of T. Albini, M.D. ¶¶ 404-11).

Further, Regeneron was aware of the materiality of references disclosing the VIEW dosing regimen, which is evidenced by its representations to the U.S.P.T.O. during prosecution of related applications and its subsequent decisions to submit a subset of said references to the U.S.P.T.O. in connection with other pending related applications. (*See, e.g.*, 681 patent PH, 6/25/2018 Applicant

[30] Fact discovery in this case is ongoing; Mylan reserves the right to amend, supplement, and/or clarify any of the statements provided herein based on any documents, deposition testimony, and/or other discovery materials that have not yet been obtained by, produced, or provided to Mylan, and/or with respect to which Mylan has not yet had adequate opportunity to review and analyze.

Remarks; 601 patent PH, 6/30/2020 Information Disclosure Statement). Further, upon information and belief, Regeneron was aware of the materiality of the misleading and inaccurate statements made to the U.S.P.T.O. during prosecution of the earlier applications. (*See, e.g.*, 338 patent PH, 9/11/2015 Applicant Remarks; 069 patent PH, 1/30/2017 Applicant Remarks; 681 patent PH, 6/25/2018 Applicant Remarks; 681 patent PH, 7/26/2018 Notice of Allowability).

Continuing this pattern of deception, during prosecution of the 267 application, Regeneron, upon information and belief, in an attempt to obscure references that it knew to be relevant to the subject matter of the pending claims, submitted hundreds of references to the U.S.P.T.O., effectively burying the references that contained anticipatory disclosures. (*See, e.g.*, 601 patent at pp. 1-8).

The most reasonable inference to be drawn from Regeneron's withholding of the above references from the U.S.P.T.O. and making misleading and inaccurate statements to the U.S.P.T.O. during the prosecution of the earlier applications in the patent family, followed by flooding the U.S.P.T.O. with hundreds of references during the prosecution of the 267 application, is that the actions were done with the intent to deceive the U.S.P.T.O.

Further, given the applicant's failure to provide relevant disclosures to the Examiner, and the misleading and inaccurate statements made to the U.S.P.T.O., during at least the prosecutions of the applications leading to the 338 patent and the 069 patent; given Regeneron's knowledge of the materiality of those actions; given that the most reasonable inference to be drawn from those actions is that they were done with the intent to deceive; and given the close relation of the claims at issue in the 338 and 069 patents to the other issued claims in the patent family; each member of the patent family, including the 601 patent, is unenforceable for inequitable conduct. *See, e.g., eSpeed, Inc. v. Brokertec USA, LLC*, 417 F. Supp. 2d 580 (D. Del. Feb. 22, 2006).

In addition, during at least PGR2021-00117, IPR2021-00880, and IPR2021-00881, Regeneron has taken positions that it knows to be misleading, inaccurate, and without merit, including, but not limited to, with respect to the identity of the VEGF Trap-Eye and aflibercept molecule, and its amino acid sequence and nucleotide sequence. (*See, e.g.*, IPR2021-00881, Patent Owner Response, Paper 40 at 24-35). Further, Regeneron has obstructed the PTAB proceedings at least through its continued pursuit of the above arguments, meritless claim construction arguments, and also by presenting expert witnesses that were unwilling to answer basic questions and provide full and truthful testimony.

For at least these reasons, the 601 patent Asserted Claims are unenforceable for inequitable conduct.

VI. INVALIDITY CONTENTIONS REGARDING THE 865 PATENT.

A. The Knowledge of a Person of Ordinary Skill in the Art.

In the context of the obviousness analysis, the scope of the prior art is directed to the field of endeavor of the invention, and includes the knowledge of a person of ordinary skill in the art. Here, a person of ordinary skill in the art would have at least a Ph.D. in chemistry, chemical engineering, biochemistry, pharmacology, or a related field, along with one to two years of experience in the development and manufacture of formulations of therapeutic proteins (or a lower degree with more practical industrial experience). The POSA would have access to biologists, biochemists, physicians, pharmaceutical formulators, and the like, with knowledge and experience in fields such as drug discovery and development and the treatment of ophthalmic conditions.

B. Prior Art Relevant to the 865 Patent.

In the context of the obviousness analysis, the scope of the prior art is directed to the field of endeavor of the invention. The scope of the prior art relates, in general, to therapeutic protein formulations, including those for ophthalmic use.

Mylan relies on at least the references identified in Appendix B in support of its Invalidity Contentions regarding the 865 patent based on anticipation and obviousness under 35 U.S.C. § 102 and 35 U.S.C. § 103. Unless otherwise and expressly stated, it should be presumed that Mylan intends to rely upon each reference in its entirety to the extent relevant or appropriate, including references cited in and/or referenced within the references identified in Appendix B. Similarly, the headings included in this section are for convenience only, and do not limit Mylan's right to rely on any reference to the extent relevant or appropriate.

C. 35 U.S.C. § 102 and § 103 – The 865 Patent Asserted Claims Are Anticipated and Rendered Obvious.

1. Claim 1.

a. Anticipation by Fraser.

The language of claim 1 of the 865 patent is set forth above.

Fraser evaluated the effect of VEGF on pituitary-ovarian function. (Fraser at 1114.) In the study, macaques were given an injection of a VEGF antagonist. (*Id.*) In Fraser's experiments, "VEGF was inhibited by administration of VEGF Trap$_{R1R2}$, a recombinant, chimeric protein comprising Ig domain 2 of human VEGF-R1 and Ig domain 3 of human VEGF-R2, expressed in sequence with the human Fc." (*Id.* at 1115). Fraser cites to, and incorporates by reference, Wulff (i.e., reference number 17) and Holash (i.e., reference number 21). (*See* Fraser at 1114-15 1119, 1122). Wulff further incorporates by reference Papadopoulos (WO 00/75319 Al). (*See* Wulff at 2798 n.1).

Fraser expressly discloses the VEGF antagonist, co-solvent, buffer and stabilizing agent elements of claim 1.[31] (*See, e.g.*, Fraser at 1115 ("VEGF Trap$_{R1R2}$ (Regeneron Pharmaceuticals,

[31] Mylan's position with respect to the "organic co-solvent" element of the 865 patent claims is set forth in Mylan's claim construction briefing. (*See* Dkt. No. 122; Dkt. No. 173-1). In short, Mylan contends that its BLA product does not comprise an "organic co-solvent." However, in the event

Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose.")).[32] Accordingly, Fraser expressly discloses the "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" elements of claim 1. (*Id.*; *see also* Marra).

Fraser also expressly discloses the first "wherein" clause of claim 1. The element "wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4" does not distinguish the claim from the prior art. Specifically, the references outlined above either explicitly or inherently disclose VEGF antagonist fusion proteins posttranslationally glycosylated at one or more asparagine residues. First, Fraser expressly cites to, and incorporates by reference, Holash for its VEGF antagonist. Holash discloses production of the VEGF antagonist in a CHO cell: "VEGF-Trap$_{R1R2}$ was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2. All of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells." (Holash at 11393-94; *see also* Rudge). Second, Fraser expressly cites to, and incorporates by reference, Wulff for its VEGF antagonist, and Wulff cites to, and incorporates by reference, Papadopoulos. A person of ordinary skill in the art would have known that Papadopoulos teaches that the fusion proteins in Fraser and claimed by the 865

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the Court adopts Regeneron's claim construction proposal, and finds that formulations comprising polysorbate at concentrations (e.g.) below 3% meet the "organic co-solvent" element of the claims, then Mylan contends the 865 patent claims are invalid for the reasons set forth herein. In other words, as described, the use of polysorbate at concentrations below 3% was expressly disclosed in at least the prior art discussed herein. Consequently, to the extent Mylan's BLA product is found to meet the "organic co-solvent" of the 865 patent claims, the prior art discloses that element for the same reasons, thus invalidating the claims.

[32] Tween-20 is a commercial brand name for polysorbate-20. (*See* Andya at [0123]).

patent are glycosylated at five asparagine residues when the protein is expressed in CHO cells. (Papadopoulos at 81:20 – 82:2 ("There are five possible N-linked glycosylation sites in Flt1D2.Flk1D3.FcΔC1(a). All five of them are found to be glycosylated to varying degrees [following expression in CHO cells.]"), Fig. 36 (underlining the five asparagine residues in SEQ ID NO: 2 that are glycosylation sites); *see also* Routier).

Fraser and Wulff incorporate by reference, Papadopoulos, which teaches the amino acid sequence of SEQ ID NO: 4, its production in CHO cells, and methods of purifying from CHO cells. Specifically, Papadopoulos teaches methods of producing VEGF antagonist fusion proteins for use in formulations and prefilled syringes, and these methods included isolating and purifying the protein product by affinity and size exclusion chromatography. (Papadopoulos at 67:25 – 68:5 ("The process for production of Flt1D2.Flk1D3.FcΔC1(a) protein … involves suspension culture of recombinant Chinese hamster ovary (CHO K1/E1A) cells which constitutively express the protein product. The cells are grown in bioreactors and the protein product is isolated and purified by affinity and size exclusion chromatography."), Examples 21-22)). As described in Example 20, Papadopoulos teaches methods for producing the VEGF-specific fusion protein of SEQ ID NO: 4 from CHO cells. (Papadopoulos at 67:4-17). Papadopoulos teaches VEGFR1R2-FcΔC1(a) (i.e., SEQ ID NO: 4) and that it "was constructed by insertion of DNA encoding amino acids SDT (corresponding to amino acids 27-29 of Figure 24A-24C) between Flt1d2-Flk1d3-FcΔC1(a) amino acids 26 and 27 of Figure 21A-21C (GG) and removal of DNA encoding amino acids GPG corresponding to amino acids 229-231 of Figure [21A-21C]." (Papadopoulos at 67:7-12). Further, Papadopoulos discloses that the purification methods applied to SEQ ID NO: 2 are useful for purifying SEQ ID NO: 4 and other similar fusion proteins. (Papadopoulos at Fig. 24A-24C, 69:15-19 (stating that "the same methodologies as described [] for Flt1D2.Flk1D3.FcΔC1(a) were used

to produce [the related fusion protein] Flt1D2.VEGFR3D3.FcΔC1(a).")). Papadopoulos describes using size exclusion chromatography "[t]o remove aggregates and other contaminants." (Papadopoulos at 39:15-19).

A person of ordinary skill in the art reading the prior art (e.g., Holash, Papadopoulos, Vitti, Rudge) therefore would have understood that SEQ ID NO: 4 is encompassed by VEGF-Trap$_{R1R2}$. Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a VEGF antagonist fusion protein that "comprises amino acids 27-457 of SEQ ID NO:4." (*See, e.g.*, Papadopoulos at 67:4-17 (Example 20)).

Claim 1 adds the element "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 merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Notwithstanding, even if some limiting effect is granted to the "98% ... native conformation" element, it is inherent in Fraser's formulation and therefore does not distinguish the claimed "vial" from the prior art. For example, Dix (U.S. Patent No. 8,110,546) discloses (among other results) over 99% VEGF antagonist remaining in "[n]ative [c]onfiguration" after storage at 5° C for two months (Table 9) for Dix's 25 mg/ml formulation, which the patentee has conceded is the identical formulation and possesses the same stability properties as Fraser. (*See* 546 patent 11/22/11 Response to 7/13/11 Office Action at 2-4 (the patentee describing Dix formulation and admitting it is identical to Fraser)).

For at least these reasons, Fraser anticipates claim 1.

b. Anticipation by Wulff.

Wulff evaluated the VEGF TrapR1R2 protein and its biological activity in inhibiting VEGF. (Wulff at 2797). Wulff describes the VEGF antagonist used in the experiments as follows:

> a recombinant chimeric protein comprising portions of the extracellular, ligand binding domains of the human VEGF receptors Flt-1 (VEGF-R1, Ig domain 2) and KDR (VEGF-R2, Ig domain 3) expressed in sequence with the Fc portion of human IgG (Fig. 1). The presence of the Fc domain results in homodimerization of the recombinant protein, thereby creating a high affinity (KD1–5pM) VEGF Trap. The VEGF trap was expressed in CHO cells and was purified by protein A affinity chromatography followed by size-exclusion chromatography. The specificity of VEGF binding and the affinity to VEGF of VEGF Trap R1R2 were determined by Biacore (Uppsala, Sweden).

(Wulff at 2798).

Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (*Id.*). Wulff discloses that a dose of the VEGF Trap was injected subcutaneously into marmosets. (*Id.*). Accordingly, Wulff expressly discloses the "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" elements of claim 1. (*Id.*; *see also* Marra).

Wulff also expressly discloses the first "wherein" clause of claim 1. The element "wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4" does not distinguish the claim from the prior art. Specifically, the references outlined above either explicitly or inherently disclose VEGF antagonist fusion proteins posttranslationally glycosylated at one or more asparagine residues. Wulff cites to, and incorporates by reference, Papadopoulos. A person of ordinary skill in the art would have known that Papadopoulos teaches that the fusion proteins in Wulff and claimed by the 865 patent are glycosylated at five asparagine residues when the protein is expressed in CHO cells. (Papadopoulos at 81:20 – 82:2 ("There are five possible N-linked glycosylation sites in Flt1D2.Flk1D3.FcΔC1(a). All five of them are found

to be glycosylated to varying degrees [following expression in CHO cells.]"), Fig. 36 (underlining the five asparagine residues in SEQ ID NO: 2 that are glycosylation sites); *see also* Routier).

Wulff further discloses that the VEGF TrapR1R2 was administered subcutaneously to the monkeys "[t]o inhibit vascular endothelial growth factor (VEGF)," (Wulff at 2797-98), and that "VEGF Trap R1R2 may be more efficient in inhibiting VEGF, because it contains an additional domain of the second VEGF receptor KDR." (*Id.* at 2804). Wulff also expressly cites to, and incorporates by reference, Papadopoulos (WO 00/75319 Al). (*See* Wulff at 2798, n.1). Papadopoulos teaches amino acid sequences encoding VEGF antagonist fusion proteins that fall within the scope of claim 1, including a protein called "Flt1D2.Flk1D3.FcΔC1(a)," which corresponds to SEQ ID NO: 2 of the 865 patent, and a protein called "VEGFRIR2-FcΔC1(a)," which corresponds to SEQ ID NO: 4 of the 865 patent (also known as "aflibercept").[33] The nucleotide and amino acid sequences of VEGFRIR2-FcΔC1(a) are provided in Papadopoulos Figs. 24A-24C. The amino acid sequence of the VEGFRIR2-FcΔC1(a) protein in Papadopoulos is identical to SEQ ID NO: 4 of the 865 patent. Papadopoulos also teaches that these VEGF antagonist fusion proteins were produced in recombinant Chinese hamster ovary (CHO) cells. (*See* 67:25 – 68:5 ("The process for production of Flt1D2.Flk1D3.FcΔC1(a) [*i.e.,* the protein of SEQ ID NO: 2 of the 865 patent] protein ... involves suspension culture of recombinant Chinese hamster

[33] U.S. Pub. No. 2016/0144025 ("Vitti") confirms that "VEGFRIR2-FcΔC1(a)" is "also known as aflibercept." (Vitti at [0086]). Vitti teaches that aflibercept is "encoded by the amino acid sequence of SEQ ID NO: 11," (*id.*), which is identical to SEQ ID NO:4 of the 865 patent. Vitti also explains that aflibercept "consists of a dimer of two polypeptides consisting of amino acids 27-457 of [SEQ ID NO:4 of the 865 patent]." (*Id.* at [0197]). The complete SEQ ID NO:4 includes, *inter alia,* a signal peptide that is removed during protein production, and an Fe sequence of human IgG that causes the protein to dimerize. (*See* Papadopoulos at Fig. 24A (identifying the signal sequence at amino acids 1-26 of SEQ ID NO: 4); *id.* at Figs. 24B-C (identifying the human Fe region "hFCΔClA" at amino acids 232-458). Accordingly, the VEGF fusion protein of SEQ ID NO:4 and the dimerized VEGF fusion protein consisting of amino acids 27-457 of SEQ ID NO:4 both refer to aflibercept, as known in the prior art.

ovary (CHO K1/E1A)) cells which constitutively express the protein product. The cells are grown in bioreactors and the protein product is isolated and purified by affinity and size exclusion chromatography."). Papadopoulos also discloses that "CHO transiently expressed VEGFRIR2-FcΔC1(a)" (i.e., the protein of SEQ ID NO: 4 of the 865 patent). (*Id.* at 82:12-13).

As described above, the element "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 merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g., In re Copaxone*, 906 F.3d at 1023-24; *Bristol-Myers*, 246 F.3d at 1375-76. Notwithstanding, even if some limiting effect is granted to the "98% ... native conformation" element, it is inherent in Wulff's formulation and therefore does not distinguish the claimed "vial" from the prior art. For example, Dix discloses (among other results) over 99% VEGF antagonist remaining in "[n]ative [c]onfiguration" after storage at 5° C for two months (Table 9) for Dix's 25 mg/ml formulation, which the patentee has conceded is the identical formulation and possesses the same stability properties as Fraser. (*See* 546 patent 11/22/11 Response to 7/13/11 Office Action at 2-4 (the patentee describing Dix formulation and admitting it is identical to Fraser)). Accordingly, Wulff discloses, either expressly or inherently, every element of the two "wherein" clauses of claim 1.

For at least these reasons, Wulff anticipates claim 1.

c. Anticipation by the 226 Patent.

The 226 patent discloses the same VEGF antagonist disclosed in the 865 patent, the structure of which is described in claim 1 of the 865 patent. (*See, e.g.*, 226 patent at claim 3, 2:3-19). The 226 patent also discloses that in specific embodiments, "the VEGF antagonist is expressed in a mammalian cell line such as a CHO cell." (*See, e.g.*, *id.* at 5:37-39).

The 226 patent also discloses a number of formulations of the VEGF antagonist, each of which comprises "an organic co-solvent," a "buffer," and a "stabilizing agent," as those terms are defined in the 865 patent. (*See, e.g.*, 226 patent at 2:15 – 3:34, 7:5-18, 7:60 – 12:10).

The 226 patent also discloses formulations that resulted in at least 98% of the VEGF antagonist being present in native conformation following storage at 5° C for two months as measured by SEC. (*See, e.g.*, 226 patent at 7:63 – 8:19).

For at least these reasons, the 226 patent anticipates claim 1.

d. Anticipation by Public Use.

Claim 1 of the 865 patent is invalid for being in public use, on sale, or otherwise available to the public before the earliest effective filing date to which claim 1 of the 865 patent is entitled. For example, the formulation of EYLEA meets each and every limitation of claim 1, either expressly or inherently. (*See, e.g.*, EYLEA Prescribing Information (Nov. 2011) at 9). EYLEA was on the market as of Nov. 2011, and was being utilized in publicly disclosed pre-clinical and clinical trials well before that date.[34]

For at least these reasons, claim 1 is invalid for being in public use, on sale, or otherwise available to the public before the earliest effective filing date to which claim 1 of the 865 patent is entitled.

[34] In addition to the evidence cited herein, Mylan reserves the right to modify and supplement this defense based on information and documents obtained through discovery in litigation.

e. Obviousness over Fraser.

Additionally, claim 1 of the 865 patent would have been obvious over at least Fraser, either alone or in combination with Dix and/or Holash and/or Liu, in view of the knowledge of a person of ordinary skill in the art.[35]

As explained, Fraser discloses, either expressly or inherently, every element of claim 1. Dix discloses the identical formulation as Fraser. Dix further confirms that the Fraser formulation[36] inherently comprises a VEGF antagonist "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." Specifically, Dix discloses that over 99% of the VEGF antagonist in the Fraser, 25 mg/ml formulation remained in "[n]ative [c]onfiguration" (i.e., native conformation) after storage at 5°C for two months. (Dix at 11:15 – 12:20, Table 9; *see also* Chi; Arvinte; Amersham; Amersham Application Note; Parkins; Frokjaer; Fyfe).

Holash describes "a very potent high-affinity VEGF blocker that has prolonged *in vivo* pharmacokinetics and pharmacodynamics, lacks nonspecific toxicities, and can effectively suppress the growth and vascularization of a number of different types of tumors *in vivo*." (Holash at 11393). Holash further describes that "VEGF-Trap$_{R1R2}$ was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2." (*Id.* at 11393-94; *see also* Rudge; Vitti; Papadopoulos). A person of ordinary skill in the art reading Holash therefore would have understood that SEQ ID NO: 4 is encompassed by VEGF-Trap$_{R1R2}$. Holash also describes that "[a]ll of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells."

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[35] To the extent that any specific limitation is found not to be explicitly or inherently disclosed in these references, it would have been achieved through routine optimization by one of ordinary skill in the art.

[36] The patentee has conceded that the Fraser formulation is one of Dix's two tested formulations. (*See* 546 patent 11/22/11 Response to 7/13/11 Office Action at 2-4).

(*Id.* at 11394). A person of ordinary skill in the art would have understood that a protein "produced and purified from Chinese hamster ovary cells," especially in order to be targeted for treatment of DR (i.e., injection into the eye), must be as pure as possible and would have expected the protein to be a fusion protein wherein at least 98% is in native conformation.

To the extent the BLA product could somehow satisfy the claim limitations, those limitations are also met by the prior art. For example, Liu (US2004/0197324) discloses optimizing formulations having a co-solvent (e.g., polysorbate 20), a buffer (e.g., histidine-HCl), and a stabilizer (e.g., trehalose or Arginine HCl) to achieve stable liquid protein formulations having at least 98% "native conformation" after storage at 5° C for two months. (*See, e.g.*, Liu at [0013] ("[T]he present invention concerns a highly concentrated antibody formulations of low turbidity comprising antibody (40-150 mg/ml), histidine (10-100 mM), sugar (e.g., trehalose or sucrose, 20-350 mM) and polysorbate (0.01%-0.1%)."); *id.* at Table 1 (reporting two liquid protein formulations—both containing polysorbate 20 and either Arginine HCl or trehalose—having >98% monomer after storage at 5° C for 3 months (i.e., 99.3% and 98.8% respectively) or longer); Lam; Daly II; Peyman; Wiegand; Daly III; Parkins; Baffert; Avery; Avastin PI; Marra; 400 patent). A person of ordinary skill in the art would have been highly motivated to combine the aforementioned teachings to achieve the "vial" of claim 1. Furthermore, a person of ordinary skill in the art would have reasonably expected success combining the aforementioned teachings to achieve a "vial" with the stability characteristics (i.e., "98%...native conformation") of claim 1. Accordingly, claim 1 of the 865 patent would have been obvious to a person of ordinary skill in the art over any one of the aforementioned combinations.

f. Obviousness over Wulff.

Additionally, claim 1 of the 865 patent would have been obvious over at least Wulff, either alone or in combination with Liu, in view of the knowledge of a person of ordinary skill in the art.[37]

As explained, Wulff discloses, either expressly or inherently, every element of claim 1. For example, Liu discloses optimizing formulations having a co-solvent (e.g., polysorbate 20), a buffer (e.g., histidine-HCl), and a stabilizer (e.g., trehalose or Arginine HCl) to achieve stable liquid protein formulations having at least 98% "native conformation" after storage at 5° C for two months. (*See, e.g.*, Liu at [0013] ("[T]he present invention concerns a highly concentrated antibody formulations of low turbidity comprising antibody (40-150 mg/ml), histidine (10-100 mM), sugar (e.g., trehalose or sucrose, 20-350 mM) and polysorbate (0.01%-0.1%)."); *id.* at Table 1 (reporting two liquid protein formulations—both containing polysorbate 20 and either Arginine HCl or trehalose—having >98% monomer after storage at 5° C for 3 months (i.e., 99.3% and 98.8% respectively) or longer); Lam; Daly II; Peyman; Wiegand; Daly III; Parkins; Baffert; Avery; Avastin PI; Marra). A person of ordinary skill in the art would have been highly motivated to combine the aforementioned teachings to achieve the "vial" of claim 1. Furthermore, a person of ordinary skill in the art would have reasonably expected success combining the aforementioned teachings to achieve a "vial" with the stability characteristics (i.e., "98%...native conformation") of claim 1. Accordingly, claim 1 of the 865 patent would have been obvious to a person of ordinary skill in the art over any one of the aforementioned combinations.

[37] To the extent that any specific limitation is found not to be explicitly or inherently disclosed in these references, it would have been achieved through routine optimization by one of ordinary skill in the art.

g. Obviousness over the 226 Patent.

Additionally, claim 1 of the 865 patent would have been obvious over at least the 226 patent, either alone or in combination with Liu, in view of the knowledge of a person of ordinary skill in the art.[38]

As explained, the 226 patent discloses, either expressly or inherently, every element of claim 1. For example, Liu discloses optimizing formulations having a co-solvent (e.g., polysorbate 20), a buffer (e.g., histidine-HCl), and a stabilizer (e.g., trehalose or Arginine HCl) to achieve stable liquid protein formulations having at least 98% "native conformation" after storage at 5° C for two months. (*See, e.g.*, Liu at [0013] ("[T]he present invention concerns a highly concentrated antibody formulations of low turbidity comprising antibody (40-150 mg/ml), histidine (10-100 mM), sugar (e.g., trehalose or sucrose, 20-350 mM) and polysorbate (0.01%-0.1%)."); *id.* at Table 1 (reporting two liquid protein formulations—both containing polysorbate 20 and either Arginine HCl or trehalose—having >98% monomer after storage at 5° C for 3 months (i.e., 99.3% and 98.8% respectively) or longer); Lam; Daly II; Peyman; Wiegand; Daly III; Parkins). A person of ordinary skill in the art would have been highly motivated to combine the aforementioned teachings to achieve the "vial" of claim 1. Furthermore, a person of ordinary skill in the art would have reasonably expected success combining the aforementioned teachings to achieve a "vial" with the stability characteristics (i.e., "98%...native conformation") of claim 1. Accordingly, claim 1 of the 865 patent would have been obvious to a person of ordinary skill in the art over any one of the aforementioned combinations.

[38] To the extent that any specific limitation is found not to be explicitly or inherently disclosed in these references, it would have been achieved through routine optimization by one of ordinary skill in the art.

h. Obviousness over LUCENTIS PI (2006).

Additionally, claim 1 of the 865 patent would have been obvious over at least one or more references describing the LUCENTIS formulation, in combination with one or more references disclosing aflibercept or VEGF Trap-Eye, further in view of the knowledge of a person of ordinary skill in the art.

For example, U.S. Patent No. 7,303,747 describes the structure and sequence of the VEGF antagonist recited in the claims of the 865 patent. (*See, e.g.*, 747 patent at 5:3-26, SEQ ID NO:6). The 747 patent also discloses the use of said VEGF antagonists for use in treating eye disorders, including macular degeneration and DR. (*See, e.g.*, 747 patent at 5:27-51, 20:17 – 22:42).

Given the disclosures of the 747 patent and other references, (*see* Holash; Rudge; Vitti; Papadopoulos), disclosing the sequence and structure of aflibercept (i.e., VEGF Trap-Eye, or VEGFR1R2-FcΔC1(a)), and its use in treating eye disorders, a person of ordinary skill in the art would have been motivated to review information about formulations of other VEGF antagonists known to be used in treating eye disorders, and formulated to safely deliver a pharmaceutical active into a patient's eye. Accordingly, one of ordinary skill in the art would have looked to the LUCENTIS formulation. LUCENTIS was provided in a vial, and included a VEGF antagonist, "an organic co-solvent," a "buffer," and a "stabilizing agent," as those terms are defined in the 865 patent. (*See, e.g.*, Shams at 31:27-30 ("Each vial contains 0.7 mL of either 6 mg/mL (0.3 mg dose level) or 10 mg/mL (0.5-mg dose level) of ranibizumab aqueous solution (pH 5.5) with 10 mM of histidine, 100 mg/mL of trehalose, and 0.01 % polysorbate."); LUCENTIS PI (2006) § 11; Liu; Fraser; Wulff; 226 patent; Lam; Daly II; Peyman; Wiegand; Daly III; Parkins; Baffert; Avery; Avastin PI; Avery 2006; Ferrara 2006; Gaudreault 2005; Duvvuri 2003; Ghate 2006). Given the approval of the LUCENTIS formulation, a person of ordinary skill in the art would have been motivated to use that formulation in formulating aflibercept/VEGF Trap-Eye. Further, a person

of ordinary skill in the art would have had a reasonable expectation of success given the successful formulation and FDA approval of LUCENTIS.

Accordingly, claim 1 of the 865 patent would have been obvious over any of the prior art references disclosing the VEGF antagonist and its use in treating eye disorders, including the 747 patent, in combination with one or more references disclosing the formulation used in the LUCENTIS formulation.

2. Claim 2.

The language of claim 2 of the 865 patent is set forth above.

Claim 2 of the 865 patent depends from claim 1 and thus incorporates the elements of claim 1. For at least the same reasons set forth above with respect to claim 1, said discussion incorporated herein by reference, claim 2 is anticipated and/or obvious.

The element "wherein said organic co-solvent comprises polysorbate" does not distinguish the claim from claim 1 or the prior art that invalidates claim 1. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said organic co-solvent comprises polysorbate." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798; *see also* 226 patent; Liu; Lam; Daly II; Peyman; Wiegand; Daly III; Parkins; Baffert; Avery; Avastin PI). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said organic co-solvent comprises polysorbate."

The additional element "wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml" does not distinguish the claim from claim 1 or the prior art that invalidates claim 1. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml." For example, Andya specifically discloses that a "lyophilized formulation can be reconstituted to generate a stable reconstituted formulation having a protein concentration which is significantly higher (*e.g.*, from about 2-40 times higher, preferably 3-10 times higher and most preferably 3-6 times higher) than the protein concentration in the pre-lyophilized formulation." (Andya at [0008]). Andya also discloses that "while the protein concentration in the pre-lyophilized formulation may be 5 mg/mL or less, the protein concentration in the reconstituted formulation is generally 50 mg/mL or more." (Andya at [0008]; *see also* Wiegand). Given that Fraser formulation's VEGF Trap concentration was 24.3 mg/ml, a person of ordinary skill would have been motivated to generate a stable formulation having a significantly higher protein concentration, *e.g.*, by following Andya's teachings to lyophilize and reconstitute in histidine buffer so as to increase the concentration by at least 2-fold (*e.g.*, from ~25 to ~50 mg/ml).

Claim 2 of the 865 patent is therefore anticipated for the same reasons stated above for claim 1. Additionally, claim 2 would have been obvious over at least, *inter alia*, the combinations identified above for claim 1, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claim 1. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including VEGF antagonist fusion protein at a concentration of 40 mg/ml and with an organic co-solvent comprising polysorbate, and would have reasonably expected success with such formulation.

3. Claim 3.

The language of claim 3 of the 865 patent is set forth above.

Claim 3 of the 865 patent depends from claim 2, which depends from claim 1, and thus claim 3 incorporates the elements of claims 1 and 2. For at least the same reasons set forth above with respect to claims 1 and 2, said discussion incorporated herein by reference, claim 3 is anticipated and/or obvious.

The additional element "wherein said organic co-solvent comprises 0.01% to 3% polysorbate" does not distinguish the claim from claims 1 and 2, or the prior art that invalidates claims 1 and 2. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said organic co-solvent comprises 0.01% to 3% polysorbate." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations where "[p]olysorbate 20 was added to the formulations at concentrations of 0.005%, 0.01%, and 0.02%." (Andya at [0175]; *see also* 226 patent; Liu; Lam; Daly II; Peyman; Wiegand; Daly III; Parkins; Baffert; Avery; Avastin PI). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said organic co-solvent comprises 0.01% to 3% polysorbate."

Claim 3 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1 and 2. Additionally, claim 3 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1 and 2, in view of (or in further combination with) the

knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1 and 2. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including an organic co-solvent comprising 0.01% to 3% polysorbate, and would have reasonably expected success with such formulation.

4. Claim 4.

The language of claim 4 of the 865 patent is set forth above.

Claim 4 of the 865 patent depends from claim 2, which depends from claim 1, and thus claim 4 incorporates the elements of claims 1 and 2. For at least the same reasons set forth above with respect to claims 1 and 2, said discussion incorporated herein by reference, claim 4 is anticipated and/or obvious.

The additional element "wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20" does not distinguish the claim from claims 1 and 2 or the prior art that invalidates claims 1 and 2. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations where "[p]olysorbate 20 was added to the formulations at concentrations of 0.005%, 0.01%, and 0.02%." (Andya at [0175]; *see also* 226 patent; Liu; Lam; Daly II; Peyman; Wiegand; Daly III; Parkins; Baffert). Moreover, a person of

ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20."

Claim 4 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1 and 2. Additionally, claim 4 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1 and 2, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1 and 2. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including an organic co-solvent comprising about 0.03% to about 0.1% polysorbate 20, and would have reasonably expected success with such formulation.

5. Claim 5.

The language of claim 5 of the 865 patent is set forth above.

Claim 5 of the 865 patent depends from claim 2, which depends from claim 1, and thus claim 5 incorporates the elements of claims 1 and 2. For at least the same reasons set forth above with respect to claims 1 and 2, said discussion incorporated herein by reference, claim 5 is anticipated and/or obvious.

The additional element "wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20" does not distinguish the claim from claims 1 and 2, or the prior art that invalidates claims 1 and 2. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 %

(wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations where "[p]olysorbate 20 was added to the formulations at concentrations of 0.005%, 0.01%, and 0.02%." (Andya at [0175]; *see also* 226 patent; Liu; Lam; Daly II; Peyman; Wiegand; Daly III; Parkins; Baffert; Avery; Avastin PI). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20."

Claim 5 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1 and 2. Additionally, claim 5 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1 and 2, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1 and 2. Given the prior art teachings, a person of skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including an organic cosolvent comprising 0.01% to 3% polysorbate 20, and would have reasonably expected success with such formulation.

6. Claim 7.

The language of claim 7 of the 865 patent is set forth above.

Claim 7 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 7 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 7 is anticipated and/or obvious.

The additional element "wherein said buffer comprises 5-25 mM buffer" does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein

said buffer comprises 5-25 mM buffer." For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]; *see also* 226 patent; Liu; Lam; Daly II; Peyman; Wiegand; Daly III; Parkins; Baffert; Avery; Avastin PI). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said buffer comprises 5-25 mM buffer."

Claim 7 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 7 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including 5-25 mM buffer, and would have reasonably expected success with such formulation.

7. Claim 8.

The language of claim 8 of the 865 patent is set forth above.

Claim 8 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 8 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 8 is anticipated and/or obvious.

The additional element "wherein said buffer comprises a pH between about 5.8-7.0" does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said buffer comprises a pH between about 5.8-7.0." For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]; *see also* 226 patent; Liu; Lam; Daly II; Peyman; Wiegand; Daly III; Parkins; Baffert; Avery; Avastin PI; Frokjaer). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said buffer comprises a pH between about 5.8-7.0."

Claim 8 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 8 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with)

the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a pH between about 5.8-7.0, and would have reasonably expected success with such formulation.

8. Claim 9.

The language of claim 9 of the 865 patent is set forth above.

Claim 9 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 9 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 9 is anticipated and/or obvious.

The additional element "wherein said buffer comprises a pH about 6.2-6.3" does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said buffer comprises a pH about 6.2-6.3." For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]; *see also* 226 patent; Liu; Lam; Daly II; Peyman; Wiegand; Daly III; Parkins; Baffert; Avery; Avastin PI).

Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said buffer comprises a pH about 6.2-6.3."

Claim 9 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 9 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a pH about 6.2-6.3, and would have reasonably expected success with such formulation.

9. Claim 10.

The language of claim 10 of the 865 patent is set forth above.

Claim 10 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 10 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 10 is anticipated and/or obvious.

The additional element "wherein said stabilizing agent comprises a sugar" does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said stabilizing agent comprises a sugar." For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and

"100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]; *see also* 226 patent; Liu; Lam; Daly II; Peyman; Wiegand; Daly III; Parkins; Baffert; Avery; Avastin PI). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said stabilizing agent comprises a sugar."

Claim 10 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 10 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a sugar, and would have reasonably expected success with such formulation.

10. Claim 11.

The language of claim 11 of the 865 patent is set forth above.

Claim 11 of the 865 patent depends from claim 10, which depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 11 incorporates the elements of claims 1, 2, 5, and 10. For at least the same reasons set forth above with respect to claims 1, 2, 5, and 10, said discussion incorporated herein by reference, claim 11 is anticipated and/or obvious.

The additional element "wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol" does not distinguish the claim from claims 1,

2, 5, and 10, or the prior art that invalidates claims 1, 2, 5, and 10. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol." For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya discloses Anti-IgE formulations "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 500 moles of sugar per mole antibody which equals a sugar concentration of 85 mM"; at "100 mg/mL of antibody in 20 mM histidine at pH 6 with a hypertonic sugar concentration of 644 mM"; and "at 25 mg/mL formulated in 5 mM histidine buffer at pH 6 with 1000 moles of sugar per mole antibody which equals a sugar concentration of 161 mM." (Andya at [0169], [0171]; *see also* 226 patent; Liu; Lam; Daly II; Peyman; Wiegand; Daly III; Parkins; Baffert; Avery; Avastin PI). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol."

Claim 11 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, 5, and 10. Additionally, claim 11 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, 5, and 10, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, 5, and 10. Given the prior art teachings, a person of ordinary skill in the art would

have been motivated to generate a stable formulation comprising the claimed combination of elements, including a sugar selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol and would have reasonably expected success with such formulation.

11. Claim 14.

The language of claim 14 of the 865 patent is set forth above.

Claim 14 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 14 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 14 is anticipated and/or obvious.

The additional element "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" does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "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." First, Fraser expressly cites to, and incorporates by reference, Holash for its VEGF antagonist. Holash discloses production of the VEGF antagonist in a CHO cell: "VEGF-Trap$_{R1R2}$ was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2. All of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells." (Holash at 11393-94). Second, Fraser expressly cites to, and incorporates by reference, Wulff for its VEGF antagonist, and Wulff cites to, and incorporates by reference, Papadopoulos. A person of ordinary skill in the art would have known that Papadopoulos teaches that the fusion proteins of the 865 patent are glycosylated at five asparagine residues when the protein is expressed in CHO cells. (Papadopoulos at 81:20 – 82:2 ("There are five possible N-linked glycosylation sites in

Flt1D2.Flk1D3.FcΔC1(a). All five of them are found to be glycosylated to varying degrees [following expression in CHO cells.]"), Fig. 36 (underlining the five asparagine residues in SEQ ID NO: 2 that are glycosylation sites); *see also* Routier). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "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."

Claim 14 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 14 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including a VEGF antagonist protein glycosylated at the claimed asparagine residues, and would have reasonably expected success with such formulation.

12. Claim 15.

The language of claim 15 of the 865 patent is set forth above.

Claim 15 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 15 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 15 is anticipated and/or obvious.

The additional element "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C" does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said formulation is capable of

providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C." First, the element "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C," merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *In re Copaxone*, 906 F.3d at 1023-24; *Bristol-Myers*, 246 F.3d at 1375-76. Notwithstanding, even if some limiting effect is granted to the "turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C" element, it is inherent in Fraser's formulation and therefore does not distinguish the claimed "vial" from the prior art. For example, Dix discloses (among other results) over 99% VEGF antagonist remaining in "[n]ative [c]onfiguration" after storage at 5° C for two months (Table 9) for Dix's 25 mg/ml formulation, which the patentee has conceded is the identical formulation and possesses the same stability properties as Fraser. (*See* 546 patent 11/22/11 Response to 7/13/11 Office Action at 2-4 (Regeneron describing Dix formulation and admitting it is identical to Fraser); *see also* Chi; Arvinte; Amersham; Amersham Application Note; Parkins; Frokjaer; Fyfe). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C."

Claim 15 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 15 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including being capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C, and would have reasonably expected success with such formulation.

13. Claim 16.

The language of claim 16 of the 865 patent is set forth above.

Claim 16 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 16 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 16 is anticipated and/or obvious.

The additional element "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography" does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography." First, the element "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography," merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Notwithstanding, even if some limiting effect is granted to the "99% ... native conformation" element, it is inherent in Fraser's formulation and therefore does not distinguish the claimed "vial" from the prior art. For example, Dix discloses (among other results) over 99% VEGF antagonist remaining in "[n]ative [c]onfiguration after storage at 5° C for two months (Table 9) for Dix's 25 mg/ml formulation, which Regeneron has conceded is the identical formulation and possesses the same stability properties as Fraser. (*See* 546 patent 11/22/11 Response to 7/13/11 Office Action at 2-4 (Regeneron describing Dix formulation and admitting it is identical to Fraser); *see also* Chi; Arvinte; Amersham; Amersham Application Note; Parkins; Frokjaer; Fyfe). Moreover, a person

of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography."

Claim 16 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 16 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including at least 99% of the VEGF antagonist protein being present in native conformation after 2 month storage at 5° C as measured by size exclusion chromatography, and would have reasonably expected success with such formulation.

14. Claim 17.

The language of claim 17 of the 865 patent is set forth above.

Claim 17 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 17 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 17 is anticipated and/or obvious.

The additional element "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography" does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size

exclusion chromatography." First, the element "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography," merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Notwithstanding, even if some limiting effect is granted to the "98% ... native conformation" element, it is inherent in Fraser's formulation and therefore does not distinguish the claimed "vial" from the prior art.

For example, Dix discloses (among other results) over 99% VEGF antagonist remaining in "[n]ative [c]onfiguration" after storage at 5° C for two months (Table 9) for Dix's 25 mg/ml formulation, which the patentee has conceded is the identical formulation and possesses the same stability properties as Fraser. (*See* 546 patent 11/22/11 Response to 7/13/11 Office Action at 2-4 (Regeneron describing Dix formulation and admitting it is identical to Fraser); *see also* Chi; Arvinte; Amersham; Amersham Application Note; Parkins; Frokjaer; Fyfe). Even more, a person of ordinary skill would have noted that Fraser's formulation was stored at 4° C and discarded within 2 weeks, (Fraser at 1115), and would have been motivated to use histidine to generate a formulation with the longer storage stability as disclosed by Andya's disclosure of histidine-buffered formulations with long-term storage stability of "at least 2 years," (Andya at [0049]). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography."

Claim 17 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 17 would have been obvious over at least, *inter alia*, the

combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including at least 98% of the VEGF antagonist protein being present in native conformation following storage at 5° C for 24 months as measured by size exclusion chromatography, and would have reasonably expected success with such formulation.

15. Claim 18.

The language of claim 18 of the 865 patent is set forth above.

Claim 18 of the 865 patent depends from claim 5, which depends from claim 2, which depends from claim 1, and thus claim 18 incorporates the elements of claims 1, 2, and 5. For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, claim 18 is anticipated and/or obvious.

The additional element "wherein said formulation does not contain phosphate" does not distinguish the claim from claims 1, 2, and 5, or the prior art that invalidates claims 1, 2, and 5. Specifically, the references outlined above either explicitly or inherently disclose a "vial" "wherein said formulation does not contain phosphate." For example, Fraser discloses "VEGF $Trap_{R1R2}$ (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798). Andya recognized that histidine was one of a small group of commonly used buffers for stabilizing proteinaceous therapeutic formulations and had

been used in multiple FDA approved products and particularly useful for formulating high concentration protein formulations. (*See* Andya at [0096]). It would have been obvious to use histidine because of its usefulness in preventing aggregation and generating a stable formulation having a protein concentration, which is significantly higher than the protein concentration in the pre-lyophilized formulation, improving its lyoprotective properties, and improving long term storage stability. (Andya; Kaisheva I; Liu). It would have been obvious to use Andya's histidine buffer in the Fraser/Wulff formulations for the additional reasons that: (1) its pKa provides maximum buffering capacity at pH 6 (the same as Fraser's formulation), (2) it had suitable pKa and buffering capacity for the VEGF TrapR1R2 protein having a pI of approximately 8, (3) it contributes less to osmolarity than Fraser/Wulff's phosphate-citrate buffers, (4) phosphate-citrate buffers were known to cause painful reactions when injected subcutaneously in contrast to histidine buffer, and (5) regulatory agencies had repeatedly approved histidine-buffered proteinaceous therapeutic formulations. A person of ordinary skill would have wanted to retain or improve the stability, binding, and potency of the Wulff/Fraser VEGF TrapR1R2, and would have been motivated to use histidine based on Andya's teaching that it was especially good at preventing degradation including aggregation. (*See* Andya at [0160], Figs. 9-10). A person of ordinary skill would further have had a reasonable expectation of achieving a formulation that maintains the stability, potency, and binding properties of Wulff/Fraser's formulation using this combination of ingredients given the numerous other FDA-approved protein therapeutics containing the same combination of excipients, and in view of Andya's teaching that histidine has an exceptional ability to act as a lyoprotectant and prevent degradation. Histidine was a well-known buffer long before the 865 patent's earliest possible priority date, and its multiple advantages were also well known and would have motivated a person of ordinary skill to use histidine buffer in Wulff/Fraser's

formulation. Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised a "vial" "wherein said formulation does not contain phosphate."

Claim 18 of the 865 patent is therefore anticipated for the same reasons stated above for claims 1, 2, and 5. Additionally, claim 18 would have been obvious over at least, *inter alia*, the combinations identified above for claims 1, 2, and 5, in view of (or in further combination with) the knowledge of a person of ordinary skill in the art for the same reasons stated above for claims 1, 2, and 5. Given the prior art teachings, a person of ordinary skill in the art would have been motivated to generate a stable formulation comprising the claimed combination of elements, including not containing phosphate, and would have reasonably expected success with such formulation.

16. Secondary Considerations.

Mylan is unaware of any evidence of secondary considerations that would render non-obvious the particular combination of elements claimed in the 865 patent, as described above and incorporated herein by reference.

Additionally, the patentee must prove the required nexus before relying on any secondary considerations of alleged non-obviousness. Mylan is not aware of any evidence that would establish the required nexus for any of the claims of the 865 patent, nor has Regeneron presented any evidence that would establish the required nexus for any of the claims of the 865 patent despite Mylan's requests for such discovery.

Further, even if there were any evidence of such secondary considerations[39] and the required nexus, the *prima facie* evidence of obviousness is sufficiently strong that it cannot be

[39] Mylan reserves the right to address any evidence of secondary considerations that is raised in litigation by any entity, or entities, attempting to assert the 865 patent.

rebutted by evidence relevant to secondary considerations of non-obviousness, including any evidence of alleged commercial success.

As a result, all claims of the 865 patent are anticipated and obvious in view of at least the references and combinations set forth above, and in view of the knowledge of a person of ordinary skill in the art.

D. Obviousness-Type Double Patenting.

The language of the 865 patent Asserted Claims is set forth above.

The 865 patent Asserted Claims are invalid for OTDP over at least each of the following, which expire no later than March 7, 2021: (i) U.S. Patent No. 9,340,594 ("594 patent"), claims 1-9, optionally in view of Papadopoulos; (ii) U.S. Patent No. 9,580,489 ("489 patent"), claims 1-29, optionally in view of Papadopoulos; and (iii) U.S. Patent No. 7,608,261 ("261 patent"), claims 1-5, optionally in view of Papadopoulos.

The 594 patent discloses and claims, *inter alia*, the following:

- Claim 1: "A pre-filled syringe suitable for intravitreal administration comprising a 1 mL luer glass syringe fitted with a plunger and a stable ophthalmic formulation of a vascular endothelial growth factor (VEGF) trap which consists of (i) a receptor component consisting essentially of an immunoglobulin-like domain 2 of a first VEGF receptor and an immunoglobulin-like domain 3 of a second VEGF receptor, and (ii) a multimerizing component, wherein the stable ophthalmic formulation comprises:

  (a) 1-100 mg/ml a VEGF antagonist;

  (b) 0.01-5% of one or more organic co-solvent;

  (c) 5-40 mM of buffer; and

  (d) optionally comprising 1.0-7.5% of a stabilizing agent."

- Claim 2: "The pre-filled syringe of claim 1, wherein the first VEGF receptor is Flt1, and the second VEGF receptor is Flk1 or Flt4."

- Claim 3: "The pre-filled syringe according to claim 2, wherein the VEGF trap is stable for at least 4 months."

- Claim 4: "The pre-filled syringe according to claim 3, wherein the VEGF trap consists of amino acids 27-457 of SEQ ID NO:4."

- Claim 5: "The pre-filled syringe according to claim 4, wherein the stable ophthalmic formulation comprises 40 mg/mL of the VEGF trap, 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, at pH 6.2-6.4."

- Claim 7: "The pre-filled syringe of claim 3, wherein the VEGF trap consists of the amino acid sequence of SEQ ID NO:4."

- Claim 8: "The pre-filled syringe according to claim 2 wherein the VEGF trap is stable for at least 5 months."

- Claim 9: "The pre-filled syringe according to claim 8, wherein the VEGF trap consists of amino acids 27-457 of SEQ ID NO:4."

As illustrated above, the 865 patent Asserted Claims are not patentably distinct from—i.e., are obvious over and/or anticipated by—the 594 patent claims. Indeed, the aforementioned 594 patent claims recite a specific formulation that falls within the scope of every Asserted Claim of the 865 patent. Furthermore, the element "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 merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Consequently, the 865 patent Asserted Claims are invalid for OTDP.

The 489 patent discloses and claims, *inter alia*, the following:

- Claim 1: "A formulation comprising:

  (a) 1-100 mg/mL of a VEGF-specific fusion protein antagonist;

  (b) 5-40 mM of a buffer;

  (c) 0.01-5% of an organic co-solvent; and

  (d) a stabilizer or 30-150 mM of a tonicity agent,

  wherein the VEGF-specific fusion protein antagonist represents at least 90% of the total weight of protein in the composition, at least 90% of the total weight of the VEGF-specific fusion protein antagonist is not present as an aggregate, and the VEGF-specific fusion

protein antagonist comprises an Ig domain 2 of human VEGF receptor 1, an Ig domain 3 of human VEGF receptor 2, and a multimerizing component."

- Claim 2: "The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist represents at least 95% of the total weight of protein in the composition."
- Claim 6: "The formulation of claim 1, wherein the buffer comprises a phosphate buffer."
- Claim 7: "The formulation of claim 6, wherein the buffer comprises sodium phosphate present at a concentration of 10 mM."
- Claim 11: "The formulation of claim 1, wherein the organic co-solvent comprises one or more of polysorbate 20, polysorbate 80, polyethylene glycol (PEG) 3350, and propylene glycol."
- Claim 19: "The formulation of claim 1, comprising a stabilizer comprising trehalose or sucrose."
- Claim 22: "The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist does not comprise amino acids 1-26 of SEQ ID NO:4."
- Claim 23: "The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist is a dimer."
- Claim 24: "The formulation of claim 1, wherein the VEGF-specific fusion protein antagonist is expressed in a Chinese hamster ovary (CHO) cell."

(*See also* 489 patent at claims 26-29 (claiming "[a] vial" containing the same formulation(s)). As illustrated above, the 865 patent Asserted Claims are not patentably distinct from—i.e., are obvious over and/or anticipated by—the 489 patent claims. Indeed, the aforementioned 489 patent claims recite a specific formulation that falls within the scope of every Asserted Claim of the 865 patent. Furthermore, the element "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 merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Consequently, the 865 patent Asserted Claims are invalid for OTDP.

The 261 patent discloses and claims, *inter alia*, the following:

- Claim 1: "An ophthalmic formulation of a vascular endothelial growth factor (VEGF) antagonist, comprising

  (a) 1-100 mg/ml of a VEGF antagonist comprising the amino acid sequence of SEQ ID NO:4;

  (b) 0.01-5% of one or more organic co-solvent(s) which is one or more of polysorbate, polyethylene glycol (PEG), and propylene glycol;

  (c) 30-150 mM of a tonicity agent selected from sodium chloride or potassium chloride; and

  (d) 5-40 mM of sodium phosphate buffer.

- Claim 2: "The ophthalmic formulation of claim 1, further comprising 1-7.5% of a stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, or mannitol, pH between about 5.8-7.0."

- Claim 3: "The ophthalmic formulation of claim 2, comprising about 1-100 mg/ml of the VEGF antagonist, 10 mM sodium phosphate buffer, 40 mM NaCl, 0.03% polysorbate, and 5% sucrose, pH about 6.2-6.3."

As illustrated above, the 865 patent Asserted Claims are not patentably distinct from—i.e., are obvious over and/or anticipated by—the 261 patent claims. Indeed, the aforementioned 261 patent claims recite a specific formulation that falls within the scope of every Asserted Claim of the 865 patent. Furthermore, the element "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 merely states an intended result of the claimed "vial" and therefore is non-limiting. *See, e.g.*, *Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Consequently, the 865 patent Asserted Claims are invalid for OTDP.

E. Lack of Enablement.

The 865 patent Asserted Claims are invalid for lack of enablement because the 865 patent fails to enable the full scope of the claims.

1. Claim 1.

The language of claim 1 of the 865 patent is set forth above.

To the extent claim 1 is not anticipated or obvious, as discussed above, the 865 patent fails to provide sufficient support for the subject matter claimed in claim 1. For example, the specification does not describe or enable anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 1 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to enable a person of ordinary skill in the art to practice the claimed "vial" without undue experimentation.

Claim 1 is invalid for lack of enablement for at least the following reasons:

- The nature of the claimed invention(s) relates to extremely broad genera of formulations claimed by their functions.

- The claimed invention(s) is directed to an unpredictable art—biological formulation, wherein slight changes in excipients and concentrations thereof can impact the overall profile of a formulation. The 865 patent does not enable the broad genera of formulations covered by the claims, which encompass an unlimited variety of excipients and concentrations thereof.

- The scope of the claims is broad with the primary limitations being the "wherein" clauses rather than the "vial" components. Further, the claims encompass a formulation suitable for any route of administration. The claims also encompass formulations comprising unlimited combinations of excipients and concentrations thereof. The 865 patent's limited disclosure fails to enable the full scope of these formulation permutations and highly variable concentrations.

- The 865 patent specification fails enable a person of ordinary skill in the art to obtain the claimed "vial" having the requisite stability. The specification further fails to adequately explain the appropriate SEC parameters and/or methodology needed to determine whether a "vial" exhibits the claimed "native conformation."

- The 865 patent disclosure fails to enable the full scope of the formulations having the claimed functionalities. The 865 patent disclosure has not demonstrated possession of all buffers encompassed in the claim term "a buffer." For example, based on a fraudulent disclosure of stability, potency, or binding properties of formulations containing histidine as a buffer in U.S. Patent No. 10,857,231 ("the 231 patent"), the 231 patent was disclaimed. (*See* Exhibit 3001, PGR2021-00117 ("[B]ased on very recently discovered information, Patent Owner has reason to question whether the data presented in Table 7 of the Dix '231 Patent corresponds to the formulation described in Example 4 at column 10, lines 27-38."); Exhibit 2048, PGR2021-00117 (copy of Regeneron's disclaimer of the 231 patent); Paper 16, PGR2021-00117 (order denying institution of Post-Grant Review based on

Regeneron's disclaiming all claims of the 231 patent)). Thus, the patentee was not in possession of, at least, formulations using histidine as a buffer. As such, the specification fails to enable the full scope of these formulations and does not enable the person of ordinary skill to make histidine containing formulations (falling within the scope of the claims) that possess the claimed functionalities.

- The quantity of experimentation necessary for a person of ordinary skill in the art to practice the full breadth of claims is not only undue, it is excessive and likely limitless. Among other things, the quantity of experimentation required to test the unlimited combinations of excipients and concentrations to determine whether each formulation meets the claimed "native conformation" element is undue and excessive.

Given the breadth of the claim, the lack of guidance in the specification, and the quantity of experimentation required, the 865 patent does not enable one skilled in the art to practice the full scope of claim 1 without undue experimentation. Thus, claim 1 is not enabled such that one of ordinary skill in the art would understand how to practice the claimed invention without undue experimentation.

Accordingly, claim 1 of the 865 patent is invalid for failing to meet the enablement requirements of 35 U.S.C. § 112

2. Claims 2-5, 7-11, and 14-18.

The language of claims 2-5, 7-11, and 14-18 of the 865 patent is set forth above.

Claims 2-5, 7-11, and 14-18 depend either directly or indirectly from claim 1, and thus incorporate the elements of claim 1. Claims 2-5, 7-11, and 14-18 do not substantially narrow the scope of claim 1, and the specification fails to provide sufficient guidance for the genera of formulations claimed therein. Therefore, for at least the same reasons set forth above with respect to claim 1, said discussion incorporated herein by reference, the 865 patent does not enable a person of ordinary skilled in the art to practice the full scope of claims 2-5, 7-11, and 14-18 without undue experimentation.

Accordingly, claims 2-5, 7-11, and 14-18 of the 865 patent are invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

* * *

For at least the reasons discussed above, the 865 patent Asserted Claims are not enabled such that one of ordinary skill in the art would understand how to practice the claimed invention without undue experimentation.

F. Lack of Written Description.

The language of the 865 patent Asserted Claims is set forth above.

The 865 patent Asserted Claims are invalid for lack of written description because the 865 patent does not convey to persons of ordinary skill in the art that the named inventors were in possession of the full scope of the claims.

To the extent the 865 patent Asserted Claims are not anticipated or obvious, as discussed above, the 865 patent fails to provide sufficient support for the subject matter claimed. For example, the specification does not describe anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that the 865 patent Asserted Claims are not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to convey to those skilled in the art that the inventor had possession of the claimed subject matter.

The 865 patent disclosure fails to describe formulations having the claimed functionalities. The 865 patent disclosure has not described all buffers encompassed in the claim term "a buffer." For example, based on a fraudulent disclosure of stability, potency, or binding properties of formulations containing histidine as a buffer in the 231 patent, the 231 patent was disclaimed. (*See* Exhibit 3001, PGR2021-00117 ("[B]ased on very recently discovered information, Patent Owner has reason to question whether the data presented in Table 7 of the Dix '231 Patent corresponds to the formulation described in Example 4 at column 10, lines 27-38."); Exhibit 2048, PGR2021-00117 (copy of Regeneron's disclaimer of the 231 patent); Paper 16, PGR2021-00117 (order

denying institution of Post-Grant Review based on Regeneron's disclaiming all claims of the 231 patent)). As such, the specification fails to describe, at least, histidine containing formulations (falling within the scope of the claims) that possess the claimed functionalities.

The 865 patent specification fails to disclose the combination of elements set forth in the 865 patent Asserted Claims, which covers unlimited combinations of excipients and concentrations. Further, the claims encompass broad, functionally-defined genera of formulations requiring stability properties. Despite claiming genera of formulations using functional language to define desired results (e.g., stability), the 865 patent specification provides no guidance or common structural features for use in a formulation to obtain the claimed functionalities. The 865 patent does not disclose a sufficient number of species to demonstrate the patentee invented the claimed genera of formulations.

For at least the reasons discussed above, the 865 patent Asserted Claims are invalid for lack of written description because the 865 patent does not convey to those skilled in the art that the named inventors were in possession of the full scope of the claims.

G. Indefiniteness.

The language of the 865 patent Asserted Claims is set forth above.

The 865 patent Asserted Claims are invalid for indefiniteness pursuant to 35 U.S.C. § 112.

The 865 patent Asserted Claims fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention for at least the following reasons.

The 865 patent Asserted Claims all require, *inter alia*, "at least 98% [or 99%] of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography." The 865 patent does not offer any disclosure or description of the steps needed to obtain a "vial" comprising a VEGF antagonist fusion protein meeting that

limitation. The 865 patent further fails to inform persons of ordinary skill in the art of the SEC parameters required to test a "vial" for VEGF antagonist in "native conformation."

The preamble claim term "vial," to the extent it is determined to be limiting, is undefined and does not convey the scope of the claimed invention(s).

Accordingly, the 865 patent Asserted Claims are invalid for indefiniteness because they fail to inform, with reasonable certainty, those of ordinary skill in the art about the scope of the invention

H. Unpatentable Subject Matter.

The language of the 865 patent Asserted Claims is set forth above.

The 865 patent Asserted Claims are invalid for failure to claim patent eligible subject matter. The 865 patent Asserted Claims are all directed toward a "vial" comprising a VEGF antagonist in "native conformation." Consequently, the claims are drawn to nothing more than the observation of a natural law in a prior art composition.

Accordingly, the 865 patent Asserted Claims are invalid for failure to claim patent eligible subject matter pursuant to 35 U.S.C. § 101.

I. Unenforceability.

For at least the following reasons, the 865 patent Asserted Claims are unenforceable due to Regeneron's inequitable conduct during prosecution of the application(s) that led to the 865 patent issuance.

The applicant failed to disclose to the U.S.P.T.O. all information it knew to be material to patentability. 37 C.F.R. § 1.56(a). For example, while arguing to the U.S.P.T.O. during prosecution of the 269 application that the disclosures supported the patentability of the pending claims, the applicant knew of at least the prior art Wulff, Papadopoulos, Dix, Holash, and/or Liu references, which were withheld from the U.S.P.T.O. The applicant was also aware of the

materiality of these references, which disclose the manufacture of formulations comprising VEGF antagonist fusion proteins at greater than 98% native conformation. Moreover, Regeneron has engaged in a pattern of deception wherein, during prosecution of its applications, Regeneron intentionally obscures references it knows to be relevant to the subject matter of the pending claims by submitting numerous other references to the U.S.P.T.O., effectively burying those that contain invalidating disclosures. (*See, e.g.*, 865 patent at pp. 1-2).

Further, in prosecuting the 610 application,[40] Regeneron included in the original application Table 7 and the data therein, and presented said data as corresponding to the formulation set forth in Example 4 at 10:27-38. Upon information and belief, the data in Table 7 does not correspond to the formulation set forth in Example 4 at 10:27-38. (*See* Exhibit 3001, PGR2021-00117 ("[B]ased on very recently discovered information, Patent Owner has reason to question whether the data presented in Table 7 of the Dix '231 Patent corresponds to the formulation described in Example 4 at column 10, lines 27-38."); Exhibit 2048, PGR2021-00117 (copy of Regeneron's disclaimer of the 231 patent); Paper 16, PGR2021-00117 (order denying institution of Post-Grant Review based on Regeneron's disclaiming all claims of the 231 patent)). In addition, during prosecution of the 610 application, the applicant stated in an interview summary that the "invention is a formulation which comprises the VEGF antagonist and exhibits less than a 3% degradation after 15 months of storage at 5° C." (231 patent PH, 10/7/2020 Applicant Summary of Interview with Examiner at 1). As amended, all the claims at issue required, *inter alia*, a buffer comprising histidine and 10-50 mg/ml of a VEGF antagonist fusion protein. There

[40] U.S. Patent No. 10,857,231, issued on December 8, 2020, from U.S. Patent Application No. 16/535,610 ("the 610 application"), filed on August 8, 2019. The 610 application was filed as a purported continuation of U.S. Patent Application No. 15/692,893 filed on August 31, 2017 (now U.S. Patent No. 10,406,226).

is no support for such a genera of formulations in the 231 patent specification. For those formulations that contain a buffer comprising histidine, as required by all claims of the 231 patent, the 231 patent specification discloses only one formulation containing "100 mg/ml VEGF trap protein" (231 patent at 10:56-66), and another that contains "50-100 mg/ml VEGF trap protein" (231 patent at 10:27-54)—the stability results of the latter formulation are in doubt. (*See* Exhibit 3001, PGR2021-00117). After amending the claims to include that the buffer must comprise histidine, the Patent Owner misrepresented that "[a]s discussed during the interview of October 6, 2020, in view of the amendments and the recited formulation components, at a minimum, the amended claims meet the written description requirement." (231 patent FH, 10/12/2020 Applicant Arguments/Remarks Made in an Amendment at 15). As such, during prosecution of the 610 application, Regeneron made material, and upon information and belief, intentional misrepresentations that the claims met the written description requirement, and, upon information and belief, relied on incorrect information relevant to the subject matter of the pending claims. Shortly after these claim amendments were made and after the misrepresentations about the claim amendments were made, the pending claims were allowed. (231 patent PH, 11/2/2020 Notice of Allowability at 3 ("Applicant amended the claims so that the reasons for the Double patenting rejection no longer apply."). In addition, the most reasonable inference to be drawn from Regeneron's failures to comply with its duties of candor, good faith and disclosure (e.g., Regeneron's intentional withholding of the above-mentioned references from the U.S.P.T.O.), is that the actions were done with the intent to deceive.

For at least these reasons, the 865 patent Asserted Claims are unenforceable for inequitable conduct.

VII. INVALIDITY CONTENTIONS REGARDING THE 715 PATENT.

A. The Knowledge of a Person of Ordinary Skill in the Art.

In the context of the obviousness analysis, the scope of the prior art is directed to the field of endeavor of the invention, and includes the knowledge of a person of ordinary skill in the art. Here, a person of ordinary skill in the art would have at least a Ph.D. in biochemical engineering, biomedical engineering or biochemistry with specialization in the fields of recombinant protein manufacturing and purification, or a masters or undergraduate degree in cell biology, biochemical engineering, biomedical engineering or biochemistry with several years of experience in the fields of recombinant protein manufacturing and purification.

B. Prior Art Relevant to the 715 Patent.

In the context of the obviousness analysis, the scope of the prior art is directed to the field of endeavor of the invention. The scope of the prior art relates, in general, to the production of therapeutic proteins, including through the use of chemically defined medium.

Mylan relies on at least the references identified in Appendix C in support of its Invalidity Contentions regarding the 715 patent based on anticipation and obviousness under 35 U.S.C. § 102 and 35 U.S.C. § 103. Unless otherwise and expressly stated, it should be presumed that Mylan intends to rely upon each reference in its entirety to the extent relevant or appropriate, including references cited in and/or referenced within the references identified in Appendix C. Similarly, the headings included in this section are for convenience only, and do not limit Mylan's right to rely on any reference to the extent relevant or appropriate.

C. 35 U.S.C. § 102 and § 103 – The 715 Patent Asserted Claims Are Anticipated and Rendered Obvious.

1. Claim 1.

The language of claim 1 of the 715 patent is set forth above.

To the extent that the patentee alleges that any aspect of Mylan's BLA process cell culture step infringes claim 1, either literally or under the doctrine of equivalents, then claim 1 is anticipated at least to the extent that any of the alleged infringing steps or compositions, including the cell culture media products used in Mylan's BLA process, were in public use and/or on sale prior to the filing date of the 715 patent. (*See, e.g.*, Kerry 2018; Zheng 2018; Fernandes 2016; Cell Boost 5 Data File, dated 2015; Park 2017a; Park 2017b; Tian 2014; Brown 2018; Luchese 2018; Poulain 2017; Freund 2018; Gagnon 2018; Cha 2017; Oliveira 2017).[41] Consequently, claim 1 of the 715 patent is anticipated at least by references documenting the availability and/or use of the cell culture media products used in Mylan's BLA process.

Claim 1 of the 715 patent is anticipated at least by references disclosing aflibercept and the production of aflibercept in cell culture media containing, among other things, antioxidants, including taurine. (*See, e.g.*, 342 patent; WO 062).

Claim 1 of the 715 patent is anticipated to the extent that EYLEA® (aflibercept) has been manufactured according to the claimed process and was on sale, in public use, or otherwise available to the public before the effective filing date of the 715 patent.

Claim 1 is obvious in view of references disclosing aflibercept, in combination with one or more of the references disclosing the production of recombinant proteins in the presence of or absence of nickel, further in combination with one or more references disclosing CDM that includes iron, copper, zinc, cysteine, and/or an antioxidant within the claimed cumulative concentration ranges, or that excludes iron, copper, zinc or cysteine.

[41] Mylan reserves the right to include additional defenses based on the commercial and/or public availability of any other cell culture media that may, through discovery, be revealed to contain one or more of the recited compounds.

Aflibercept was known in the art as a therapeutic protein with purported uses in treating angiogenic eye disorders, and its production, including in eukaryotic cells, had been described. (*See, e.g.*, EYLEA Label; 094 publication; Holash; 610 publication; WO 062; 249 publication; 432 publication; 930 publication; 531 publication).

It also was known in the art that "[c]ell cultures may … be supplemented with nutrients and/or other medium components including hormones and/or other growth factors, particular ions (such as sodium, chloride, calcium, magnesium, and phosphate), buffers, vitamins, nucleosides or nucleotides, trace elements (inorganic compounds usually present at very low final concentrations), amino acids, lipids, or glucose or other energy source." (WO 408 at [0009]; *see also, e.g.*, CN 729; CN 648; CN 732; Okamoto; Olakanmi; 216 patent; Tanaka; Krattenmacher; Ritacco 2018; Graham; 710 patent; 732 patent; 401 patent; WO 498; WO 578; 727 publication; 533 publication; 507 publication; 519 patent; 342 patent; WO 062; MEM (Sigma-Aldrich); DMEM (Biochrom); Ham's F-12 (Biochrom); Ham's F-12 (Elabscience); DMEM/Ham's F-12 (Sigma-Aldrich); DMEM/Ham's F-12 (Biochrom); DMEM/Ham's F-12 (SAFC); Iscove (Biochrom); RPMI 1640 (Biochrom); RPMI 1640 (SAFC); MEM/Joklik (Sigma-Aldrich); 056 patent; ThermoFisher Handbook; Gorfien; Pan; Reinhart; Rodrigues; Zhang). Further, the addition of these components was well known to be required for production of recombinant proteins. (*See, e.g.*, WO 408; CN 729; CN 648; CN 732; Okamoto; Olakanmi; 216 patent; Tanaka; Krattenmacher; Ritacco 2018; Graham; 710 patent; 732 patent; 401 patent; WO 498; WO 578; 727 publication; 533 publication; 507 publication; 519 patent; 342 patent; WO 062). Accordingly, it would have been obvious to incorporate additional components, excluding nickel or using nickel in low concentrations, into cell culture processes for the production of aflibercept, and a person of ordinary skill in the art would have been motivated to do so to in order to aid in the production of

the recombinantly expressed protein, including for the purpose of reducing color in the drug substance and/or drug product. (*See, e.g.*, 710 patent; 732 patent; Krattenmacher; 342 patent; WO 062; 1999 ICH; Du 2019; Vijayasankaran 2013; Vijayasankaran 2018; Prentice; Song; Ritacco 2018; Li 2014; Liu 2014; Xu 2014; Graham; Schöneich 2000). A person skilled in the art also would have been motivated to use such CDM in order to avoid batch-to-batch variability and because all the contents are known and without animal-derived components or peptones, as well as in order to avoid potentially deleterious effects of supplementing media with non-defined components such as peptones. (*See, e.g.*, 342 patent; WO 062; Gu).

Moreover, a person of ordinary skill in the art would have had a reasonable expectation of success given that these components were already being added to CDM and shown to result in the production of recombinant protein. (*See, e.g.*, WO 408; CN 729; CN 648; CN 732; Okamoto; Olakanmi; 216 patent; Tanaka; Krattenmacher; Ritacco 2018; Graham; 710 patent; 732 patent; 401 patent; WO 498; WO 578; 727 publication; 533 publication; 507 publication; 519 patent; 342 patent; WO 062; 469 patent; 938 patent; 084 patent; Zang; Wyatt; González-Leal; Gu). Indeed, Regeneron had already reported expressing recombinant VEGF antagonist proteins—whose amino acid sequences are nearly identical to that of aflibercept—in CDM. (959 patent at 16:22-26; 29:37-44; 757 patent at 16:27-30; 29:51-58; 30:29-33).

As a result, claim 1 of the 715 patent is rendered obvious by at least, *inter alia*, one or more of the aflibercept references, in combination with one or more of the references disclosing the production of recombinant proteins in the presence of or absence of nickel, further in combination with one or more references disclosing CDM that includes iron, copper, zinc, cysteine, and/or an antioxidant.

2. Claim 2.

The language of claim 2 of the 715 patent is set forth above.

Claim 2 of the 715 patent depends from claim 1 and thus incorporates the elements of claim 1. The reasons why claim 1 is anticipated and/or obvious are incorporated by reference. The additional element "wherein said harvest has a color no more yellow-brown than European Color Standard BY2, wherein the aflibercept concentration is 5.0 g/L" is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. To the extent this element is limiting, it does not distinguish the claim from the prior art. For example, the prior art disclosed that the inclusion of antioxidants and/or reducing the concentration of other ingredients would result in reduction of the color intensity, which, in any event, would have been an inherent aspect of the use of said antioxidants. (*See, e.g.*, 710 patent; 732 patent; Krattenmacher; 342 patent; WO 062; 1999 ICH; Du; Vijayasankaran 2013; Vijayasankaran 2018; Xu 2014; Prentice; Song; Ritacco 2018; Li 2014; Liu 2014; Xu 2014; Graham; Schöneich 2000).

3. Claim 3.

The language of claim 3 of the 715 patent is set forth above.

Claim 3 of the 715 patent depends from claim 2 and thus incorporates the elements of claim 2. The reasons why claim 2 is anticipated and/or obvious are incorporated by reference. The additional element "anti-oxidants are taurine, hypotaurine, glycine, thioctic acid, glutathione, choline, hydrocortisone, Vitamin C, Vitamin E or combinations thereof" does not distinguish the claim from the prior art. For example, the prior art disclosed the use of one or more of these antioxidants in CDM. (*See, e.g.*, 710 patent; 732 patent; 401 patent; WO 498; WO 578; 727 publication; 533 publication; 507 publication; 519 patent; 216 patent; CN 648; CN 732; WO 408; 342 patent; WO 062).

4. Claim 4.

The language of claim 4 of the 715 patent is set forth above.

Claim 4 of the 715 patent depends from claim 1 and thus incorporates the elements of claim 1. The reasons why claim 1 is anticipated and/or obvious are incorporated by reference. The additional element "cumulative concentration of an anti-oxidant in said CDM is about 0.001 mM to about 10.0 mM for any single anti-oxidant and the cumulative concentration of all anti-oxidants is about 30.0 mM or less than 30.0 mM" does not distinguish the claim from the prior art. For example, the prior art disclosed the concentrations of antioxidants at these concentrations. (*See, e.g.*, 710 patent; 732 patent; 401 patent; WO 498; WO 578; 727 publication; 533 publication; 507 publication; 519 patent; 216 patent; CN 648; CN 732; WO 408; 342 patent; WO 062).

5. Claim 5.

The language of claim 5 of the 715 patent is set forth above.

Claim 5 of the 715 patent depends from claim 1 and thus incorporates the elements of claim 1. The reasons why claim 1 is anticipated and/or obvious are incorporated by reference. The additional element "aflibercept titer, viable cell concentration, viability, ammonia or osmolality is substantially unchanged" does not distinguish the claim from the prior art. (*See, e.g.*, 710 patent; 732 patent).

6. Claim 6.

The language of claim 6 of the 715 patent is set forth above.

Claim 6 of the 715 patent depends from claim 1, and thus incorporates the elements of claim 1. The reasons why claim 1 is anticipated and/or obvious are incorporated by reference. The additional element "wherein said host cell is selected from the group consisting of CHO, NS0, Sp2/0, embryonic kidney cell and BHK" does not distinguish the claim from the prior art. For example, these host cells were used in the prior art. (*See, e.g.*, 710 patent; 732 patent; WO 498; CN 729; CN 648; CN 732; WO 408; Krattenmacher; Ritacco 2018; Graham; 342 patent; WO 062).

7. Claim 12.

The language of claim 12 of the 715 patent is set forth above.

Claim 12 of the 715 patent depends from claim 1 and thus incorporates the elements of claim 1. The reasons why claim 1 is anticipated and/or obvious are incorporated by reference. The additional element "wherein said anti-oxidants are taurine, hypotaurine, glycine, thioctic acid, glutathione, choline, hydrocortisone, Vitamin C, Vitamin E or combinations thereof" does not distinguish the claim from the prior art. For example, the prior art disclosed the use of one or more of these antioxidants in CDM. (*See, e.g.*, 710 patent; 732 patent; 401 patent; WO 498; WO 578; 727 publication; 533 publication; 507 publication; 519 patent; 216 patent; CN 648; CN 732; WO 408; 342 patent; WO 062).

8. Claim 13.

The language of claim 13 of the 715 patent is set forth above.

Claim 13 of the 715 patent depends from claim 1 and thus incorporates the elements of claim 1. The reasons why claim 1 is anticipated and/or obvious are incorporated by reference. The additional element requiring a specific harvest color is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. To the extent this element is limiting, it does not distinguish the claim from the prior art. For example, the prior art disclosed that the inclusion of antioxidants would result in reduction of the color intensity. (*See, e.g.*, 710 patent; 732 patent).

9. Claim 14.

The language of claim 14 of the 715 patent is set forth above.

Claim 14 of the 715 patent depends from claim 1 and thus incorporates the elements of claim 1. The reasons why claim 1 is anticipated and/or obvious are incorporated by reference. The additional element requiring a specific harvest color does not distinguish the claim from the

prior art. For example, the prior art disclosed that the inclusion of antioxidants would result in reduction of the color intensity, which is an inherent aspect of the use of said antioxidants. (*See, e.g.*, 710 patent; 732 patent; Krattenmacher; 342 patent; WO 062).

10. Claim 15.

The language of claim 15 of the 715 patent is set forth above.

To the extent that the patentee alleges that any aspect of Mylan's BLA process cell culture step infringes claim 15, either literally or under the doctrine of equivalents, then claim 15 is anticipated at least to the extent that any of the alleged infringing steps or compositions, including the cell culture media products used in Mylan's BLA process, were in public use and/or on sale prior to the filing date of the 715 patent. (*See, e.g.*, Kerry 2018; Zheng 2018; Fernandes 2016; Cell Boost 5 Data File, dated 2015; Park 2017a; Park 2017b; Tian 2014; Brown 2018; Luchese 2018; Poulain 2017; Freund 2018; Gagnon 2018; Cha 2017; Oliveira 2017).[42] The claim language regarding the color of the harvest is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Because the recognition of a property or use of a previously known composition or process cannot impart patentability to a claim, the claimed feature of a specific harvest color is not entitled to patentable weight, or is at least an inherent property of the prior art. Consequently, claim 15 of the 715 patent is anticipated at least by references documenting the availability and/or use of the cell culture media products used in Mylan's BLA process.

[42] Mylan reserves the right to include additional defenses based on the commercial and/or public availability of any other cell culture media that may, through discovery, be revealed to contain one or more of the recited compounds.

Claim 15 of the 715 patent is anticipated at least by references disclosing aflibercept and the production of aflibercept in cell culture media containing, among other things, antioxidants, including taurine. (*See, e.g.*, 342 patent; WO 062).

Claim 15 of the 715 patent is anticipated to the extent that EYLEA® (aflibercept) has been manufactured according to the claimed process and was on sale, in public use, or otherwise available to the public before the effective filing date of the 715 patent.

Claim 15 is obvious in view of references disclosing aflibercept, in combination with one or more of the references disclosing the production of recombinant proteins in the presence of nickel, further in combination with one or more references disclosing CDM that includes iron, copper, zinc, cysteine, and/or an antioxidant within the claimed cumulative concentration ranges, or that excludes iron, copper, zinc or cysteine, and further in combination with one or more references disclosing a specific host color.

Aflibercept was known in the art as a therapeutic protein with purported uses in treating angiogenic eye disorders, and its production, including in eukaryotic cells, had been described. (*See, e.g.*, EYLEA Label; 094 publication; Holash; 610 publication; WO 062; 249 publication; 432 publication; 930 publication; 531 publication).

It also was known in the art that "[c]ell cultures may … be supplemented with nutrients and/or other medium components including hormones and/or other growth factors, particular ions (such as sodium, chloride, calcium, magnesium, and phosphate), buffers, vitamins, nucleosides or nucleotides, trace elements (inorganic compounds usually present at very low final concentrations), amino acids, lipids, or glucose or other energy source." (WO 408 at [0009]; *see also, e.g.*, CN 729; CN 648; CN 732; Okamoto; Olakanmi; 216 patent; Tanaka; Krattenmacher; Ritacco 2018; Graham; 710 patent; 732 patent; 401 patent; WO 498; WO 578; 727 publication;

533 publication; 507 publication; 519 patent; 342 patent; WO 062; MEM (Sigma-Aldrich); DMEM (Biochrom); Ham's F-12 (Biochrom); Ham's F-12 (Elabscience); DMEM/Ham's F-12 (Sigma-Aldrich); DMEM/Ham's F-12 (Biochrom); DMEM/Ham's F-12 (SAFC); Iscove (Biochrom); RPMI 1640 (Biochrom); RPMI 1640 (SAFC); MEM/Joklik (Sigma-Aldrich); 056 patent; ThermoFisher Handbook; Gorfien; Pan; Reinhart; Rodrigues; Zhang). Further, the addition of these components was well known to be required for production of recombinant proteins. (*See, e.g.*, WO 408; CN 729; CN 648; CN 732; Okamoto; Olakanmi; 216 patent; Tanaka; Krattenmacher; Ritacco 2018; Graham; 710 patent; 732 patent; 401 patent; WO 498; WO 578; 727 publication; 533 publication; 507 publication; 519 patent; 342 patent; WO 062). In addition, the prior art disclosed the inclusion of various antioxidants and metals results in reduction of color intensity for the harvest. (*See, e.g.*, 710 patent; 732 patent; Krattenmacher; 342 patent; WO 062; 1999 ICH; Du 2019; Vijayasankaran 2013; Vijayasankaran 2018; Xu 2014; Prentice; Song; Ritacco 2018; Li 2014; Liu 2014; Xu 2014; Graham; Schöneich 2000). Accordingly, it would have been obvious to incorporate additional components, excluding nickel or using nickel in low concentrations, into cell culture processes for the production of aflibercept, and a person of ordinary skill in the art would have been motivated to do so to in order to aid in the production of the recombinantly expressed protein, including for the purpose of reducing color in the drug substance and/or drug product. (*See, e.g.*, 710 patent; 732 patent; Krattenmacher; 342 patent; WO 062; 1999 ICH; Du 2019; Vijayasankaran 2013; Vijayasankaran 2018; Xu 2014; Prentice; Song; Ritacco 2018; Li 2014; Liu 2014; Xu 2014; Graham; Schöneich 2000). A person skilled in the art also would have been motivated to use such CDM in order to avoid batch-to-batch variability and because all the contents are known and without animal-derived components or peptones. (*See, e.g.*, 342 patent; WO 062; Gu).

Moreover, a person of ordinary skill in the art would have had a reasonable expectation of success given that these components were already being added to CDM and shown to result in the production of recombinant protein. (*See, e.g.*, WO 408; CN 729; CN 648; CN 732; Okamoto; Olakanmi; 216 patent; Tanaka; Krattenmacher; Ritacco 2018; Graham; 710 patent; 732 patent; 401 patent; WO 498; WO 578; 727 publication; 533 publication; 507 publication; 519 patent; 342 patent; WO 062). Indeed, Regeneron had already reported expressing recombinant VEGF antagonist proteins—whose amino acid sequences are nearly identical to that of aflibercept—in CDM. (959 patent at 16:22-26; 29:37-44; 757 patent at 16:27-30; 29:51-58; 30:29-33).

As a result, claim 15 of the 715 patent is rendered obvious by at least, *inter alia*, one or more of the aflibercept references, in combination with one or more of the references disclosing the production of recombinant proteins in the presence of nickel, further in combination with one or more references disclosing CDM that includes iron, copper, zinc, cysteine, and/or an antioxidant, and further in combination with one or more references disclosing a specific host color.

11. Claim 16.

The language of claim 16 of the 715 patent is set forth above.

To the extent that the patentee alleges that any aspect of Mylan's BLA process cell culture step infringes claim 16, either literally or under the doctrine of equivalents, then claim 16 is anticipated at least to the extent that any of the alleged infringing steps or compositions, including the cell culture media products used in Mylan's BLA process, were in public use and/or on sale prior to the filing date of the 715 patent. (*See, e.g.*, Kerry 2018; Zheng 2018; Fernandes 2016; Cell Boost 5 Data File, dated 2015; Park 2017a; Park 2017b; Tian 2014; Brown 2018; Luchese

2018; Poulain 2017; Freund 2018; Gagnon 2018; Cha 2017; Oliveira 2017).[43] Consequently, claim 16 of the 715 patent is anticipated at least by references documenting the availability and/or use of the cell culture media products used in Mylan's BLA process.

Claim 16 of the 715 patent is anticipated at least by references disclosing aflibercept and the production of aflibercept in cell culture media containing, among other things, antioxidants, including taurine. (*See, e.g.*, 342 patent; WO 062).

Claim 16 of the 715 patent is anticipated to the extent that EYLEA® (aflibercept) has been manufactured according to the claimed process and was on sale, in public use, or otherwise available to the public before the effective filing date of the 715 patent.

Claim 16 is obvious in view of references disclosing aflibercept, in combination with one or more of the references disclosing the production of recombinant proteins in the presence of or absence of nickel, further in combination with one or more references disclosing CDM that includes iron, copper, zinc, cysteine, and/or an antioxidant within the claimed cumulative concentration ranges, or that excludes iron, copper, zinc or cysteine.

Aflibercept was known in the art as a therapeutic protein with purported uses in treating angiogenic eye disorders, and its production, including in eukaryotic cells, had been described. (*See, e.g.*, EYLEA Label; 094 publication; Holash; 610 publication; WO 062; 249 publication; 432 publication; 930 publication; 531 publication).

It also was known in the art that "[c]ell cultures may … be supplemented with nutrients and/or other medium components including hormones and/or other growth factors, particular ions (such as sodium, chloride, calcium, magnesium, and phosphate), buffers, vitamins, nucleosides or

[43] Mylan reserves the right to include additional defenses based on the commercial and/or public availability of any other cell culture media that may, through discovery, be revealed to contain one or more of the recited compounds.

nucleotides, trace elements (inorganic compounds usually present at very low final concentrations), amino acids, lipids, or glucose or other energy source." (WO 408 at [0009]; *see also, e.g.*, CN 729; CN 648; CN 732; Okamoto; Olakanmi; 216 patent; Tanaka; Krattenmacher; Ritacco 2018; Graham; 710 patent; 732 patent; 401 patent; WO 498; WO 578; 727 publication; 533 publication; 507 publication; 519 patent; 342 patent; WO 062; MEM (Sigma-Aldrich); DMEM (Biochrom); Ham's F-12 (Biochrom); Ham's F-12 (Elabscience); DMEM/Ham's F-12 (Sigma-Aldrich); DMEM/Ham's F-12 (Biochrom); DMEM/Ham's F-12 (SAFC); Iscove (Biochrom); RPMI 1640 (Biochrom); RPMI 1640 (SAFC); MEM/Joklik (Sigma-Aldrich); 056 patent; ThermoFisher Handbook; Gorfien; Pan; Reinhart; Rodrigues; Zhang). Further, the addition of these components was well known to be required for production of recombinant proteins. (*See, e.g.*, WO 408; CN 729; CN 648; CN 732; Okamoto; Olakanmi; 216 patent; Tanaka; Krattenmacher; Ritacco 2018; Graham; 710 patent; 732 patent; 401 patent; WO 498; WO 578; 727 publication; 533 publication; 507 publication; 519 patent; 342 patent; WO 062). Accordingly, it would have been obvious to incorporate additional components, excluding nickel or using nickel in low concentrations, into cell culture processes for the production of aflibercept, and a person of ordinary skill in the art would have been motivated to do so to in order to aid in the production of the recombinantly expressed protein, including for the purpose of reducing color in the drug substance and/or drug product. (*See, e.g.*, 710 patent; 732 patent; Krattenmacher; 342 patent; WO 062; 1999 ICH; Du 2019; Vijayasankaran 2013; Vijayasankaran 2018; Prentice; Song; Ritacco 2018; Li 2014; Liu 2014; Xu 2014; Graham; Schöneich 2000). A person skilled in the art also would have been motivated to use such CDM in order to avoid batch-to-batch variability and because all the contents are known and without animal-derived components or peptones. (*See, e.g.*, 342 patent; WO 062; Gu).

Moreover, a person of ordinary skill in the art would have had a reasonable expectation of success given that these components were already being added to CDM and shown to result in the production of recombinant protein. (*See, e.g.*, WO 408; CN 729; CN 648; CN 732; Okamoto; Olakanmi; 216 patent; Tanaka; Krattenmacher; Ritacco 2018; Graham; 710 patent; 732 patent; 401 patent; WO 498; WO 578; 727 publication; 533 publication; 507 publication; 519 patent; 342 patent; WO 062; 469 patent; 938 patent; 084 patent; Zang; Wyatt; González-Leal; Gu). Indeed, Regeneron had already reported expressing recombinant VEGF antagonist proteins—whose amino acid sequences are nearly identical to that of aflibercept—in CDM. (959 patent at 16:22-26; 29:37-44; 757 patent at 16:27-30; 29:51-58; 30:29-33).

As a result, claim 16 of the 715 patent is rendered obvious by at least, *inter alia*, one or more of the aflibercept references, in combination with one or more of the references disclosing the production of recombinant proteins in the presence of or absence of nickel, further in combination with one or more references disclosing CDM that includes iron, copper, zinc, cysteine, and/or an antioxidant.

12. Secondary Considerations.

Mylan is unaware of any evidence of secondary considerations that would render non-obvious the particular combination of elements claimed in the 715 patent, as described above and incorporated herein by reference.

Additionally, the patentee must prove the required nexus before relying on any secondary considerations of alleged non-obviousness. Mylan is not aware of any evidence that would establish the required nexus for any of the claims of the 715 patent, nor has Regeneron presented any evidence that would establish the required nexus for any of the claims of the 715 patent despite Mylan's requests for such discovery.

Further, even if there were any evidence of such secondary considerations[44] and the required nexus, the *prima facie* evidence of obviousness is sufficiently strong that it cannot be rebutted by evidence relevant to secondary considerations of non-obviousness, including any evidence of alleged commercial success.

As a result, all claims of the 715 patent are anticipated and obvious in view of at least the references and combinations set forth above, and in view of the knowledge of a person of ordinary skill in the art.

D. Enablement.

The 715 patent Asserted Claims are invalid for lack of enablement under 35 U.S.C. § 112.

1. Claim 1.

The language of claim 1 of the 715 patent is set forth above.

To the extent claim 1 of the 715 patent is not anticipated or obvious, as discussed above, the 715 patent fails to provide sufficient support for the subject matter claimed in claim 1. For example, the 715 patent specification does not provide any working examples of the claimed method, and also does not provide any guidance elsewhere in the specification for how to carry out the claimed invention. Claim 1 is drawn to "producing aflibercept harvested from a host cell cultured in a chemically defined medium (CDM)," "wherein the cumulative concentration of nickel in said CDM is less than or equal to 0.4 μM or about 0.4 μM and one or more of the following: i. the cumulative concentration of iron in said CDM is less than or equal to 55.0 μM; ii. the cumulative concentration of copper in said CDM is less than or equal to 0.8 μM; iii. The cumulative concentration of zinc in said CDM is less than or equal to 56.0 μM; iv. The cumulative

[44] Mylan reserves the right to address any evidence of secondary considerations that is raised in litigation by any entity, or entities, attempting to assert the 715 patent.

concentration of cysteine in said CDM is less than or equal to 10.0 mM, and v. said CDM includes anti-oxidants where the cumulative concentration of an antioxidant is about 0.001 mM to about 10.0 mM for any single anti-oxidant" and harvesting the aflibercept. However, the specification only provides working examples of producing aflibercept in cell culture in which the media contained a limited number of potential antioxidants, some of which had no effect, and where the concentration of claimed metals were decreased or increased in concert Regeneron Protected Material

Regeneron Protected Material

Regeneron Protected Material Further, the examples are limited to testing a very narrow set of media conditions that are not commensurate in scope with the breadth of the claim, which broadly covers an almost limitless variety of CDMs comprising different combinations and concentrations of media components, and places no limits on the type of host cell cultured or the type of antioxidant used in the media. (*See, e.g.*, 715 patent at 120:46 – 123:19). Regeneron Protected Material

Regeneron Protected Material

Additionally, the specification only discloses an example using limited concentrations of the components listed above. (*See, e.g.*, 715 patent at 120:46 – 123:19).

As a result, the 715 patent specification does not enable a person of ordinary skill in the art to make and use the full scope of the subject matter claimed in claim 1 without undue experimentation.

Accordingly, claim 1 of the 715 patent is invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

2. Claims 2-6 and 12-14.

The language of claims 2-6 and 12-14 of the 715 patent is set forth above.

Claims 2-6 and 12-14 of the 715 patent all depend from claim 1 and thus incorporate the elements of claim 1. Thus, for at least the same reasons set forth above with respect to claim 1, said discussion incorporated herein by reference, and because the limitations of claims 2-6 and 12-14 do not suffice to cure the failures of claim 1 to meet the requirements of 35 U.S.C. § 112, claims 2-6 and 12-14 of the 715 patent are invalid for failing to meet the enablement requirements of 35 U.S.C. § 112. For example, none of the dependent claims narrow the scope of claim 1 to any useful or guiding parameters, but rather, only underscore the staggering and unsupported breadth of claim 1.

Further, the specification does not enable claim 2 and the claims that depend therefrom, and claim 13, because the specification does not provide any guidance for measuring BY color of a harvest material. The 715 patent explains that the BY system is not a precise or objective way to measure color. (*See, e.g.*, 715 patent at 57:51-54).

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Regeneron Protected Material

The specification does not enable claim 14, because the specification does not provide any disclosure of a harvest material whose color corresponds to the claimed CIELAB values, or how to obtain a harvest material whose color corresponds to the claimed CIELAB values.

In addition, given the limited disclosures of the specification, the applicants have not enabled the method to meet all the claimed criteria (claim 5), for all the claimed host cells (claim 6), all antioxidants (claim 12), and all the claimed color criteria (claims 2, 13, and 14).

As a result, and for at least these reasons, claims 2-6 and 12-14 of the 715 patent are invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

3. Claim 15.

The language of claim 15 of the 715 patent is set forth above.

To the extent claim 15 of the 715 patent is not anticipated or obvious, as discussed above, the 715 patent fails to provide sufficient support for the subject matter claimed in claim 15. For example, the 715 patent specification does not provide any working examples of the claimed method, and also does not provide any guidance elsewhere in the specification for how to carry out the claimed invention. Claim 15 is drawn to "producing aflibercept harvested from a host cell cultured in a chemically defined medium (CDM)," "wherein the cumulative concentration of nickel in said CDM is about 0.4 μM and one or more of the following: i. the cumulative concentration of iron in said CDM is less than or equal to 55.0 μM; ii. the cumulative concentration of copper in said CDM is less than or equal to 0.8 μ M; iii. The cumulative concentration of zinc in said CDM is less than or equal to 56.0 μM; iv. The cumulative concentration of cysteine in said CDM is less than or equal to 10.0 mM; and v. said CDM includes anti-oxidants where the cumulative concentration of an antioxidant is about 0.001 mM to about 10.0 mM for any single anti-oxidant" and harvesting with a specific harvest color. However, the specification only provides working examples of producing aflibercept in cell culture in which the media contained a limited number of potential antioxidants, some of which had no effect, and where the concentration of claimed metals were decreased or increased in concert

Regeneron Protected Material

Regeneron Protected Material Further, the examples are limited to testing a very narrow set of media conditions that are not commensurate in scope with the breadth of the claim, which broadly covers an almost limitless variety of CDMs comprising different combinations and concentrations of media

components, and places no limits on the type of host cell cultured or the type of antioxidant used in the media. (*See, e.g.*, 715 patent at 120:46 – 123:19). Regeneron Protected Material

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Additionally, the specification only discloses an example using limited concentrations of the components listed above. (*See, e.g.*, 715 patent at 120:46 – 123:19).

As a result, the 715 patent specification does not enable a person of ordinary skill in the art to make and use the full scope of the subject matter claimed in claim 15 without undue experimentation.

Accordingly, claim 15 of the 715 patent is invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

4. Claim 16.

The language of claim 16 of the 715 patent is set forth above.

To the extent claim 16 of the 715 patent is not anticipated or obvious, as discussed above, the 715 patent fails to provide sufficient support for the subject matter claimed in claim 1. For example, the 715 patent specification does not provide any working examples of the claimed method, and also does not provide any guidance elsewhere in the specification for how to carry out the claimed invention. Claim 16 is drawn to "producing aflibercept harvested from a host cell cultured in a chemically defined medium (CDM)," "wherein the cumulative concentration of nickel in said CDM is less than or equal to 0.4 μM or about 0.4 μM and one or more of the following: i. the cumulative concentration of iron in said CDM is less than or equal to 55.0 μM; ii. the cumulative concentration of copper in said CDM is less than or equal to 0.8 μM; iii. The cumulative concentration of zinc in said CDM is less than or equal to 56.0 μM; iv. The cumulative concentration of cysteine in said CDM is less than or equal to 10.0 mM, and v. said CDM includes

anti-oxidants where the cumulative concentration of an antioxidant is about 0.001 mM to about 10.0 mM for any single anti-oxidant" and harvesting the aflibercept. However, the specification only provides working examples of producing aflibercept in cell culture in which the media contained a limited number of potential antioxidants, some of which had no effect, and where the concentration of claimed metals were decreased or increased in concert— Regeneron Protected Material

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Regeneron Protected Material Further, the examples are limited to testing a very narrow set of media conditions that are not commensurate in scope with the breadth of the claim, which broadly covers an almost limitless variety of CDMs comprising different combinations and concentrations of media components, and places no limits on the type of host cell cultured or the type of antioxidant used in the media. (*See, e.g.*, 715 patent at 120:46 – 123:19). Regeneron Protected Material

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Additionally, the specification only discloses an example using limited concentrations of the components listed above. (*See, e.g.*, 715 patent at 120:46 – 123:19).

As a result, the 715 patent specification does not enable a person of ordinary skill in the art to make and use the full scope of the subject matter claimed in claim 16 without undue experimentation.

Accordingly, claim 16 of the 715 patent is invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

E. Written Description.

The 715 patent Asserted Claims are invalid for lack of written description under 35 U.S.C. § 112.

1. Claim 1.

To the extent claim 1 of the 715 patent is not anticipated or obvious, as discussed above, the 715 patent fails to provide sufficient support for the subject matter claimed in claim 1. For example, the specification does not describe anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 1 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to convey to those skilled in the art that the inventor had possession of the claimed subject matter.

Claim 1 also is invalid for failure to meet the written description requirement of 35 U.S.C. § 112, because the claims are not commensurate in scope with the limited disclosures of the specification. For example, the specification does not provide any working examples of the claimed method, and also does not provide any description elsewhere in the specification for how to carry out the claimed invention. (*See, e.g.*, 715 patent at 75:4-9, 120:46 – 123:19). Further, the examples are limited to testing a very narrow set of media conditions that are not commensurate in scope with the breadth of the claim, which broadly covers an almost limitless variety of CDMs comprising different combinations and concentrations of media components, and places no limits on the type of host cell cultured or the type of antioxidant used in the media. (*See, e.g.*, *id.*).

Regeneron Protected Material Moreover, the specification only provides working examples of producing aflibercept in cell culture in which the media contained a limited number of potential

antioxidants and where the concentration of claimed metals was decreased or increased in concert. Additionally, the specification only discloses an example using limited concentrations of the components listed above. (*See, e.g.*, 715 patent at 120:46 – 123:19).

Further, Regeneron has taken the position during claim construction proceedings that the 715 patent claims cover methods in which cells are cultured in CDM for part of the cell culture and in hydrolysate (non-CDM) for another part of the cell culture. To the extent one or more claims are construed to cover such a scenario, said claims are invalid because no such method is described in the 715 patent.

As a result, the 715 patent specification does not convey to those of ordinary skill in the art that the inventors had possession of the full scope of claim 1 as of the filing date.

Accordingly, claim 1 of the 715 patent is invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

2. Claims 2-6 and 12-14.

The language of claims 2-6 and 12-14 of the 715 patent is set forth above.

Claims 2-6 and 12-14 of the 715 patent all depend from claim 1 and thus incorporate the elements of claim 1. Thus, for at least the same reasons set forth above with respect to claim 1, said discussion incorporated herein by reference, and because the limitations of claims 2-6 and 12-14 do not suffice to cure the failures of claim 1 to meet the requirements of 35 U.S.C. § 112, claims 2-6 and 12-14 of the 715 patent are invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

In addition, given the limited disclosures of the specification, it does not convey to those of ordinary skill in the art that the inventors had possession of the full scope of the method with all the claimed criteria, (claim 5), with all the claimed host cells (claim 6), with all antioxidants (claim 12), and with all the claimed color criteria (claims 2, 13, and 14).

Further, the specification does not provide written description support for claim 2 and the claims that depend therefrom, and claim 13, because the specification does not provide adequate written description of measuring BY color of a harvest material. For example, the 715 patent explains that the BY system is not a precise or objective way to measure color. (*See, e.g.*, 715 patent at 57:51-54). Regeneron Protected Material

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The specification does not provide written description support for claim 14, because the specification does not provide any disclosure of a harvest material whose color corresponds to the claimed CIELAB values, or how to obtain a harvest material whose color corresponds to the claimed CIELAB values.

As a result, and for at least these reasons, claims 2-6 and 12-14 of the 715 patent are invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

3. Claim 15.

To the extent claim 15 of the 715 patent is not anticipated or obvious, as discussed above, the 715 patent fails to provide sufficient support for the subject matter claimed in claim 15. For example, the specification does not describe anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 15 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to convey to those skilled in the art that the inventor had possession of the claimed subject matter.

Claim 15 also is invalid for failure to meet the written description requirement of 35 U.S.C. § 112, because the claims are not commensurate in scope with the limited disclosures of the specification. For example, the specification does not provide any working examples of the claimed method, and also does not provide any description elsewhere in the specification for how to carry out the claimed invention. (*See, e.g.*, 715 patent at 75:4-9, 120:46 – 123:19). Further, the examples are limited to testing a very narrow set of media conditions that are not commensurate in scope with the breadth of the claim, which broadly covers an almost limitless variety of CDMs comprising different combinations and concentrations of media components, and places no limits on the type of host cell cultured or the type of antioxidant used in the media. (*See, e.g.*, *id.*).

 Moreover, the specification only provides working examples of producing aflibercept in cell culture in which the media contained a limited number of potential antioxidants and where the concentration of claimed metals was decreased or increased in concert

 Additionally, the specification only discloses an example using limited concentrations of the components listed above. (*See, e.g.*, 715 patent at 120:46 – 123:19).

Further, Regeneron has taken the position during claim construction proceedings that the 715 patent claims cover methods in which cells are cultured in CDM for part of the cell culture and in hydrolysate (non-CDM) for another part of the cell culture. To the extent one or more

claims are construed to cover such a scenario, said claims are invalid because no such method is described in the 715 patent.

As a result, the 715 patent specification does not convey to those of ordinary skill in the art that the inventors had possession of the full scope of claim 15 as of the filing date.

Accordingly, claim 15 of the 715 patent is invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

4. Claim 16.

To the extent claim 16 of the 715 patent is not anticipated or obvious, as discussed above, the 715 patent fails to provide sufficient support for the subject matter claimed in claim 16. For example, the specification does not describe anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 16 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to convey to those skilled in the art that the inventor had possession of the claimed subject matter.

Claim 16 also is invalid for failure to meet the written description requirement of 35 U.S.C. § 112, because the claims are not commensurate in scope with the limited disclosures of the specification. For example, the specification does not provide any working examples of the claimed method, and also does not provide any description elsewhere in the specification for how to carry out the claimed invention. (*See, e.g.*, 715 patent at 75:4-9, 120:46 – 123:19). Further, the examples are limited to testing a very narrow set of media conditions that are not commensurate in scope with the breadth of the claim, which broadly covers an almost limitless variety of CDMs comprising different combinations and concentrations of media components, and places no limits on the type of host cell cultured or the type of antioxidant used in the media. (*See, e.g., id.*).

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Regeneron Protected Material Moreover, the specification only provides working examples of producing aflibercept in cell culture in which the media contained a limited number of potential antioxidants and where the concentration of claimed metals was decreased or increased in concert Regeneron Protected Material

Regeneron Protected Material

Regeneron Protected Material Additionally, the specification only discloses an example using limited concentrations of the components listed above. (*See, e.g.*, 715 patent at 120:46 – 123:19).

Further, Regeneron has taken the position during claim construction proceedings that the 715 patent claims cover methods in which cells are cultured in CDM for part of the cell culture and in hydrolysate (non-CDM) for another part of the cell culture. To the extent one or more claims are construed to cover such a scenario, said claims are invalid because no such method is described in the 715 patent.

As a result, the 715 patent specification does not convey to those of ordinary skill in the art that the inventors had possession of the full scope of claim 16 as of the filing date.

Accordingly, claim 16 of the 715 patent is invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

F. Indefiniteness

The 715 patent Asserted Claims are invalid for indefiniteness under 35 U.S.C. § 112.

1. Claim 1.

The language of claim 1 of the 715 patent is set forth above.

Claim 1 is invalid for indefiniteness for failure to inform with reasonable certainty those skilled in the art about the scope of the invention. For example, at least the claim terms "CDM under conditions suitable" and "less than or equal to" are indefinite. No details are provided in terms of the composition of the cell culture medium, or what constitutes "conditions suitable." Further, the scope of "less than or equal to" is not clear given that the term could be read to include the absence of the compound.

 Moreover, the specification only provides working examples of producing aflibercept in cell culture in which the media contained a limited number of potential antioxidants and where the concentration of claimed metals was decreased or increased in concert— As a result, the scope of the claims is unclear.

Further, Regeneron has taken the position during claim construction proceedings that the 715 patent claims cover methods in which cells are cultured in CDM for part of the cell culture and in hydrolysate (non-CDM) for another part of the cell culture. No such method is described in the 715 patent, and such a position conflicts with the plain language of the claims and the intrinsic record, rendering the claims indefinite. For example, a person of ordinary skill in the art would be left to guess as to how much or how little hydrolysate was sufficient to fall within or outside the scope of the claims, and the amount of time a cell culture could be in hydrolysate before falling within or outside the scope of the claims.

The term "anti-oxidants" is indefinite. The specification fails to offer any limitations or bounds on what might be considered an antioxidant, making the breadth of the term nearly limitless.

As a result, and for at least these reasons, claim 1 of the 715 patent fails to inform, with reasonable certainty, those skilled in the art about the scope of the invention, and therefore is invalid for indefiniteness under 35 U.S.C. § 112.

2. Claims 2-6 and 12-14.

The language of claims 2-6 and 12-14 of the 715 patent is set forth above.

Claims 2-6 and 12-14 of the 715 patent are invalid for indefiniteness pursuant to 35 U.S.C. § 112. Claims 2-6 and 12-14 all depend from claim 1 and thus incorporate the elements of claim 1. Thus, for at least the same reasons set forth above with respect to claim 1, said discussion incorporated herein by reference, and because the limitations of claims 2-6 and 12-14 do not suffice to cure the failures of claim 1 to meet the requirements of 35 U.S.C. § 112, claims 2-6 and 12-14 of the 715 patent are invalid for indefiniteness under 35 U.S.C. § 112.

In addition, at least the claim term "or combinations thereof" (claims 3, 12) is indefinite. No details are provided in terms of what combinations are suitable.

Further, claim 2 and the claims that depend therefrom, and claim 13, are indefinite because the specification does not provide any description of measuring BY color of a harvest material, and the 715 patent specification itself explains that the BY system is not a precise or objective way to measure color. (*See, e.g.*, 715 patent at 57:51-54; 58:43-45).

 Further, there are no guidelines in the claims that disclose how to conduct the assessment of BY color with a harvest material, where it is clear from the specification that there are several variables that can impact the final determination, including but not limited

to, the standards used; the depth of the containers; the width of the containers; the type of glass containers; the observation distance; the background lighting; the number of observers; the axis of observation; etc. (*See, e.g.*, 715 patent at 57:35-50). Further, the term "harvest" in claim 2 renders the claim indefinite. The harvest process is not a single step, but a complex, multi-step process typically including, but not limited to, centrifugation and filtration steps, and multiple holding tanks. The specification does not provide any guidance or certainty about where in that multi-step process samples are to be taken and analyzed for color.

Claim 4 is indefinite for the reasons stated above for the term "anti-oxidant" in claim 1.

Claim 5 is indefinite for failing to state at which step of the claimed method the claimed characteristics are to be analyzed. Biologic manufacturing is typically a multi-stage process involving dozens of discrete steps, and the analysis of each of the claimed characteristics can change substantially depending on when that analysis is conducted. Claim 5 is further indefinite because the term "substantially unchanged" does not provide any certainty about the scope of the purported invention. No comparator is provided, and no additional guidance is provided in the claims or specification, leaving the person of ordinary skill in the art to wonder how to assess whether any of the characteristics are "substantially unchanged."

Claim 14 is indefinite because the specification does not provide any disclosure of a harvest material whose color corresponds to the claimed CIELAB values, or how to obtain a harvest material whose color corresponds to the claimed CIELAB values.

As a result, and for at least these reasons, claims 2-6 and 12-14 of the 715 patent fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention, and therefore are invalid for indefiniteness under 35 U.S.C. § 112.

3. Claim 15.

The language of claim 15 of the 715 patent is set forth above.

Claim 15 is invalid for indefiniteness for failure to inform with reasonable certainty those skilled in the art about the scope of the invention. For example, at least the claim terms "CDM under conditions suitable" and "less than or equal to" are indefinite. No details are provided in terms of the composition of the cell culture medium, or what constitutes "conditions suitable." Further, the scope of "less than or equal to" is not clear given that the term could be read to include the absence of the compound.

 Moreover, the specification only provides working examples of producing aflibercept in cell culture in which the media contained a limited number of potential antioxidants and where the concentration of claimed metals was decreased or increased in concert—

 As a result, the scope of the claims is unclear.

Further, Regeneron has taken the position during claim construction proceedings that the 715 patent claims cover methods in which cells are cultured in CDM for part of the cell culture and in hydrolysate (non-CDM) for another part of the cell culture. No such method is described in the 715 patent, and such a position conflicts with the plain language of the claims and the intrinsic record, rendering the claims indefinite. For example, a person of ordinary skill in the art would be left to guess as to how much or how little hydrolysate was sufficient to fall within or outside the scope of the claims, and the amount of time a cell culture could be in hydrolysate before falling within or outside the scope of the claims.

Further, claim 15 is indefinite because the specification does not provide any description of measuring BY color of a harvest material, and the 715 patent specification itself explains that the BY system is not a precise or objective way to measure color. (*See, e.g.*, 715 patent at 57:51-54; 58:43-45). Regeneron Protected Material Regeneron Protected Material Further, there are no guidelines in the claims that disclose how to conduct the assessment of BY color with a harvest material, where it is clear from the specification that there are several variables that can impact the final determination, including but not limited to, the standards used; the depth of the containers; the width of the containers; the type of glass containers; the observation distance; the background lighting; the number of observers; the axis of observation; etc. (*See, e.g.*, 715 patent at 57:35-50).

Further, the term "harvest" in claim 15 renders the claim indefinite. The harvest process is not a single step, but a complex, multi-step process typically including, but not limited to, centrifugation and filtration steps, and multiple holding tanks. The specification does not provide any guidance or certainty about where in that multi-step process samples are to be taken and analyzed for color.

The term "anti-oxidants" is indefinite. The specification fails to offer any limitations or bounds on what might be considered an antioxidant, making the breadth of the term nearly limitless.

As a result, and for at least these reasons, claim 15 of the 715 patent fails to inform, with reasonable certainty, those skilled in the art about the scope of the invention, and therefore is invalid for indefiniteness under 35 U.S.C. § 112.

4. Claim 16.

The language of claim 16 of the 715 patent is set forth above.

Claim 16 is invalid for indefiniteness for failure to inform with reasonable certainty those skilled in the art about the scope of the invention. For example, at least the claim terms "CDM under conditions suitable" and "less than or equal to" are indefinite. No details are provided in terms of the composition of the cell culture medium, or what constitutes "conditions suitable." Further, the scope of "less than or equal to" is not clear given that the term could be read to include the absence of the compound.

 Moreover, the specification only provides working examples of producing aflibercept in cell culture in which the media contained a limited number of potential antioxidants and where the concentration of claimed metals was decreased or increased in concert As a result, the scope of the claims is unclear.

Further, Regeneron has taken the position during claim construction proceedings that the 715 patent claims cover methods in which cells are cultured in CDM for part of the cell culture and in hydrolysate (non-CDM) for another part of the cell culture. No such method is described in the 715 patent, and such a position conflicts with the plain language of the claims and the intrinsic record, rendering the claims indefinite. For example, a person of ordinary skill in the art would be left to guess as to how much or how little hydrolysate was sufficient to fall within or outside the scope of the claims, and the amount of time a cell culture could be in hydrolysate before falling within or outside the scope of the claims.

The term "anti-oxidants" is indefinite. The specification fails to offer any limitations or bounds on what might be considered an antioxidant, making the breadth of the term nearly limitless.

As a result, and for at least these reasons, claim 16 of the 715 patent fails to inform, with reasonable certainty, those skilled in the art about the scope of the invention, and therefore is invalid for indefiniteness under 35 U.S.C. § 112.

G. Unenforceability.

Upon information and belief, Regeneron failed to disclose to the U.S.P.T.O. all information it knew to be material to patentability with a specific intent to mislead and deceive the Patent Office. 37 C.F.R. § 1.56(a); *Minerva Surgical, Inc. v. Hologic, Inc.*, 141 S. Ct. 2298, 2309 n.3 (2021). For example, while arguing to the U.S.P.T.O. during prosecution of the 030 application, Regeneron knew, yet failed to disclose, prior art and commercial cell culture products that were already on the market before the 715 patent's earliest purported priority date, including much of the prior art and each of the products discussed above. Moreover, Regeneron misrepresented the teachings of the prior art to the Examiner during prosecution of the 030 application. (*See, e.g.*, 715 patent PH, 3/2/2021 Applicant Remarks). Regeneron was also aware of the materiality of these misrepresentations, and withheld references and products, to the claimed subject matter.

Moreover, Regeneron has engaged in a pattern of deception wherein, during prosecution of its applications, Regeneron intentionally obscures references it knows to be relevant to the subject matter of the pending claims by submitting numerous other references to the U.S.P.T.O., effectively burying those that contain invalidating disclosures.

Further, Regeneron, through its agent, Jonathan Caplan, when amending the claims in the June 11, 2021 submission, knew that the specification and the experiments described in the working examples failed to support the claims as drafted. For example, Jonathan Caplan knew

that in the underlying experiments, the metal concentrations were only raised or lowered together, and that there was no support or description for only lowering the concentration of nickel, yet intentionally chose to draft the claims in a way that would mislead the Examiner and the public into believing that such experiments were included in the specification and provided support for the claims. This action was material, for if the Examiner had been aware that the metal concentrations were only increased or decreased together, the Examiner would have been alerted to the lack of support and disclosure in the specification, and the claims in their current form would not have issued.

The most reasonable inference to be drawn from Regeneron's failures to comply with its duties of candor, good faith, and disclosure (e.g., Regeneron's intentional withholding of the above-mentioned references from the U.S.P.T.O. and its misleading representations during prosecution of *inter alia* the 030 application), is that the actions were done with the intent to deceive.

For at least these reasons, the 715 patent Asserted Claims are unenforceable for inequitable conduct.

VIII. INVALIDITY CONTENTIONS REGARDING THE 572 PATENT.

A. The Knowledge of a Person of Ordinary Skill in the Art.

In the context of the obviousness analysis, the scope of the prior art is directed to the field of endeavor of the invention, and includes the knowledge of a person of ordinary skill in the art. Here, a person of ordinary skill in the art would have: (1) knowledge regarding the diagnosis and treatment of angiogenic eye disorders, including the administration of therapies to treat said disorders; and (2) the ability to understand results and findings presented or published by others in the field, including the publications discussed herein. Typically, such a person would have an advanced degree, such as an M.D. or Ph.D. (or equivalent, or less education but considerable

professional experience in the medical, biotechnological, or pharmaceutical field), with practical academic or medical experience in (i) developing treatments for angiogenic eye disorders (such as AMD), including through the use of VEGF antagonists, or (ii) treating of same, including through the use of VEGF antagonists.[45]

B. Prior Art Relevant to the 572 Patent.

In the context of the obviousness analysis, the scope of the prior art is directed to the field of endeavor of the invention. The scope of the prior art relates, in general, to treatments for angiogenic eye disorders, including through the use of VEGF antagonists.

Mylan relies on at least the references identified in Appendix A in support of its Invalidity Contentions regarding the 572 patent based on anticipation and obviousness under 35 U.S.C. § 102 and 35 U.S.C. § 103. Unless otherwise and expressly stated, it should be presumed that Mylan intends to rely upon each reference in its entirety to the extent relevant or appropriate, including references cited in and/or referenced within the references identified in Appendix A. Similarly, the headings included in this section are for convenience only, and do not limit Mylan's right to rely on any reference to the extent relevant or appropriate.

[45] In its Decision Granting Institution of *Inter Partes* Review of the related 601 patent, the Board has adopted this definition of the person of ordinary skill in the art. *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01226, Paper 22 (PTAB Jan. 11, 2023).

C. 35 U.S.C. § 102 and § 103 – The 572 Patent Claims are Anticipated and Rendered Obvious.[46]

1. Claim 1.

a. Anticipation by the 747 Patent.[47]

The language of claim 1 of the 572 patent is set forth above.

Claim 1 of the 572 patent is anticipated by Regeneron's patents disclosing dosing regimens for the treatment of eye disorders. For example, the 747 patent discloses a method of treating eye disorders, including macular degeneration. The 747 patent further discloses treatment with the fusion polypeptide of SEQ ID NO:6 (VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). The 747 patent further discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 2-8 weeks, or 1-6 months apart, which a person of ordinary skill in the art would have immediately envisaged could encompass, e.g., "each secondary dose is administered approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose." (*See, e.g.*, 747 patent; 049 patent; 799 patent).

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[46] The 572 patent Asserted Claims are invalid for at least the reasons set forth in the Final Written Decisions in IPR2021-00880 (Paper 89, Nov. 9, 2022) and IPR2021-00881 (Paper 94, Nov. 9, 2022). As noted, Mylan further incorporates by reference all grounds of invalidity set forth in IPR2021-00880, IPR2021-00881, IPR2022-01225, IPR2022-01226, IPR2022-01524, IPR2023-00099, and IPR2023-00442.

[47] The 799 patent and 049 patent are related to the 747 patent and contain the same disclosures. Claim 1 is also anticipated by the 799 patent and 049 patent.

b. Anticipation by the VIEW References.

Claim 1 of the 572 patent is anticipated by at least each of the VIEW References that disclose the dosing regimen used in the VIEW trials. For example, the VIEW References disclose a method of treating AMD, by intravitreally administering to a patient in need thereof 2 mg of VEGF Trap-Eye (i.e., aflibercept), using three monthly doses, followed by every-8-week dosing. (*See, e.g.*, Dixon; Adis; NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release). In addition, it was well known among those of ordinary skill in the art that aflibercept and VEGF Trap-Eye were different terms for the same molecule, and were often used interchangeably, and also that aflibercept was the molecule used in the VIEW trials. (*See, e.g.*, Dixon; Adis; Regeneron 2009 10-Q; 757 patent Petition for Patent Term Extension; 758 patent Petition for Patent Term Extension; 959 patent Petition for Patent Term Extension; Nguyen 2009a; Dix; 095 patent). As a result, each of the references disclosing the every-8-week dosing regimen used in the VIEW clinical trials, including Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release anticipates claim 1 of the 572 patent.

Further, the aflibercept dosing regimen recited in claim 1 of the 572 patent claims the same every-8-week dosing regimen claimed by an earlier patent in the same family, the 338 patent. In a Final Written Decision relating to the 338 patent, the Board determined that the Dixon reference anticipates the aflibercept dosing regimen claimed by the 338 patent and repeated in claim 1 of the 572 patent. *See* 338 FWD. Given that the Board already found the substantively identical dosing regimen is disclosed in Dixon, claim 1 of the 572 patent is likewise anticipated by Dixon for the same reasons articulated by the Board in the 338 IPR.

Claim 1 contains the element "wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose." This element is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Since the method steps are "performed in the same way regardless whether or not the patient experiences" a clinical change, this element is non-limiting. *Bristol-Myers*, 246 F.3d at 1375; *see also Prometheus*, 2013 WL 5333033, at *5-6 (phrase that merely "expresses the intended result of a process step positively recited" is non-limiting); *Minton*, 336 F.3d at 1381.[48]

To the extent "wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose" is limiting, claim 1 of the 572 patent is anticipated by at least each of the VIEW References that disclose the dosing regimen and VEGF Trap-Eye/aflibercept used in the VIEW trials. Claim 1 expressly defines an effective amount as 2 mg, which was disclosed in the prior art references disclosing the VIEW clinical trial dosing regimens. The CLEAR-IT-2 data demonstrate success at treating patients with AMD using fewer doses, on average, than in the VIEW every-8-week dosing regimen. (*See, e.g.*, Heier 2009; Dixon; Adis; Retina Society Meeting

[48] Mylan incorporates fully herein the arguments set forth in its claim construction briefs, served on November 29, 2022 and December 15, 2022.

Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). The VIEW data confirm that therapeutic effect resulted from, and was an inherent aspect of, the operation of the VIEW regimen. (*See, e.g.*, 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release; Heier 2012). In addition, it was well known among those of ordinary skill in the art that aflibercept and VEGF Trap-Eye were different terms for the same molecule, and were often used interchangeably, and also that aflibercept was the molecule used in the VIEW trials. (*See, e.g.*, Dixon; Adis; Regeneron 2009 10-Q; 757 patent Petition for Patent Term Extension; 758 patent Petition for Patent Term Extension; 959 patent Petition for Patent Term Extension). As a result, each of the references cited above disclosing the VIEW dosing regimen anticipates claim 1 of the 572 patent for at least these additional reasons.

c. Anticipation by Public Use.

Claim 1 of the 572 patent is invalid for being in public use, including in this country, or otherwise available to the public, more than one year before the filing of the 572 patent's earliest priority application. The public use of the claimed invention is evidenced by at least the VIEW References discussed above. (*See, e.g.*, Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-

2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q; 2008 Retina Society Slides).

d. Obviousness over the 747 Patent.[49]

Claim 1 of the 572 patent is obvious in view of Regeneron's patents disclosing dosing regimens for the treatment of eye disorders. For example, the 747 patent discloses a method of treating eye disorders, including macular degeneration. The 747 patent further discloses treatment with the fusion polypeptide of SEQ ID NO:6 (VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). The 747 patent further discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 2-8 weeks, or 1-6 months apart, which a person of ordinary skill in the art would have immediately envisaged could encompass, e.g., "each secondary dose is administered approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose." (*See, e.g.*, 747 patent; 049 patent; 799 patent). A person of ordinary skill in the art would have been motivated to refine the regimens disclosed in the above references to arrive at the claimed regimen in view of the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration. A person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed regimens. Positive results from a variety of regimens, including single intravitreal injections, had been reported for VEGF Trap-Eye/aflibercept. (*See,*

[49] The 799 patent and 049 patent are related to the 747 patent and contain the same disclosures. Claim 1 is also rendered obvious by the 799 patent and 049 patent.

e.g., Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). Accordingly, claim 1 of the 572 patent is obvious in view of at least each of the 747, 049, and 799 patents, and, if necessary, in combination with one or more of the references disclosing the Phase 1 and Phase 2 clinical trial results.

e. Obviousness over the VIEW References.

Claim 1 of the 572 patent is obvious in view of the VIEW references, either alone or in combination. For the reasons discussed above, that discussion incorporated herein, each VIEW reference discloses expressly or inherently each and every claim element. (*See, e.g.*, Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release). Further, the motivation to adopt the claimed dosing regimens for VEGF Trap-Eye comes from the references themselves, which persons of ordinary skill in the art would have appreciated set forth dosing regimens that allowed for dosing less frequently than monthly, as well as the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration.

Also, a person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed VIEW dosing regimens at least because of the Phase 1 and/or CLEAR-IT-2 Phase 2 results, which were obtained using single injections and extended dosing regimens of VEGF Trap-Eye. (*See, e.g.*, Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q).

Accordingly, claim 1 of the 572 patent is obvious in view of at least each of the VIEW references cited above, and, if necessary, in combination with one or more of the references cited above disclosing the Phase 1 and Phase 2 CLEAR-IT-2 results.

In addition, a person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed VIEW dosing regimens at least because of the widely publicized results of the VIEW trials, which were made available to the public before the earliest filing date listed on the face of the 572 patent. (*See, e.g.*, 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release).

Accordingly, claim 1 of the 572 patent is obvious in view of at least each of the VIEW references cited above, and, if necessary, in combination with one or more of the references cited above disclosing the VIEW trial results.

2. Claim 2.

The language of claim 2 of the 572 patent is set forth above.

Claim 2 of the 572 patent depends from claim 1 and thus incorporates the elements of claim 1. The reasons why claim 1 is obvious and/or anticipated are incorporated by reference.

The additional element "wherein the patient achieves a gain in Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Since the method steps are "performed in the same way regardless whether or not the patient experiences" a clinical change, the additional element of claim 2 is non-limiting. *Bristol-Myers*, 246 F.3d at 1375; *see also Prometheus*, 2013 WL 5333033, at *5-6 (phrase that merely "expresses the intended result of a process step positively recited" is non-limiting); *Minton*, 336 F.3d at 1381.[50]

Separately, this element represents nothing more than the natural result flowing from the prior art method of administration disclosed in the VIEW References, using a measure (BCVA) which had already been disclosed in the prior art as a clinical trial measurement and/or endpoint, including in the VEGF Trap-Eye Phase 1, Phase 2, and Phase 3 AMD trials. In addition, the prior art disclosures of the results of those trials provide further support for the inherency of the subject matter of claim 2. For example, 29% of the patients receiving monthly 2.0 mg doses for three months, followed by as-needed dosing in the VEGF Trap-Eye Phase 2 AMD trial exhibited an increase in BCVA of ≥ 15 letters; and 30.6% of the patients receiving three monthly doses followed by every-8-week dosing in the Phase 3 VIEW1 trial gained ≥ 15 letters. (*See, e.g.*, Dixon; Retina Society Meeting Presentation; 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release; Heier 2012). Accordingly, claim 2 is anticipated at

[50] Mylan incorporates fully herein the arguments set forth in its claim construction briefs, served on November 29, 2022 and December 15, 2022.

least by each of the references disclosing the VIEW dosing regimen, including, but not limited to, Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release.

To the extent this element is limiting, the element is expressly set forth in the prior art. For example, the VIEW References identify improvement by > 15 letters as a metric in assessing AMD treatment, including as a secondary outcome measure for the VIEW trials. (*See, e.g.*, Dixon; NCT-795; NCT-377; 5-8-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 5-8-2008 Bayer Press Release). Therefore, a person of ordinary skill in the art reading each of the VIEW References would have understood and been aware of the secondary endpoint identified for those trials.

Further, a person of ordinary skill in the art would have understood from the prior art that the BCVA letter measure is an obvious choice to use when assessing clinical trials relating to AMD treatments. (*See, e.g.*, Nguyen 2009a; Dixon; Adis; NCT-795; NCT-377; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; Heier 2009; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-

Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; Brown 2006; Rosenfeld 2006; Lucentis Medical Review; Fung 2007; Lalwani 2009; Avila 2009; Bashshur 2008; Wu 2009). Further a person of ordinary skill in the art would have had a reasonable expectation of success at meeting the BCVA criteria set forth in claim 2 when using the recited regimen, in light of the positive Phase 1 and Phase 2 results discussed above and reported in the prior art. (*See, e.g.*, Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). Further, the results from the VIEW trials provide further evidence of the reasonable expectation of success that a person of ordinary skill in the art would have had in meeting the criteria set forth in claim 2 when using the recited regimen. (*See, e.g.*, 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release).

Accordingly, claim 2 of the 572 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claim 1, including combinations incorporating one or more references disclosing the use of BCVA in assessing AMD, and/or results of the Phase 1, Phase 2, or Phase 3 trials, in view of the knowledge of a person of ordinary skill in the art.

3. Claim 3.

The language of claim 3 of the 572 patent is set forth above.

Claim 3 of the 572 patent depends from claim 2 which depends from claim 1 and thus incorporates the elements of claims 1 and 2. The reasons why claims 1 and 2 are anticipated and/or obvious are incorporated by reference.

The additional element "wherein the patient gains at least 7 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Since the method steps are "performed in the same way regardless whether or not the patient experiences" a clinical change, the additional element of claim 3 is non-limiting. *Bristol-Myers*, 246 F.3d at 1375; *see also Prometheus*, 2013 WL 5333033, at *5-6 (phrase that merely "expresses the intended result of a process step positively recited" is non-limiting); *Minton*, 336 F.3d at 1381.[51]

Separately, this element represents nothing more than the natural result flowing from the prior art method of administration disclosed in the VIEW References, using a measure (BCVA) which had already been disclosed in the prior art as a clinical trial measurement and/or endpoint, including in the VEGF Trap-Eye Phase 1, Phase 2, and Phase 3 AMD trials. In addition, the prior art disclosures of the results of those trials provide further support for the inherency of the subject matter of claim 3. For example, 29% of the patients receiving monthly 2.0 mg doses for three months, followed by as-needed dosing in the VEGF Trap-Eye Phase 2 AMD trial exhibited an increase in BCVA of ≥ 15 letters; and 30.6% of the patients receiving three monthly doses followed by every-8-week dosing in the Phase 3 VIEW1 trial gained ≥ 15 letters. (*See, e.g.*, Dixon; Retina Society Meeting Presentation; 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press

[51] Mylan incorporates fully herein the arguments set forth in its claim construction briefs, served on November 29, 2022 and December 15, 2022.

Release; 1-18-2011 Regeneron Press Release; Heier 2012). Accordingly, claim 3 is anticipated at least by each of the references disclosing the VIEW dosing regimen, including, but not limited to, Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release.

To the extent this element is limiting, the element is expressly set forth in the prior art. For example, the VIEW References identify improvement by > 15 letters as a metric in assessing AMD treatment, including as a secondary outcome measure for the VIEW trials. (*See, e.g.*, Dixon; NCT-795; NCT-377; 5-8-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 5-8-2008 Bayer Press Release). Therefore, a person of ordinary skill in the art reading each of the VIEW References would have understood and been aware of the secondary endpoint identified for those trials.

Further, a person of ordinary skill in the art would have understood from the prior art that the BCVA letter measure is an obvious choice to use when assessing clinical trials relating to AMD treatments. (*See, e.g.*, Nguyen 2009a; Dixon; Adis; NCT-795; NCT-377; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; Heier 2009; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008

Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; Brown 2006; Rosenfeld 2006; Lucentis Medical Review; Fung 2007; Lalwani 2009; Avila 2009; Bashshur 2008; Wu 2009). Further a person of ordinary skill in the art would have had a reasonable expectation of success at meeting the BCVA criteria set forth in claim 3 when using the recited regimen, in light of the positive Phase 1 and Phase 2 results discussed above and reported in the prior art. (*See, e.g.*, Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). Further, the results from the VIEW trials provide further evidence of the reasonable expectation of success that a person of ordinary skill in the art would have had in meeting the criteria set forth in claim 3 when using the recited regimen. (*See, e.g.*, 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release).

Accordingly, claim 3 of the 572 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claims 1 and 2, including combinations incorporating one or more references disclosing the use of BCVA in assessing AMD, and/or results of the Phase 1, Phase 2, or Phase 3 trials, in view of the knowledge of a person of ordinary skill in the art.

4. Claim 4.

The language of claim 4 of the 572 patent is set forth above.

Claim 4 of the 572 patent depends from claim 3 which depends from claim 2 which depends from claim 1 and thus incorporates the elements of claims 1-3. The reasons why claims 1-3 are anticipated and/or obvious are incorporated by reference.

The additional element "wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose" is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Since the method steps are "performed in the same way regardless whether or not the patient experiences" a clinical change, the additional element of claim 4 is non-limiting. *Bristol-Myers*, 246 F.3d at 1375; *see also Prometheus*, 2013 WL 5333033, at *5-6 (phrase that merely "expresses the intended result of a process step positively recited" is non-limiting); *Minton*, 336 F.3d at 1381.[52]

Separately, this element represents nothing more than the natural result flowing from the prior art method of administration disclosed in the VIEW References, including in the VEGF Trap-Eye Phase 1, Phase 2, and Phase 3 AMD trials. In addition, the prior art disclosures of the results of those trials provide further support for the inherency of the subject matter of claim 4. For example, 29% of the patients receiving monthly 2.0 mg doses for three months, followed by as-needed dosing in the VEGF Trap-Eye Phase 2 AMD trial exhibited an increase in BCVA of ≥ 15 letters; and 30.6% of the patients receiving three monthly doses followed by every-8-week dosing in the Phase 3 VIEW1 trial gained ≥ 15 letters. (*See, e.g.*, Dixon; Retina Society Meeting Presentation; 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release; Heier 2012). Accordingly, claim 4 is anticipated at least by each of the references disclosing the VIEW dosing regimen, including, but not limited to, Dixon, Adis,

[52] Mylan incorporates fully herein the arguments set forth in its claim construction briefs, served on November 29, 2022 and December 15, 2022.

NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release.

Accordingly, claim 4 of the 572 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claims 1-3, including combinations incorporating one or more references disclosing the results of the Phase 1, Phase 2, or Phase 3 trials, in view of the knowledge of a person of ordinary skill in the art.

5. Claim 5.

The language of claim 5 of the 572 patent is set forth above.

Claim 5 of the 572 patent depends from claim 3 which depends from claim 2 which depends from claim 1 and thus incorporates the elements of claims 1-3. The reasons why claims 1-3 are anticipated and/or obvious are incorporated by reference.

The additional element "wherein only two secondary doses are administered to the patient" does not distinguish the claim from the prior art.

The prior art disclosures of the results of the VEGF Trap-Eye Phase 1, Phase 2, and Phase 3 AMD trials provide support for the invalidity of the subject matter of claim 5. For example, 29% of the patients receiving monthly 2.0 mg doses for three months ("only two secondary doses"), followed by as-needed dosing in the VEGF Trap-Eye Phase 2 AMD trial exhibited an increase in BCVA of ≥ 15 letters; and 30.6% of the patients receiving three monthly doses followed by every-8-week dosing in the Phase 3 VIEW1 trial gained ≥ 15 letters. (*See, e.g.*, Dixon; Retina Society

Meeting Presentation; 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release; Heier 2012). Accordingly, claim 5 is anticipated at least by each of the references disclosing the VIEW dosing regimen, including, but not limited to, Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release.

Accordingly, claim 5 of the 572 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claims 1-3, including combinations incorporating one or more references disclosing the results of the Phase 1, Phase 2, or Phase 3 trials, in view of the knowledge of a person of ordinary skill in the art.

6. Claim 6.

The language of claim 6 of the 572 patent is set forth above.

Claim 6 of the 572 patent depends from claim 3 which depends from claim 2 which depends from claim 1 and thus incorporates the elements of claims 1-3. The reasons why claims 1-3 are anticipated and/or obvious are incorporated by reference.

The additional element "wherein the aflibercept is formulated as an isotonic solution" does not distinguish the claim from the prior art.

For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20,

with either 20% glycerol or 20% sucrose." (Fraser at 1115). And, Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798; *see also*, *e.g.*, Andya; Kaisheva I; Kaisheva; Lucentis PI 2006). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised aflibercept formulated "as an isotonic solution."

Accordingly, claim 6 of the 572 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claims 1-3, including combinations incorporating one or more references disclosing the results of the Phase 1, Phase 2, or Phase 3 trials, in view of the knowledge of a person of ordinary skill in the art.

7. Claim 7.

The language of claim 7 of the 572 patent is set forth above.

Claim 7 of the 572 patent depends from claim 3 which depends from claim 2 which depends from claim 1 and thus incorporates the elements of claims 1-3. The reasons why claims 1-3 are anticipated and/or obvious are incorporated by reference.

The additional element "wherein the aflibercept is formulated with a nonionic surfactant" does not distinguish the claim from the prior art.

For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). And, Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride."

(Wulff at 2798; *see also*, *e.g.*, Andya; Kaisheva I; Kaisheva; Lucentis PI 2006). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised aflibercept formulated with "a nonionic surfactant."

Accordingly, claim 7 of the 572 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claims 1-3, including combinations incorporating one or more references disclosing the results of the Phase 1, Phase 2, or Phase 3 trials, in view of the knowledge of a person of ordinary skill in the art.

8. Claim 8.

The language of claim 8 of the 572 patent is set forth above.

Claim 8 of the 572 patent depends from claim 2 which depends from claim 1 and thus incorporates the elements of claims 1 and 2. The reasons why claims 1 and 2 are anticipated and/or obvious are incorporated by reference.

The additional element "wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Since the method steps are "performed in the same way regardless whether or not the patient experiences" a clinical change, the additional element of claim 8 is non-limiting. *Bristol-Myers*, 246 F.3d at 1375; *see also Prometheus*, 2013 WL 5333033, at *5-6 (phrase that merely "expresses the intended result of a process step positively recited" is non-limiting); *Minton*, 336 F.3d at 1381.[53]

[53] Mylan incorporates fully herein the arguments set forth in its claim construction briefs, served on November 29, 2022 and December 15, 2022.

Separately, this element represents nothing more than the natural result flowing from the prior art method of administration disclosed in the VIEW References, using a measure (BCVA) which had already been disclosed in the prior art as a clinical trial measurement and/or endpoint, including in the VEGF Trap-Eye Phase 1, Phase 2, and Phase 3 AMD trials. In addition, the prior art disclosures of the results of those trials provide further support for the inherency of the subject matter of claim 8. For example, 29% of the patients receiving monthly 2.0 mg doses for three months, followed by as-needed dosing in the VEGF Trap-Eye Phase 2 AMD trial exhibited an increase in BCVA of ≥ 15 letters; and 30.6% of the patients receiving three monthly doses followed by every-8-week dosing in the Phase 3 VIEW1 trial gained ≥ 15 letters. (*See, e.g.*, Dixon; Retina Society Meeting Presentation; 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release; Heier 2012). Accordingly, claim 8 is anticipated at least by each of the references disclosing the VIEW dosing regimen, including, but not limited to, Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release.

To the extent this element is limiting, the element is expressly set forth in the prior art. For example, the VIEW References identify improvement by > 15 letters as a metric in assessing AMD treatment, including as a secondary outcome measure for the VIEW trials. (*See, e.g.*, Dixon; NCT-795; NCT-377; 5-8-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 5-8-2008 Bayer Press Release). Therefore, a person of ordinary skill in the art reading each of the VIEW

References would have understood and been aware of the secondary endpoint identified for those trials.

Further, a person of ordinary skill in the art would have understood from the prior art that the BCVA letter measure is an obvious choice to use when assessing clinical trials relating to AMD treatments. (*See, e.g.*, Nguyen 2009a; Dixon; Adis; NCT-795; NCT-377; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; Heier 2009; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; Brown 2006; Rosenfeld 2006; Lucentis Medical Review; Fung 2007; Lalwani 2009; Avila 2009; Bashshur 2008; Wu 2009). Further a person of ordinary skill in the art would have had a reasonable expectation of success at meeting the BCVA criteria set forth in claim 8 when using the recited regimen, in light of the positive Phase 1 and Phase 2 results discussed above and reported in the prior art. (*See, e.g.*, Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). Further, the results from the VIEW trials provide further

evidence of the reasonable expectation of success that a person of ordinary skill in the art would have had in meeting the criteria set forth in claim 8 when using the recited regimen. (*See, e.g.*, 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release).

Accordingly, claim 8 of the 572 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claims 1 and 2, including combinations incorporating one or more references disclosing the use of BCVA in assessing AMD, and/or results of the Phase 1, Phase 2, or Phase 3 trials, in view of the knowledge of a person of ordinary skill in the art.

9. Claim 9.

The language of claim 9 of the 572 patent is set forth above.

Claim 9 of the 572 patent depends from claim 8 which depends from claim 2 which depends from claim 1 and thus incorporates the elements of claims 1, 2, and 8. The reasons why claims 1, 2, and 8 are anticipated and/or obvious are incorporated by reference.

The additional element "wherein the patient achieves the gain in visual acuity within 24 weeks following the initial dose" is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Since the method steps are "performed in the same way regardless whether or not the patient experiences" a clinical change, the additional element of claim 9 is non-limiting. *Bristol-Myers*, 246 F.3d at 1375; *see also Prometheus*, 2013 WL 5333033, at *5-6 (phrase that merely "expresses the intended result of a process step positively recited" is non-limiting); *Minton*, 336 F.3d at 1381.[54]

[54] Mylan incorporates fully herein the arguments set forth in its claim construction briefs, served on November 29, 2022 and December 15, 2022.

Separately, this element represents nothing more than the natural result flowing from the prior art method of administration disclosed in the VIEW References, including in the VEGF Trap-Eye Phase 1, Phase 2, and Phase 3 AMD trials. In addition, the prior art disclosures of the results of those trials provide further support for the inherency of the subject matter of claim 9. For example, 29% of the patients receiving monthly 2.0 mg doses for three months, followed by as-needed dosing in the VEGF Trap-Eye Phase 2 AMD trial exhibited an increase in BCVA of ≥ 15 letters; and 30.6% of the patients receiving three monthly doses followed by every-8-week dosing in the Phase 3 VIEW1 trial gained ≥ 15 letters. (*See, e.g.*, Dixon; Retina Society Meeting Presentation; 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release; Heier 2012). Accordingly, claim 9 is anticipated at least by each of the references disclosing the VIEW dosing regimen, including, but not limited to, Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release.

Accordingly, claim 9 of the 572 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claims 1, 2, and 8, including combinations incorporating one or more references disclosing the results of the Phase 1, Phase 2, or Phase 3 trials, in view of the knowledge of a person of ordinary skill in the art.

10. Claim 10.

The language of claim 10 of the 572 patent is set forth above.

Claim 10 of the 572 patent depends from claim 2 which depends from claim 1 and thus incorporates the elements of claims 1 and 2. The reasons why claims 1 and 2 are anticipated and/or obvious are incorporated by reference.

The additional element "wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Since the method steps are "performed in the same way regardless whether or not the patient experiences" a clinical change, the additional element of claim 10 is non-limiting. *Bristol-Myers*, 246 F.3d at 1375; *see also Prometheus*, 2013 WL 5333033, at *5-6 (phrase that merely "expresses the intended result of a process step positively recited" is non-limiting); *Minton*, 336 F.3d at 1381.[55]

Separately, this element represents nothing more than the natural result flowing from the prior art method of administration disclosed in the VIEW References, using a measure (BCVA) which had already been disclosed in the prior art as a clinical trial measurement and/or endpoint, including in the VEGF Trap-Eye Phase 1, Phase 2, and Phase 3 AMD trials. In addition, the prior art disclosures of the results of those trials provide further support for the inherency of the subject matter of claim 10. For example, 29% of the patients receiving monthly 2.0 mg doses for three months, followed by as-needed dosing in the VEGF Trap-Eye Phase 2 AMD trial exhibited an increase in BCVA of ≥ 15 letters; and 30.6% of the patients receiving three monthly doses followed by every-8-week dosing in the Phase 3 VIEW1 trial gained ≥ 15 letters. (*See, e.g.*, Dixon; Retina Society Meeting Presentation; 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press

[55] Mylan incorporates fully herein the arguments set forth in its claim construction briefs, served on November 29, 2022 and December 15, 2022.

Release; 1-18-2011 Regeneron Press Release; Heier 2012). Accordingly, claim 10 is anticipated at least by each of the references disclosing the VIEW dosing regimen, including, but not limited to, Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release.

To the extent this element is limiting, the element is expressly set forth in the prior art. For example, the VIEW References identify improvement by > 15 letters as a metric in assessing AMD treatment, including as a secondary outcome measure for the VIEW trials. (*See, e.g.*, Dixon; NCT-795; NCT-377; 5-8-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 5-8-2008 Bayer Press Release). Therefore, a person of ordinary skill in the art reading each of the VIEW References would have understood and been aware of the secondary endpoint identified for those trials.

Further, a person of ordinary skill in the art would have understood from the prior art that the BCVA letter measure is an obvious choice to use when assessing clinical trials relating to AMD treatments. (*See, e.g.*, Nguyen 2009a; Dixon; Adis; NCT-795; NCT-377; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; Heier 2009; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008

Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; Brown 2006; Rosenfeld 2006; Lucentis Medical Review; Fung 2007; Lalwani 2009; Avila 2009; Bashshur 2008; Wu 2009). Further a person of ordinary skill in the art would have had a reasonable expectation of success at meeting the BCVA criteria set forth in claim 8 when using the recited regimen, in light of the positive Phase 1 and Phase 2 results discussed above and reported in the prior art. (*See, e.g.*, Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). Further, the results from the VIEW trials provide further evidence of the reasonable expectation of success that a person of ordinary skill in the art would have had in meeting the criteria set forth in claim 10 when using the recited regimen. (*See, e.g.*, 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release).

Accordingly, claim 10 of the 572 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claims 1 and 2, including combinations incorporating one or more references disclosing the use of BCVA in assessing AMD, and/or results of the Phase 1, Phase 2, or Phase 3 trials, in view of the knowledge of a person of ordinary skill in the art.

11. Claim 11.

The language of claim 11 of the 572 patent is set forth above.

Claim 11 of the 572 patent depends from claim 10 which depends from claim 2 which depends from claim 1 and thus incorporates the elements of claims 1, 2, and 10. The reasons why claims 1, 2, and 10 are anticipated and/or obvious are incorporated by reference.

The additional element "wherein only two secondary doses are administered to the patient" does not distinguish the claim from the prior art.

The prior art disclosures of the results of the VEGF Trap-Eye Phase 1, Phase 2, and Phase 3 AMD trials provide support for the invalidity of the subject matter of claim 11. For example, 29% of the patients receiving monthly 2.0 mg doses for three months ("only two secondary doses"), followed by as-needed dosing in the VEGF Trap-Eye Phase 2 AMD trial exhibited an increase in BCVA of ≥ 15 letters; and 30.6% of the patients receiving three monthly doses followed by every-8-week dosing in the Phase 3 VIEW1 trial gained ≥ 15 letters. (*See, e.g.*, Dixon; Retina Society Meeting Presentation; 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release; Heier 2012). Accordingly, claim 11 is anticipated at least by each of the references disclosing the VIEW dosing regimen, including, but not limited to, Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release.

Accordingly, claim 11 of the 572 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claims 1, 2, and 10, including combinations incorporating one or more references disclosing the

results of the Phase 1, Phase 2, or Phase 3 trials, in view of the knowledge of a person of ordinary skill in the art.

12. Claim 12.

The language of claim 12 of the 572 patent is set forth above.

Claim 12 of the 572 patent depends from claim 10 which depends from claim 2 which depends from claim 1 and thus incorporates the elements of claims 1, 2, and 10. The reasons why claims 1, 2, and 10 are anticipated and/or obvious are incorporated by reference.

The additional element "wherein the aflibercept is formulated as an isotonic solution" does not distinguish the claim from the prior art.

For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). And, Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798; *see also*, *e.g.*, Andya; Kaisheva I; Kaisheva; Lucentis PI 2006). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised aflibercept formulated "as an isotonic solution."

Accordingly, claim 12 of the 572 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claims 1, 2, and 10, including combinations incorporating one or more references disclosing the results of the Phase 1, Phase 2, or Phase 3 trials, in view of the knowledge of a person of ordinary skill in the art.

13. Claim 13.

The language of claim 13 of the 572 patent is set forth above.

Claim 13 of the 572 patent depends from claim 10 which depends from claim 2 which depends from claim 1 and thus incorporates the elements of claims 1, 2, and 10. The reasons why claims 1, 2, and 10 are anticipated and/or obvious are incorporated by reference.

The additional element "wherein the aflibercept is formulated with a nonionic surfactant" does not distinguish the claim from the prior art.

For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). And, Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798; *see also*, *e.g.*, Andya; Kaisheva I; Kaisheva; Lucentis PI 2006). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised aflibercept formulated with "a nonionic surfactant."

Accordingly, claim 13 of the 572 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claims 1, 2, and 10, including combinations incorporating one or more references disclosing the results of the Phase 1, Phase 2, or Phase 3 trials, in view of the knowledge of a person of ordinary skill in the art.

14. Claim 14.

The language of claim 14 of the 572 patent is set forth above.

Claim 14 of the 572 patent depends from claim 1 and thus incorporates the elements of claim 1. The reasons why claim 1 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein exclusion criteria for the patient include both of: (1) active ocular inflammation; and (2) active ocular or periocular infection" does not distinguish the claim from the prior art. For example, the claimed exclusion criteria elements constitute mental steps and/or written material, and thus are not entitled to patentable weight. *See, e.g.*, *Mylan Pharms. Inc. v. Regeneron Pharms., Inc.*, IPR2022-01226, Paper 22, at 11-15 (PTAB Jan. 11, 2023); *id.* at 15 ("[T]he information provided by the exclusionary criteria can be considered to be optional information, in that there is no direction to the practitioner to perform, or not perform, any specific step based upon the provided criteria. Thus, the exclusionary criteria are strictly informational, without requiring the practitioner to act, or refrain from acting, in a specified manner, and not functionally related to the practice of the claimed method.").

To the extent the exclusion criteria element is entitled to patentable weight, claim 14 of the 572 patent is inherently anticipated by at least each of the VIEW References that disclose the dosing regimen used in the VIEW trials. For example, the Eylea® Medical Review shows that a list of 37 non-confidential exclusion criteria, including the "exclusion criteria" listed in claim 14, were necessarily and inevitably applied in connection with practicing the claimed, and publicly disclosed, VIEW dosing regimen. (Eylea® Medical Review at 112-114; *see also, e.g.*, Heier 2012 at Appendix 2). The application of the claimed exclusion criteria thus was a natural result flowing from the application of the VIEW trial study protocol. As a result, each of the VIEW References, including Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009

Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release inherently anticipates claim 14 of the 572 patent.

Claim 14 of the 572 patent is obvious in view of the VIEW References and combinations presented above, further in combination with references disclosing the exclusion criteria employed in the Lucentis ANCHOR and MARINA trials. For the reasons discussed above, that discussion incorporated herein, each VIEW reference discloses expressly or inherently each and every claim element, and as discussed above, the recited exclusion criteria are not entitled to patentable weight and/or are inherent aspects of the VIEW study protocols. In addition to not being entitled to patentable weight, the claimed exclusion criteria were disclosed in the prior art. For example, the Lucentis AMD MARINA and ANCHOR trials, involving monthly intravitreal administration of the VEGF antagonist Lucentis® (ranibizumab), employed exclusion criteria that included, among other relevant criteria, active intraocular inflammation in the study eye; history of idiopathic or autoimmune-associated uveitis in either eye; and infectious conjunctivitis, keratitis, scleritis, or endophthalmitis in either eye. (*See, e.g.*, Lucentis Medical Review; Rosenfeld 2006; Brown 2006; NCT 836; NCT 594). The Lucentis Medical Review further disclosed that dose-holding criteria included intraocular inflammation and local or systemic infection, including infectious conjunctivitis, infectious keratitis, infectious scleritis, or endophthalmitis in either eye. (Lucentis Medical Review at 66-67). Accordingly, it would have been obvious to adopt such exclusion criteria for the VEGF Trap-Eye clinical trials, particularly in light of the inclusion of monthly ranibizumab as a comparator arm in the VIEW clinical trials.

For at least these reasons, claim 14 of the 572 patent is obvious in view of at least each of the VIEW References and combinations cited above, in combination with one or more of the references cited above disclosing the ranibizumab MARINA and ANCHOR clinical trial exclusion criteria.

Claim 14 of the 572 patent is obvious in view of the references disclosing the VIEW regimens, and combinations presented above, further in combination with references disclosing exclusion criteria employed in the context of Macugen® (pegaptanib). For the reasons discussed above, that discussion incorporated herein, each VIEW reference discloses expressly or inherently each and every claim element, and as discussed above, the recited exclusion criteria are not entitled to patentable weight and/or are inherent aspects of the VIEW study protocols. In addition to not being entitled to patentable weight, the claimed exclusion criteria were disclosed in the prior art. For example, the pegaptanib trials involving intravitreal administration in treating AMD employed exclusion criteria that included, among other relevant criteria, choroiditis, and acute ocular or periocular infection. (*See, e.g.*, Macugen Medical Review; Macugen Study Group; Gragoudas 2004). Accordingly, it would have been obvious to adopt such exclusion criteria for the VEGF Trap-Eye clinical trials, which also involved intravitreal administration to patients with angiogenic eye disorders.

For at least these reasons, claim 14 of the 572 patent is obvious in view of at least each of the VIEW References and combinations cited above, in combination with one or more of the references cited above disclosing the pegaptanib clinical trial exclusion criteria.

Claim 14 of the 572 patent is obvious in view of the VIEW References and combinations presented above, further in combination with references disclosing general guidelines, precautions, and general potential complications of intravitreal administration. For the reasons discussed

above, that discussion incorporated herein, each VIEW reference discloses expressly or inherently each and every claim element, and as discussed above, the recited exclusion criteria are not entitled to patentable weight and/or are inherent aspects of the VIEW study protocols. In addition to not being entitled to patentable weight, the claimed exclusion criteria were obvious from the prior art. For example, it was known among those of ordinary skill in the art that intravitreal administration could be associated with serious side effects if proper, aseptic technique is not adhered to. Consequently, persons of ordinary skill in the art recognized, and reported on, the need to avoid injecting eyes that are infected or show signs of infection (i.e., inflammation). (*See, e.g.*, Aiello 2004; Jager 2004; Donahue; De Caro; Heimann; CATT Study; Regillo 2008; MACTEL Study; Jaffe; Lucentis PI 2006; Retinal Physician II; Dixon). Accordingly, it would have been obvious to adopt exclusion criteria for the VEGF Trap-Eye clinical trials that included active intraocular inflammation or active ocular or periocular infection.

For at least these reasons, claim 14 of the 572 patent is obvious in view of at least each of the VIEW References and combinations cited above, in combination with one or more of the references cited above disclosing general guidelines and precautions for intravitreal injections.

Additionally, claim 14 of the 601 patent is obvious because the claimed exclusion criteria were well known in the art for treatments involving intravitreal injections of VEGF antagonists. For example, with respect to the first claimed exclusion criterion, "active intraocular inflammation," the CATT, MACTEL, and PIER studies describe the exclusion criteria for clinical trials of the leading prior art anti-VEGF treatments—bevacizumab (Avastin) and ranibizumab (Lucentis). (*See, e.g.*, CATT Study, Exclusion Criteria (disclosing the criterion verbatim: "[a]ctive or recent (within 4 weeks) intraocular inflammation"); Regillo 2008, Supplemental Table A (disclosing the criterion verbatim: "[a]ctive intraocular inflammation (grade trace or above) in the

study eye"); MACTEL Study). With respect to the second claimed exclusion criterion, "active ocular or periocular infection," the prior art again includes nearly verbatim exclusion criteria. (*See* MACTEL Study, Exclusion Criteria; CATT Study, Exclusion Criteria; Regillo 2008, Supplemental Table A). The person of ordinary skill in the art understood that the exclusion criteria disclosed in the CATT, MACTEL, and PIER studies reflected basic safety precautions designed to minimize the known risks, and the person of ordinary skill in the art would have been motivated to adopt the exclusion criteria from these studies in order to mitigate potential complications for intravitreal injections of aflibercept, which posed the same potential risks as prior anti-VEGF agents that were administered intravitreally. (*See, e.g.*, Jaffe; Lucentis PI 2006; Regillo 2008; Retinal Physician II; Dixon; Jager 2004). Indeed, the person of ordinary skill in the art would have had a strong motivation to look to exclusion criteria from prior studies involving anti-VEGF intravitreal injections such as those disclosed by the CATT, MACTEL, and PIER studies, and to apply them to the aflibercept dosing regimen recited by Dixon. Further, because the known risks associated with intravitreal injections are common to all intravitreal injections, including injections of VEGF antagonists, the person of ordinary skill in the art would reasonably expect that the exclusion criteria developed for prior art VEGF antagonists could be successfully applied to aflibercept. Accordingly, it would have been obvious to adopt exclusion criteria for the VEGF Trap-Eye clinical trials that included active intraocular inflammation or active ocular or periocular infection.

For at least these reasons, claim 14 of the 572 patent is obvious in view of Dixon, in combination with one or more of the references cited above disclosing the exclusion criteria from the CATT, MACTEL, and PIER studies.

Accordingly, claim 14 of the 572 patent is invalid under 35 U.S.C. §§ 102 and 103 for at least these additional reasons.

15. Claim 15.

a. Anticipation by the 747 Patent.[56]

The language of claim 15 of the 572 patent is set forth above.

Claim 15 of the 572 patent is anticipated by Regeneron's patents disclosing dosing regimens for the treatment of eye disorders. For example, the 747 patent discloses a method of treating eye disorders, including DR, and one of its complications, retinal edema (i.e., DME). The 747 patent further discloses treatment with the fusion polypeptide of SEQ ID NO:6 (VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). The 747 patent further discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 1-6 months apart, which a person of ordinary skill in the art would have immediately envisaged could encompass, e.g., "wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose and; wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose." (*See, e.g.*, 747 patent; 049 patent; 799 patent).

b. Anticipation by the Phase 2 DME References.

Claim 15 also is anticipated by prior art disclosing Regeneron's Phase 2 VEGF Trap-Eye clinical trial in DME. For example, the 9-14-2009 Regeneron Press Release, disclosed VEGF

[56] The 799 patent and 049 patent are related to the 747 patent and contain the same disclosures. Claim 15 is also anticipated by the 799 patent and 049 patent.

Trap-Eye (aflibercept), a drug for intravitreal administration, being administered to patients in 2 mg doses every eight weeks after three loading doses or on an as-needed (PRN) basis after three monthly loading doses. A possible dosing schedule falling within the Phase 2 PRN dosing regimen and immediately envisaged by a person of ordinary skill in the art would have been "wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose and; wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose." (9-14-2009 Regeneron Press Release; *see also, e.g.*, 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release).

Further, the aflibercept dosing regimen recited in claim 15 of the 572 patent claims the same every-8-week dosing regimen claimed by an earlier patent in the same family, the 338 patent. In a Final Written Decision relating to the 338 patent, the Board determined that the Dixon reference anticipates the aflibercept dosing regimen claimed by the 338 patent and repeated in claim 15 of the 572 patent. *See* 338 FWD. Given that the Board already found the substantively identical dosing regimen is disclosed in Dixon, claim 15 of the 572 patent is likewise anticipated by Dixon for the same reasons articulated by the Board in the 338 IPR.

Claim 15 does not contain efficacy limitations.[57] To the extent that Regeneron later argues that one or more claim limitations carry efficacy limitations,[58] claim 15 of the 572 patent is

[57] To the extent Regeneron argues that the "method for treating" preamble of claim 15 requires a "high level of efficacy" or any particular level of efficacy, Mylan relies on and incorporates the Board's findings rejecting this argument in the related 338 IPR, (*see, e.g.*, 338 FWD at 18), as well as Mylan's IPR briefing on the issue, all of which is expressly incorporated by reference herein.

[58] Mylan does not concede that any term in claim 15 carries specific efficacy limitations, and reserves the right to contest any effort to read such limitations into the claims, including, but not limited to, in connection with district court claim construction proceedings and any appeals related thereto. Mylan also incorporates herein arguments made and evidence presented, by Mylan, in

inherently anticipated by at least each of the references disclosed above. First, claim 15 expressly defines "an effective amount" as 2 mg, an acknowledgement that effectiveness is a natural result flowing from the administration of 2 mg of aflibercept, which was in the prior art. Second, inherency is evidenced by, among other things, the Phase 2 and Phase 3 DME clinical trials, which showed efficacious treatment of DME using regimens that fall within the scope of the prior art cited above. (*See, e.g.*, 2-18-2010 Bayer Press Release, and 12-20-2010 Bayer Press Release; Do 2011; Do 2012; Brown 2015; Korobelnik 2014; Heier 2016; Larsen 2015). Thus, the Phase 2 and Phase 3 results illustrate that any therapeutic effect was a natural result flowing from the operation of dosing regimens disclosed in the prior art, including at least 747 patent, 049 patent, 799 patent, 9-14-2009 Regeneron Press Release, 2-18-2010 Regeneron Press Release, and 12-20-2010 Regeneron Press Release. As a result, each of these references also inherently anticipates claim 15 of the 572 patent for at least these additional reasons.

c. Anticipation by the VIVID/VISTA References.

In addition, to the extent claim 15 is found to have a later priority date, then claim 15 also is anticipated by references disclosing the dosing regimen used in the VEGF Trap-Eye VIVID and VISTA clinical trials. (*See, e.g.*, Korobelnik 2014; Brown 2015; Keating 2015; Heier 2016; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01512966 (Japanese VIVID); NCT01331681 (US VIVID); NCT01363440 (US VISTA)). The VISTA and VIVID trials employed a regimen of 2 mg aflibercept administered intravitreally every 8 weeks after 5 initial monthly doses (i.e., 2 mg approximately every 4 weeks for the first 5 injections followed by 2 mg approximately once every

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IPR2021-00880 and IPR2021-00881, relating to the meaning of terms in the related 338 and 069 patents.

8 weeks or once every 2 months.) Further, to the extent that Regeneron later argues that one or more claim limitations carry efficacy limitations, claim 15 of the 572 patent is anticipated by at least each of the references disclosed above. First, claim 15 expressly defines "an effective amount" as 2 mg, an acknowledgement that effectiveness is a natural result flowing from the administration of 2 mg of aflibercept, which was in the above prior art references. Second, efficacy is evidenced by, among other things, the results reported for the VIVID and VISTA clinical trials, including reductions in retinal thickness and improvements in BCVA. (*See, e.g.*, Korobelnik 2014; Brown 2015; Keating 2015; Heier 2016; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01512966 (Japanese VIVID); NCT01331681 (US VIVID); NCT01363440 (US VISTA)). As a result, each of the references disclosing the dosing regimen used in the VEGF Trap-Eye VIVID and VISTA clinical trials anticipates claim 15 of the 572 patent for at least these additional reasons.

d. Anticipation by Public Use.

Claim 15 of the 572 patent is invalid for being in public use, including in this country, or otherwise available to the public, more than one year before the filing of the 572 patent's earliest priority application and/or more than one year before the earliest priority date to which claim 15 is entitled. The public use of the claimed invention is evidenced by at least the references discussed above disclosing the VEGF Trap-Eye DME clinical trials. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Korobelnik 2014; Brown 2015; Keating 2015; Heier 2016; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01512966 (Japanese VIVID); NCT01331681 (US VIVID); NCT01363440 (US VISTA)).

e. Obviousness over the 747 Patent.[59]

Claim 15 of the 572 patent is obvious in view of Regeneron's patents disclosing dosing regimens for the treatment of eye disorders. For example, the 747 patent discloses a method of treating eye disorders, including DR, and one of its complications, retinal edema (i.e., DME). The 747 patent further discloses treatment with the fusion polypeptide of SEQ ID NO:6 (VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). The 747 patent further discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 2-8 weeks, or 1-6 months apart, which a person of ordinary skill in the art would have immediately envisaged could encompass, e.g., "wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose." (*See, e.g.*, 747 patent; 049 patent; 799 patent). A person of ordinary skill in the art would have been motivated to refine the regimens disclosed in the above references to arrive at the claimed regimen in view of the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration. A person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed regimens. First, there are no efficacy limitations in the claim. Second, positive results from single intravitreal injections, had been reported for VEGF Trap-Eye/aflibercept. (*See, e.g.*, Do 2007; Do 2009). Accordingly,

[59] The 799 patent and 049 patent are related to the 747 patent and contain the same disclosures. Claim 15 is also rendered obvious by the 799 patent and 049 patent.

claim 15 of the 572 patent is obvious in view of at least each of the 747, 049, and 799 patents, and, if necessary, in combination with one or more of the references disclosing the Phase 1 DME clinical trial results.

f. Obviousness over the Phase 2 DME References.

Claim 15 of the 572 patent is obvious in view of the references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the results of the VEGF Trap-Eye DME Phase 1 clinical trial. For the reasons discussed above, that discussion incorporated herein, each reference disclosing the VEGF Trap-Eye Phase 2 DME clinical trial regimen expressly or inherently discloses each and every claim element. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; and 12-20-2010 Regeneron Press Release). In addition, these references render claim 15 obvious, because the claimed regimen is nothing more than an obvious embodiment of the disclosed regimens. For example, a person of ordinary skill in the art would have assessed the outcomes of the Phase 2 trial using three monthly loading doses followed by PRN or every-eight-week dosing, and would have been motivated to make routine adjustments to the number of loading doses in order to achieve, or come close to achieving, the results obtained with every-month dosing.

In addition, the person of ordinary skill in the art would have had a reasonable expectation of success in view of the results observed in the Phase 1 VEGF Trap-Eye DME trial, in which patients receiving a single intravitreal injection of VEGF Trap-Eye experienced improvements in BCVA and retinal thickness. (*See, e.g.*, Do 2007; Do 2009).

Accordingly, for at least these reasons, claim 15 is rendered obvious by references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the results of the VEGF Trap-Eye Phase 1 DME clinical trial.

Claim 15 of the 572 patent is obvious in view of the references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the results of the VEGF Trap-Eye Phase 2 DME clinical trial. For the reasons discussed above, that discussion incorporated herein, each reference disclosing the VEGF Trap-Eye Phase 2 DME clinical trial regimen expressly or inherently discloses each and every claim element. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012). In addition, these references render claim 15 obvious, because the claimed regimen is nothing more than an obvious embodiment of the disclosed regimens. For example, 5 monthly injections followed by injections every 8 weeks is an obvious variation of the PRN regimen disclosed in the references describing the VEGF Trap-Eye Phase 2 DME clinical trial. In addition, a person of ordinary skill in the art would have assessed the outcomes of the Phase 2 trial using three monthly loading doses followed by PRN or every-eight-week dosing, and would have been motivated to make routine adjustments to the number of loading doses in order to achieve, or come close to achieving, the results obtained with every-month dosing.

The person of ordinary skill in the art would have had a reasonable expectation of success in view of the results observed in the Phase 2 VEGF Trap-Eye DME trial, in which patients experienced improvements in BCVA and retinal thickness. (*See, e.g.*, 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Tolentino 2011; Boyer 2011; Do 2012).

Accordingly, for at least these reasons, claim 15 is rendered obvious by references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the results of the VEGF Trap-Eye Phase 2 DME clinical trial.

Claim 15 of the 572 patent is obvious in view of the references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the use of

ranibizumab in treating DME. For the reasons discussed above, that discussion incorporated herein, each reference disclosing the VEGF Trap-Eye Phase 2 DME clinical trial regimen expressly or inherently discloses each and every claim element. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; and 12-20-2010 Regeneron Press Release; Do 2011; Do 2012). In addition, these references render claim 15 obvious, because the claimed regimen is nothing more than an obvious embodiment of the disclosed regimens. For example, 5 monthly injections followed by injections every 8 weeks is an obvious variation of the PRN regimen disclosed in the references describing the VEGF Trap-Eye Phase 2 DME clinical trial. In addition, a person of ordinary skill in the art would have assessed the outcomes of the Phase 2 trial using three monthly loading doses followed by PRN or every-eight-week dosing, and would have been motivated to make routine adjustments to the number of loading doses in order to achieve, or come close to achieving, the results obtained with every-month dosing.

Further, the person of ordinary skill in the art would have had a reasonable expectation of success in view of the results observed in the ranibizumab DME clinical trials, in which patients being treated with dosing regimens that included every other month dosing after a series of loading doses, experienced improvements in BCVA and retinal thickness, similar to the BCVA and retinal thickness results observed in the use of ranibizumab to treat AMD. (*See, e.g.*, Chun 2006; Nguyen 2006b; Campochiaro 2006; Nguyen 2009b; Querques 2009; Rodriguez-Fontal 2009; Schwartz 2009; Hansen 2010; Schachat 2010; Waisbourd 2011).

Accordingly, for at least these reasons, claim 15 is rendered obvious by references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the results of the ranibizumab DME clinical trials.[60]

Accordingly, for at least the reasons set forth herein, claim 15 of the 572 patent is anticipated and rendered obvious by each of the references and combinations set forth above.

16. Claim 16.

The language of claim 16 of the 572 patent is set forth above.

Claim 16 of the 572 patent depends from claim 15 and thus incorporates the elements of claim 15. The reasons why claim 15 is obvious and/or anticipated are incorporated by reference.

The additional element "wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose" is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Since the method steps are "performed in the same way regardless whether or not the patient experiences" a clinical change, the additional element of claim 16 is non-limiting. *Bristol-Myers*, 246 F.3d at 1375; *see also Prometheus*, 2013 WL 5333033, at *5-6 (phrase that merely "expresses the intended result of a process step positively recited" is non-limiting); *Minton*, 336 F.3d at 1381.[61]

To the extent this element is limiting, claim 16 of the 572 patent is anticipated by Regeneron's patents disclosing dosing regimens for the treatment of eye disorders. For example, the 747 patent discloses a method of treating eye disorders, including macular degeneration. The 747 patent further discloses treatment with the fusion polypeptide of SEQ ID NO:6 (VEGFR1R2-

[60] To the extent that any specific limitation is found not to be explicitly or inherently disclosed in these references, it would have been achieved through routine optimization by one of ordinary skill in the art.

[61] Mylan incorporates fully herein the arguments set forth in its claim construction briefs, served on November 29, 2022 and December 15, 2022.

FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). The 747 patent further discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 2-8 weeks, or 1-6 months apart, which a person of ordinary skill in the art would have immediately envisaged could encompass, e.g., "each secondary dose is administered approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose." (*See, e.g.*, 747 patent; 049 patent; 799 patent).

Furthermore, for the same reasons outlined above for claim 15, this claim is anticipated, both expressly and inherently, by prior art disclosing Regeneron's Phase 2 and Phase 3 VEGF Trap-Eye clinical trials in DME. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Brown 2015; Korobelnik 2014; Heier 2016; Larsen 2015; Keating 2015; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01512966 (Japanese VIVID); NCT01331681 (US VIVID); NCT01363440 (US VISTA)). Also, for the same reasons outlined above for claim 15, this claim is obvious in view of the references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the results of the VEGF Trap-Eye DME Phase 1 and/or Phase 2 clinical trials. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; and 12-20-2010 Regeneron Press Release; Do 2007; Do 2009; Do 2011; Do 2012). In addition, for the same reasons outlined above for claim 15, this claim is obvious in view of the references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the use of ranibizumab in treating DME. (*See, e.g.*, 9-14-2009 Regeneron Press

Release; 2-18-2010 Regeneron Press Release; and 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Chun 2006; Nguyen 2006b; Campochiaro 2006; Nguyen 2009b; Querques 2009; Rodriguez-Fontal 2009; Schwartz 2009; Hansen 2010; Schachat 2010; Waisbourd 2011). While the claim element "wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose" merely recites a natural law resulting from the claimed method and should not be entitled to patentable weight, the references disclosing the DME Phase 1 and Phase 2 data also confirm that therapeutic effect inherently resulted from the operation of the prior art regimens.

Claim 16 of the 572 patent is anticipated by at least each of the VIEW References that disclose the dosing regimen used in the VIEW trials. For example, the VIEW References disclose a method of treating an angiogenic eye disorder, by intravitreally administering to a patient in need thereof 2 mg of VEGF Trap-Eye (i.e., aflibercept), using three monthly doses, followed by every-8-week dosing. (*See, e.g.*, Dixon; Adis; NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release). In addition, it was well known among those of ordinary skill in the art that aflibercept and VEGF Trap-Eye were different terms for the same molecule, and were often used interchangeably, and also that aflibercept was the molecule used in the VIEW trials. (*See, e.g.*, Dixon; Adis; Regeneron 2009 10-Q; 757 patent Petition for Patent Term Extension; 758 patent Petition for Patent Term Extension; 959 patent Petition for Patent Term Extension; Nguyen 2009a; Dix; 095 patent). As a result, each of the references disclosing the every-8-week dosing regimen used in the VIEW clinical trials, including Dixon,

Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release anticipates claim 16 of the 572 patent.

Claim 16 of the 572 patent is invalid for being in public use, including in this country, or otherwise available to the public, more than one year before the filing of the 572 patent's earliest priority application. The public use of the claimed invention is evidenced by at least the DME and VIEW References discussed above.

Claim 16 of the 572 patent is obvious in view of Regeneron's patents disclosing dosing regimens for the treatment of eye disorders. For example, the 747 patent discloses a method of treating eye disorders, including macular degeneration. The 747 patent further discloses treatment with the fusion polypeptide of SEQ ID NO:6 (VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). The 747 patent further discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 2-8 weeks, or 1-6 months apart, which a person of ordinary skill in the art would have immediately envisaged could encompass, e.g., "each secondary dose is administered approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered approximately 8 weeks following the immediately preceding dose." (*See, e.g.*, 747 patent; 049 patent; 799 patent). A person of ordinary skill in the art would have been motivated to refine the regimens disclosed in the above references to arrive

at the claimed regimen in view of the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration. A person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed regimens. Positive results from a variety of regimens, including single intravitreal injections, had been reported for VEGF Trap-Eye/aflibercept. (*See, e.g.*, Do 2007; Do 2009; Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). Accordingly, claim 16 of the 572 patent is obvious in view of at least each of the 747, 049, and 799 patents, and, if necessary, in combination with one or more of the references disclosing the Phase 1 and Phase 2 clinical trial results.

Claim 16 of the 572 patent is obvious in view of the VIEW References, either alone or in combination. For the reasons discussed above, that discussion incorporated herein, each VIEW reference discloses expressly or inherently each and every claim element. (*See, e.g.*, Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008

Bayer Press Release). Further, the motivation to adopt the claimed dosing regimens for VEGF Trap-Eye comes from the references themselves, which persons of ordinary skill in the art would have appreciated set forth dosing regimens that allowed for dosing less frequently than monthly, as well as the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration.

Also, a person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed DME and VIEW dosing regimens discussed above at least because of the Phase 1 and/or Phase 2 results, which were obtained using single injections and extended dosing regimens of VEGF Trap-Eye.

Accordingly, claim 16 of the 572 patent is obvious in view of at least each of the DME and VIEW References cited above, and, if necessary, in combination with one or more of the references cited above disclosing the Phase 1 and Phase 2 results.

In addition, a person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed DME and VIEW dosing regimens at least because of the widely publicized results of the DME and VIEW trials.

Accordingly, claim 16 of the 572 patent is obvious in view of at least each of the above references cited above, and, if necessary, in combination with one or more of the references cited above disclosing the VEGF Trap-Eye DME and/or angiogenic eye disorder clinical trial results.[62]

Accordingly, for at least the reasons set forth herein, claim 16 of the 572 patent is anticipated and rendered obvious by each of the references and combinations set forth above.

[62] To the extent that any specific limitation is found not to be explicitly or inherently disclosed in these references, it would have been achieved through routine optimization by one of ordinary skill in the art.

17. Claim 17.

The language of claim 17 of the 572 patent is set forth above.

Claim 17 of the 572 patent depends from claim 16 which depends from claim 15 and thus incorporates the elements of claims 15 and 16. The reasons why claims 15 and 16 are obvious and/or anticipated are incorporated by reference.

The additional element "wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Since the method steps are "performed in the same way regardless whether or not the patient experiences" a clinical change, the additional element of claim 17 is non-limiting. *Bristol-Myers*, 246 F.3d at 1375; *see also Prometheus*, 2013 WL 5333033, at *5-6 (phrase that merely "expresses the intended result of a process step positively recited" is non-limiting); *Minton*, 336 F.3d at 1381.[63]

Separately, this element represents nothing more than the natural result flowing from the prior art method of administration disclosed in the VIEW References, using a measure (BCVA) which had already been disclosed in the prior art as a clinical trial measurement and/or endpoint, including in Regeneron's DME and AMD clinical trials. Accordingly, claim 17 is anticipated at least by each of the references disclosing the DME and VIEW dosing regimens discussed above.

To the extent this element is limiting, the element is expressly and inherently set forth in the prior art. For example, for the same reasons outlined above for claim 15, this claim is anticipated, both expressly and inherently, by prior art disclosing Regeneron's Phase 2 and Phase

[63] Mylan incorporates fully herein the arguments set forth in its claim construction briefs, served on November 29, 2022 and December 15, 2022.

3 VEGF Trap-Eye clinical trials in DME. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Brown 2015; Korobelnik 2014; Heier 2016; Larsen 2015; Keating 2015; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01512966 (Japanese VIVID); NCT01331681 (US VIVID); NCT01363440 (US VISTA); Dixon; NCT-795; NCT-377; 5-8-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 5-8-2008 Bayer Press Release). Also, for the same reasons outlined above for claim 15, this claim is obvious in view of the references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the results of the VEGF Trap-Eye DME Phase 1 and/or Phase 2 clinical trials. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; and 12-20-2010 Regeneron Press Release; Do 2007; Do 2009; Do 2011; Do 2012). In addition, for the same reasons outlined above for claim 15, this claim is obvious in view of the references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the use of ranibizumab in treating DME. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; and 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Chun 2006; Nguyen 2006b; Campochiaro 2006; Nguyen 2009b; Querques 2009; Rodriguez-Fontal 2009; Schwartz 2009; Hansen 2010; Schachat 2010; Waisbourd 2011). While the claim element "wherein the patient gains at least 9 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" merely recites a natural law resulting from the claimed method and should not be entitled to patentable weight, the references disclosing the DME Phase 1 and Phase 2 data also confirm that therapeutic effect inherently resulted from the operation of the prior art regimens.

Fourth, a person of ordinary skill in the art would have understood from the prior art that the BCVA letter measure is an obvious choice to use when assessing patients in clinical trials relating to angiogenic eye disorder treatments. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Brown 2015; Korobelnik 2014; Heier 2016; Larsen 2015; Keating 2015; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; Nguyen 2009a; Dixon; Adis; NCT-795; NCT-377; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; Heier 2009; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; Brown 2006; Rosenfeld 2006; Lucentis Medical Review; Fung 2007; Lalwani 2009; Avila 2009; Bashshur 2008; Wu 2009). Further a person of ordinary skill in the art would have had a reasonable expectation of success at meeting the BCVA criteria set forth in claim 17 when using the recited regimen, in light of the positive Phase 1 and Phase 2 results discussed above and reported in the prior art. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Brown 2015; Korobelnik 2014; Heier 2016; Larsen 2015; Keating 2015; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; Do 2007; Do 2009; Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008

Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). Further, the results from the DME and VIEW trials provide further evidence of the reasonable expectation of success that a person of ordinary skill in the art would have had in meeting the criteria set forth in claim 17 when using the recited regimen.

Accordingly, claim 17 of the 572 patent is anticipated and rendered obvious by each of the above references, and obvious in view of each of the prior art combinations set forth above for claims 15 and 16, including combinations incorporating one or more references disclosing the use of BCVA in assessing DME and/or other angiogenic eye disorders, and/or results of VEGF Trap-Eye DME and/or angiogenic eye disorder clinical trials, in view of the knowledge of a person of ordinary skill in the art.

18. Claim 18.

The language of claim 18 of the 572 patent is set forth above.

Claim 18 of the 572 patent depends from claim 17 which depends from claim 16 which depends from claim 15 and thus incorporates the elements of claims 15-17. The reasons why claims 15-17 are anticipated and/or obvious are incorporated by reference.

The additional element "wherein the aflibercept is formulated as an isotonic solution" does not distinguish the claim from the prior art.

For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20,

with either 20% glycerol or 20% sucrose." (Fraser at 1115). And, Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798; *see also*, *e.g.*, Andya; Kaisheva I; Kaisheva; Lucentis PI 2006). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised aflibercept formulated "as an isotonic solution."

Accordingly, claim 18 of the 572 patent is anticipated and rendered obvious by each of the above references, and obvious in view of each of the prior art combinations set forth above for claims 15-17, including combinations incorporating one or more references disclosing the results of the VEGF Trap-Eye DME and/or angiogenic eye disorder clinical trials, in view of the knowledge of a person of ordinary skill in the art.

19. Claim 19.

The language of claim 19 of the 572 patent is set forth above.

Claim 19 of the 572 patent depends from claim 17 which depends from claim 16 which depends from claim 15 and thus incorporates the elements of claims 15-17. The reasons why claims 15-17 are anticipated and/or obvious are incorporated by reference.

The additional element "wherein the aflibercept is formulated with a non-ionic surfactant" does not distinguish the claim from the prior art.

For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). And, Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride."

(Wulff at 2798; *see also*, *e.g.*, Andya; Kaisheva I; Kaisheva; Lucentis PI 2006). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised aflibercept formulated with "a nonionic surfactant."

Accordingly, claim 19 of the 572 patent is anticipated and rendered obvious by each of the above references, and obvious in view of each of the prior art combinations set forth above for claims 15-17, including combinations incorporating one or more references disclosing the results of the VEGF Trap-Eye DME and/or angiogenic eye disorder clinical trials, in view of the knowledge of a person of ordinary skill in the art.

20. Claim 20.

The language of claim 20 of the 572 patent is set forth above.

Claim 20 of the 572 patent depends from claim 17 which depends from claim 16 which depends from claim 15 and thus incorporates the elements of claims 15-17. The reasons why claims 15-17 are anticipated and/or obvious are incorporated by reference.

The additional element "wherein the patient achieves a gain in visual acuity within 24 weeks following the initial dose" is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Since the method steps are "performed in the same way regardless whether or not the patient experiences" a clinical change, the additional element of claim 20 is non-limiting. *Bristol-Myers*, 246 F.3d at 1375; *see also Prometheus*, 2013 WL 5333033, at *5-6 (phrase that merely "expresses the intended result of a process step positively recited" is non-limiting); *Minton*, 336 F.3d at 1381.[64]

[64] Mylan incorporates fully herein the arguments set forth in its claim construction briefs, served on November 29, 2022 and December 15, 2022.

Separately, this element represents nothing more than the natural result flowing from the prior art method of administration disclosed in the DME and VIEW References. In addition, the prior art disclosures of the results of those trials provide further support for the inherency of the subject matter of claim 20. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Brown 2015; Korobelnik 2014; Heier 2016; Larsen 2015; Keating 2015; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; Do 2007; Do 2009; Dixon; Retina Society Meeting Presentation; 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release; Heier 2012). Accordingly, claim 20 is anticipated at least by each of the references disclosing the DME and VIEW dosing regimens discussed above.

Accordingly, claim 20 of the 572 patent is anticipated and rendered obvious by each of the above references, and obvious in view of each of the prior art combinations set forth above for claims 15-17, including combinations incorporating one or more references disclosing the results of the VEGF Trap-Eye DME and/or angiogenic eye disorder clinical trials, in view of the knowledge of a person of ordinary skill in the art.

21. Claim 21.

The language of claim 21 of the 572 patent is set forth above.

Claim 21 of the 572 patent depends from claim 16 which depends from claim 15 and thus incorporates the elements of claims 15 and 16. The reasons why claims 15 and 16 are anticipated and/or obvious are incorporated by reference.

The additional element "wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*,

906 F.3d at 1023-24. Since the method steps are "performed in the same way regardless whether or not the patient experiences" a clinical change, the additional element of claim 21 is non-limiting. *Bristol-Myers*, 246 F.3d at 1375; *see also Prometheus*, 2013 WL 5333033, at *5-6 (phrase that merely "expresses the intended result of a process step positively recited" is non-limiting); *Minton*, 336 F.3d at 1381.[65]

Separately, this element represents nothing more than the natural result flowing from the prior art method of administration disclosed in the Phase 2 and Phase 3 VEGF Trap-Eye clinical trials in DME. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Brown 2015; Korobelnik 2014; Heier 2016; Larsen 2015; Keating 2015; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01512966 (Japanese VIVID); NCT01331681 (US VIVID); NCT01363440 (US VISTA)). Also, for the same reasons outlined above for claim 15, this claim is obvious in view of the references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the results of the VEGF Trap-Eye DME Phase 1 and/or Phase 2 clinical trials. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; and 12-20-2010 Regeneron Press Release; Do 2007; Do 2009; Do 2011; Do 2012). In addition, for the same reasons outlined above for claim 15, this claim is obvious in view of the references disclosing the VEGF Trap-Eye Phase 2 DME clinical trial alone, or in combination with references disclosing the use of ranibizumab in treating DME. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; and 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Chun

[65] Mylan incorporates fully herein the arguments set forth in its claim construction briefs, served on November 29, 2022 and December 15, 2022.

2006; Nguyen 2006b; Campochiaro 2006; Nguyen 2009b; Querques 2009; Rodriguez-Fontal 2009; Schwartz 2009; Hansen 2010; Schachat 2010; Waisbourd 2011). While the claim element "wherein the patient gains at least 8 letters Best Corrected Visual Acuity (BCVA) according to Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" merely recites a natural law resulting from the claimed method and should not be entitled to patentable weight, the references disclosing the DME Phase 1 and Phase 2 data also confirm that therapeutic effect inherently resulted from the operation of the prior art regimens.

Further, this element represents nothing more than the natural result flowing from the prior art method of administration disclosed in the VIEW References, using a measure (BCVA) which had already been disclosed in the prior art for assessing efficacy in patients with angiogenic eye disorders, including in Regeneron's DME and AMD clinical trials. Accordingly, claim 21 is anticipated at least by each of the references disclosing the DME and VIEW dosing regimens discussed above.

To the extent this element is limiting, the element is expressly set forth in the prior art. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Brown 2015; Korobelnik 2014; Heier 2016; Larsen 2015; Keating 2015; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; Dixon; NCT-795; NCT-377; 5-8-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 5-8-2008 Bayer Press Release).

Further, a person of ordinary skill in the art would have understood from the prior art that the BCVA letter measure is an obvious choice to use when assessing clinical trials relating to angiogenic eye disorder treatments. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010

Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Brown 2015; Korobelnik 2014; Heier 2016; Larsen 2015; Keating 2015; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; Nguyen 2009a; Dixon; Adis; NCT-795; NCT-377; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; Heier 2009; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; Brown 2006; Rosenfeld 2006; Lucentis Medical Review; Fung 2007; Lalwani 2009; Avila 2009; Bashshur 2008; Wu 2009). Further a person of ordinary skill in the art would have had a reasonable expectation of success at meeting the BCVA criteria set forth in claim 21 when using the recited regimen, in light of the positive Phase 1 and Phase 2 results discussed above and reported in the prior art. (*See, e.g.*, 9-14-2009 Regeneron Press Release; 2-18-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; Do 2011; Do 2012; Brown 2015; Korobelnik 2014; Heier 2016; Larsen 2015; Keating 2015; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; Do 2007; Do 2009; Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008

Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). Further, the results from the DME and VIEW trials provide further evidence of the reasonable expectation of success that a person of ordinary skill in the art would have had in meeting the criteria set forth in claim 21 when using the recited regimen.

Accordingly, claim 21 of the 572 patent is anticipated and rendered obvious by each of the above references, and obvious in view of each of the prior art combinations set forth above for claims 15 and 16, including combinations incorporating one or more references disclosing the use of BCVA in assessing DME and other angiogenic eye disorders, and/or results of the VEGF Trap-Eye DME and/or angiogenic eye disorder clinical trials, in view of the knowledge of a person of ordinary skill in the art.

22. Claim 22.

The language of claim 22 of the 572 patent is set forth above.

Claim 22 of the 572 patent depends from claim 21 which depends from claim 16 which depends from claim 15 and thus incorporates the elements of claims 15, 16, and 21. The reasons why claims 15, 16, and 21 are anticipated and/or obvious are incorporated by reference.

The additional element "wherein the aflibercept is formulated as an isotonic solution" does not distinguish the claim from the prior art.

For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). And, Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride."

(Wulff at 2798; *see also*, *e.g.*, Andya; Kaisheva I; Kaisheva; Lucentis PI 2006). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised aflibercept formulated "as an isotonic solution."

Accordingly, claim 22 of the 572 patent is anticipated and rendered obvious by each of the above references, and obvious in view of each of the prior art combinations set forth above for claims 15, 16, and 21, including combinations incorporating one or more references disclosing the results of the VEGF Trap-Eye DME and/or angiogenic eye disorder clinical trials, in view of the knowledge of a person of ordinary skill in the art.

23. Claim 23.

The language of claim 23 of the 572 patent is set forth above.

Claim 23 of the 572 patent depends from claim 21 which depends from claim 16 which depends from claim 15 and thus incorporates the elements of claims 15, 16, and 21. The reasons why claims 15, 16, and 21 are anticipated and/or obvious are incorporated by reference.

The additional element "wherein the aflibercept is formulated with a nonionic surfactant" does not distinguish the claim from the prior art.

For example, Fraser discloses "VEGF TrapR1R2 (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose." (Fraser at 1115). And, Wulff discloses a formulation containing a polysorbate ("0.1 % (wt/vol) Tween 20"), a buffer ("5 mM phosphate, 5 mM citrate"), a stabilizing agent comprising a sugar ("20% (wt/vol) sucrose"), and "100 mM sodium chloride." (Wulff at 2798; *see also*, *e.g.*, Andya; Kaisheva I; Kaisheva; Lucentis PI 2006). Moreover, a person of ordinary skill in the art would have known that the prior art compositions comprised aflibercept formulated with "a nonionic surfactant."

Accordingly, claim 23 of the 572 patent is anticipated and rendered obvious by each of the above references, and obvious in view of each of the prior art combinations set forth above for claims 15, 16, and 21, including combinations incorporating one or more references disclosing the results of the VEGF Trap-Eye DME and/or angiogenic eye disorder clinical trials, in view of the knowledge of a person of ordinary skill in the art.

24. Claim 25.

The language of claim 25 of the 572 patent is set forth above.

Claim 25 of the 572 patent depends from claim 15 and thus incorporates the elements of claim 15. The reasons why claim 15 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein four secondary doses are administered to the patient" does not distinguish the claim from the prior art, which disclosed such regimens. (*See, e.g.*, 747 patent; 049 patent; 799 patent; Korobelnik 2014; Brown 2015; Keating 2015; Heier 2016; Ziemssen 2016; Wykoff 2017a; Wykoff 2017b; Cai 2018; Eylea Label 10/2014; Eylea Label 3/2015; Eylea Label 5/2016; Dhoot 2018; NCT01512966 (Japanese VIVID); NCT01331681 (US VIVID); NCT01363440 (US VISTA)).

Accordingly, claim 25 of the 572 patent is anticipated and rendered obvious by each of the above references, and obvious in view of each of the prior art combinations set forth above for claim 15, including combinations incorporating one or more references disclosing the results of the VEGF Trap-Eye DME and/or angiogenic eye disorder clinical trials, in view of the knowledge of a person of ordinary skill in the art.

25. Claim 26.

a. Anticipation by the 747 Patent.[66]

The language of claim 26 of the 572 patent is set forth above.

Claim 26 of the 572 patent is anticipated by Regeneron's patents disclosing dosing regimens for the treatment of eye disorders. For example, the 747 patent discloses a method of treating eye disorders, including macular degeneration. The 747 patent further discloses treatment with the fusion polypeptide of SEQ ID NO:6 (VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). The 747 patent further discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 2-8 weeks, or 1-6 months apart, which a person of ordinary skill in the art would have immediately envisaged could encompass, e.g., "wherein each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose." (*See, e.g.*, 747 patent; 049 patent; 799 patent).

b. Anticipation by the VIEW References.

Claim 26 of the 572 patent is anticipated by at least each of the VIEW References that disclose the dosing regimen used in the VIEW trials. For example, the VIEW References disclose a method of treating AMD, by intravitreally administering to a patient in need thereof 2 mg of VEGF Trap-Eye (i.e., aflibercept), using three monthly doses, followed by every-8-week dosing.

[66] The 799 patent and 049 patent are related to the 747 patent and contain the same disclosures. Claim 26 is also anticipated by the 799 patent and 049 patent.

(*See, e.g.*, Dixon; Adis; NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release). In addition, it was well known among those of ordinary skill in the art that aflibercept and VEGF Trap-Eye were different terms for the same molecule, and were often used interchangeably, and also that aflibercept was the molecule used in the VIEW trials. (*See, e.g.*, Dixon; Adis; Regeneron 2009 10-Q; 757 patent Petition for Patent Term Extension; 758 patent Petition for Patent Term Extension; 959 patent Petition for Patent Term Extension; Nguyen 2009a; Dix; 095 patent). As a result, each of the references disclosing the every-8-week dosing regimen used in the VIEW clinical trials, including Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release anticipates claim 26 of the 572 patent.

Further, the aflibercept dosing regimen recited in claim 26 of the 572 patent claims the same every-8-week dosing regimen claimed by an earlier patent in the same family, the 338 patent. In a Final Written Decision relating to the 338 patent, the Board determined that the Dixon reference anticipates the aflibercept dosing regimen claimed by the 338 patent and repeated in claim 26 of the 572 patent. *See* 338 FWD. Given that the Board already found the substantively

identical dosing regimen is disclosed in Dixon, claim 26 of the 572 patent is likewise anticipated by Dixon for the same reasons articulated by the Board in the 338 IPR.

Claim 26 contains the element "wherein the method is as effective in achieving a gain in visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose." This element is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Since the method steps are "performed in the same way regardless whether or not the patient experiences" a clinical change, this element is non-limiting. *Bristol-Myers*, 246 F.3d at 1375; *see also Prometheus*, 2013 WL 5333033, at *5-6 (phrase that merely "expresses the intended result of a process step positively recited" is non-limiting); *Minton*, 336 F.3d at 1381.[67]

To the extent the "achieving a gain in visual acuity" element is limiting, claim 26 of the 572 patent is anticipated by at least each of the VIEW References that disclose the dosing regimen and VEGF Trap-Eye/aflibercept used in the VIEW trials. Claim 26 expressly defines an effective amount as 2 mg, which was disclosed in the prior art references disclosing the VIEW clinical trial dosing regimens. The CLEAR-IT-2 data demonstrate success at treating patients with AMD using fewer doses, on average, than in the VIEW every-8-week dosing regimen. (*See, e.g.*, Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-

[67] Mylan incorporates fully herein the arguments set forth in its claim construction briefs, served on November 29, 2022 and December 15, 2022.

2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). The VIEW data confirm that therapeutic effect resulted from the operation of the VIEW regimen. (*See, e.g.*, 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release; Heier 2012). In addition, it was well known among those of ordinary skill in the art that aflibercept and VEGF Trap-Eye were different terms for the same molecule, and were often used interchangeably, and also that aflibercept was the molecule used in the VIEW trials. (*See, e.g.*, Dixon; Adis; Regeneron 2009 10-Q; 757 patent Petition for Patent Term Extension; 758 patent Petition for Patent Term Extension; 959 patent Petition for Patent Term Extension). As a result, each of the references cited above disclosing the VIEW dosing regimen anticipates claim 26 of the 572 patent for at least these additional reasons.

c. Anticipation by Public Use.

Claim 26 of the 572 patent is invalid for being in public use, including in this country, or otherwise available to the public, more than one year before the filing of the 572 patent's earliest priority application. The public use of the claimed invention is evidenced by at least the VIEW References discussed above. (*See, e.g.*, Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q; 2008 Retina Society Slides).

d. Obviousness over the 747 Patent.[68]

Claim 26 of the 572 patent is obvious in view of Regeneron's patents disclosing dosing regimens for the treatment of eye disorders. For example, the 747 patent discloses a method of treating eye disorders, including macular degeneration. The 747 patent further discloses treatment with the fusion polypeptide of SEQ ID NO:6 (VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). The 747 patent further discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 2-8 weeks, or 1-6 months apart, which a person of ordinary skill in the art would have immediately envisaged could encompass, e.g., "each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose." (*See, e.g.*, 747 patent; 049 patent; 799 patent). A person of ordinary skill in the art would have been motivated to refine the regimens disclosed in the above references to arrive at the claimed regimen in view of the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration. A person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed regimens. Positive results from a variety of regimens, including single intravitreal injections, had been reported for VEGF Trap-Eye/aflibercept. (*See, e.g.*, Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-

[68] The 799 patent and 049 patent are related to the 747 patent and contain the same disclosures. Claim 26 is also rendered obvious by the 799 patent and 049 patent.

2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). Accordingly, claim 26 of the 572 patent is obvious in view of at least each of the 747, 049, and 799 patents, and, if necessary, in combination with one or more of the references disclosing the Phase 1 and Phase 2 clinical trial results.

e. Obviousness over the VIEW References.

Claim 26 of the 572 patent is obvious in view of the VIEW References, either alone or in combination. For the reasons discussed above, that discussion incorporated herein, each VIEW reference discloses expressly or inherently each and every claim element. (*See, e.g.*, Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release). Further, the motivation to adopt the claimed dosing regimens for VEGF Trap-Eye comes from the references themselves, which persons of ordinary skill in the art would have appreciated set forth dosing regimens that allowed for dosing less frequently than monthly, as well as the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration.

Also, a person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed VIEW dosing regimens at least because of the Phase 1 and/or

CLEAR-IT-2 Phase 2 results, which were obtained using single injections and extended dosing regimens of VEGF Trap-Eye. (*See, e.g.*, Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q).

Accordingly, claim 26 of the 572 patent is obvious in view of at least each of the VIEW References cited above, and, if necessary, in combination with one or more of the references cited above disclosing the Phase 1 and Phase 2 CLEAR-IT-2 results.

In addition, a person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed VIEW dosing regimens at least because of the widely publicized results of the VIEW trials, which were made available to the public before the earliest filing date listed on the face of the 572 patent. (*See, e.g.*, 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release).

Accordingly, claim 26 of the 572 patent is obvious in view of at least each of the VIEW References cited above, and, if necessary, in combination with one or more of the references cited above disclosing the VIEW trial results.[69]

26. Claim 27.

The language of claim 27 of the 572 patent is set forth above.

[69] To the extent that any specific limitation is found not to be explicitly or inherently disclosed in these references, it would have been achieved through routine optimization by one of ordinary skill in the art.

Claim 27 of the 572 patent depends from claim 26 and thus incorporates the elements of claim 26. The reasons why claim 26 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein only two secondary doses are administered to the patient" does not distinguish the claim from the prior art.

The prior art disclosures of the results of the VEGF Trap-Eye Phase 1, Phase 2, and Phase 3 AMD trials provide support for the invalidity of the subject matter of claim 27. For example, 29% of the patients receiving monthly 2.0 mg doses for three months, ("only two secondary doses"), followed by as-needed dosing in the VEGF Trap-Eye Phase 2 AMD trial exhibited an increase in BCVA of ≥ 15 letters; and 30.6% of the patients receiving three monthly doses followed by every-8-week dosing in the Phase 3 VIEW1 trial gained ≥ 15 letters. (*See, e.g.*, Dixon; Retina Society Meeting Presentation; 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release; Heier 2012). Accordingly, claim 27 is anticipated at least by each of the references disclosing the VIEW dosing regimen, including, but not limited to, Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release.

Accordingly, claim 27 of the 572 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claim 26, including combinations incorporating one or more references disclosing the results of

the Phase 1, Phase 2, or Phase 3 trials, in view of the knowledge of a person of ordinary skill in the art.

27. Claim 28.

The language of claim 28 of the 572 patent is set forth above.

Claim 28 of the 572 patent depends from claim 26 and thus incorporates the elements of claim 26. The reasons why claim 26 is anticipated and/or obvious are incorporated by reference.

The additional element "wherein the gain in visual acuity is measured using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" does not distinguish the claim from the prior art, as disclosed above with respect to claim 26.

A person of ordinary skill in the art would have known, from their background knowledge, and from the prior art cited above, that BCVA scores were assessed using an ETDRS letter score. (*See, e.g.*, Nguyen 2009a; Dixon; Adis; NCT-795; NCT-377; 5-8-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 5-8-2008 Bayer Press Release; Lucentis Medical Review; Brown 2006; Rosenfeld 2006; Lalwani 2009; Avila 2009; Bashshur 2008; Wu 2009).

Accordingly, claim 28 of the 572 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claim 26, including combinations incorporating one or more references disclosing the use of BCVA (ETDRS) in assessing AMD, and/or results of the Phase 1, Phase 2, or Phase 3 trials, in view of the knowledge of a person of ordinary skill in the art.

28. Claim 29.

a. Anticipation by the 747 Patent.[70]

The language of claim 29 of the 572 patent is set forth above.

Claim 29 of the 572 patent is anticipated by Regeneron's patents disclosing dosing regimens for the treatment of eye disorders. For example, the 747 patent discloses a method of treating eye disorders, including macular degeneration. The 747 patent further discloses treatment with the fusion polypeptide of SEQ ID NO:6 (VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). The 747 patent further discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 2-8 weeks, or 1-6 months apart, which a person of ordinary skill in the art would have immediately envisaged could encompass, e.g., "each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose." (*See, e.g.*, 747 patent; 049 patent; 799 patent).

b. Anticipation by the VIEW References.

Claim 29 of the 572 patent is anticipated by at least each of the VIEW References that disclose the dosing regimen used in the VIEW trials. For example, the VIEW References disclose a method of treating AMD, by intravitreally administering to a patient in need thereof 2 mg of VEGF Trap-Eye (i.e., aflibercept), using three monthly doses, followed by every-8-week dosing.

[70] The 799 patent and 049 patent are related to the 747 patent and contain the same disclosures. Claim 29 is also anticipated by the 799 patent and 049 patent.

(*See, e.g.*, Dixon; Adis; NCT 795; NCT 377; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; 3-31-2010 Regeneron 10-Q; 6-30-2010 Regeneron 10-Q; 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release). In addition, it was well known among those of ordinary skill in the art that aflibercept and VEGF Trap-Eye were different terms for the same molecule, and were often used interchangeably, and also that aflibercept was the molecule used in the VIEW trials. (*See, e.g.*, Dixon; Adis; Regeneron 2009 10-Q; 757 patent Petition for Patent Term Extension; 758 patent Petition for Patent Term Extension; 959 patent Petition for Patent Term Extension; Nguyen 2009a; Dix; 095 patent). As a result, each of the references disclosing the every-8-week dosing regimen used in the VIEW clinical trials, including Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release anticipates claim 29 of the 572 patent.

Further, the aflibercept dosing regimen recited in claim 29 of the 572 patent claims the same every-8-week dosing regimen claimed by an earlier patent in the same family, the 338 patent. In a Final Written Decision relating to the 338 patent, the Board determined that the Dixon reference anticipates the aflibercept dosing regimen claimed by the 338 patent and repeated in claim 29 of the 572 patent. *See* 338 FWD. Given that the Board already found the substantively

identical dosing regimen is disclosed in Dixon, claim 29 of the 572 patent is likewise anticipated by Dixon for the same reasons articulated by the Board in the 338 IPR.

Claim 29 contains the element "wherein the method is as effective in maintaining visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with age-related macular degeneration at 52 weeks following the initial dose." This element is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Since the method steps are "performed in the same way regardless whether or not the patient experiences" a clinical change, this element is non-limiting. *Bristol-Myers*, 246 F.3d at 1375; *see also Prometheus*, 2013 WL 5333033, at *5-6 (phrase that merely "expresses the intended result of a process step positively recited" is non-limiting); *Minton*, 336 F.3d at 1381.[71]

To the extent the "maintaining visual acuity" element is limiting, claim 29 of the 572 patent is anticipated by at least each of the VIEW References that disclose the dosing regimen and VEGF Trap-Eye/aflibercept used in the VIEW trials. Claim 29 expressly defines an effective amount as 2 mg, which was disclosed in the prior art references disclosing the VIEW clinical trial dosing regimens. The CLEAR-IT-2 data demonstrate success at treating patients with AMD using fewer doses, on average, than in the VIEW every-8-week dosing regimen. (*See, e.g.*, Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-

[71] Mylan incorporates fully herein the arguments set forth in its claim construction briefs, served on November 29, 2022 and December 15, 2022.

2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). The VIEW data confirm that therapeutic effect resulted from the operation of the VIEW regimen. (*See, e.g.*, 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release; Heier 2012). In addition, it was well known among those of ordinary skill in the art that aflibercept and VEGF Trap-Eye were different terms for the same molecule, and were often used interchangeably, and also that aflibercept was the molecule used in the VIEW trials. (*See, e.g.*, Dixon; Adis; Regeneron 2009 10-Q; 757 patent Petition for Patent Term Extension; 758 patent Petition for Patent Term Extension; 959 patent Petition for Patent Term Extension). As a result, each of the references cited above disclosing the VIEW dosing regimen anticipates claim 29 of the 572 patent for at least these additional reasons.

c. Anticipation by Public Use.

Claim 29 of the 572 patent is invalid for being in public use, including in this country, or otherwise available to the public, more than one year before the filing of the 572 patent's earliest priority application. The public use of the claimed invention is evidenced by at least the VIEW References discussed above. (*See, e.g.*, Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q; 2008 Retina Society Slides).

d. Obviousness over the 747 Patent.[72]

Claim 29 of the 572 patent is obvious in view of Regeneron's patents disclosing dosing regimens for the treatment of eye disorders. For example, the 747 patent discloses a method of treating eye disorders, including macular degeneration. The 747 patent further discloses treatment with the fusion polypeptide of SEQ ID NO:6 (VEGFR1R2-FcΔC1(a)) (i.e., VEGF Trap-Eye or aflibercept). The 747 patent further discloses intravitreal administration of the VEGF trap protein, and treatment with 25-4000 micrograms of the VEGF trap (i.e., 2 mg). The 747 patent further discloses treatment on a monthly basis, with a preferred embodiment including an initial treatment followed by subsequent treatments between 2-8 weeks, or 1-6 months apart, which a person of ordinary skill in the art would have immediately envisaged could encompass, e.g., "each secondary dose is administered to the patient by intravitreal injection approximately 4 weeks following the immediately preceding dose; and wherein each tertiary dose is administered to the patient by intravitreal injection approximately 8 weeks following the immediately preceding dose." (*See, e.g.*, 747 patent; 049 patent; 799 patent). A person of ordinary skill in the art would have been motivated to refine the regimens disclosed in the above references to arrive at the claimed regimen in view of the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration. A person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed regimens. Positive results from a variety of regimens, including single intravitreal injections, had been reported for VEGF Trap-Eye/aflibercept. (*See, e.g.*, Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-

[72] The 799 patent and 049 patent are related to the 747 patent and contain the same disclosures. Claim 29 is also rendered obvious by the 799 patent and 049 patent.

2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). Accordingly, claim 29 of the 572 patent is obvious in view of at least each of the 747, 049, and 799 patents, and, if necessary, in combination with one or more of the references disclosing the Phase 1 and Phase 2 clinical trial results.

e. Obviousness over the VIEW References.

Claim 29 of the 572 patent is obvious in view of the VIEW References, either alone or in combination. For the reasons discussed above, that discussion incorporated herein, each VIEW reference discloses expressly or inherently each and every claim element. (*See, e.g.*, Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q; 5-8-2008 Bayer Press Release; 8-19-2008 Bayer Press Release). Further, the motivation to adopt the claimed dosing regimens for VEGF Trap-Eye comes from the references themselves, which persons of ordinary skill in the art would have appreciated set forth dosing regimens that allowed for dosing less frequently than monthly, as well as the understanding among those of ordinary skill in the art that less frequent dosing is preferred given the risks and potential complications associated with intravitreal administration.

Also, a person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed VIEW dosing regimens at least because of the Phase 1 and/or

CLEAR-IT-2 Phase 2 results, which were obtained using single injections and extended dosing regimens of VEGF Trap-Eye. (*See, e.g.*, Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q).

Accordingly, claim 29 of the 572 patent is obvious in view of at least each of the VIEW References cited above, and, if necessary, in combination with one or more of the references cited above disclosing the Phase 1 and Phase 2 CLEAR-IT-2 results.

In addition, a person of ordinary skill in the art would have had a reasonable expectation of success at using the disclosed VIEW dosing regimens at least because of the widely publicized results of the VIEW trials, which were made available to the public before the earliest filing date listed on the face of the 572 patent. (*See, e.g.*, 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release).

Accordingly, claim 29 of the 572 patent is obvious in view of at least each of the VIEW References cited above, and, if necessary, in combination with one or more of the references cited above disclosing the VIEW trial results.[73]

29. Claim 30.

The language of claim 30 of the 572 patent is set forth above.

[73] To the extent that any specific limitation is found not to be explicitly or inherently disclosed in these references, it would have been achieved through routine optimization by one of ordinary skill in the art.

Claim 30 of the 572 patent depends from claim 29 and thus incorporates the elements of claim 29. The reasons why claim 29 is obvious and/or anticipated are incorporated by reference.

The additional element "wherein maintenance of visual acuity means loss of less than 15 letters Best Corrected Visual Acuity (BCVA) as measured by using the Early Treatment Diabetic Retinopathy Study (ETDRS) letter score" is a non-limiting statement of intended result. *See Bristol-Myers*, 246 F.3d at 1375-76; *Copaxone*, 906 F.3d at 1023-24. Since the method steps are "performed in the same way regardless whether or not the patient experiences" a clinical change, the additional element of claim 30 is non-limiting. *Bristol-Myers*, 246 F.3d at 1375; *see also Prometheus*, 2013 WL 5333033, at *5-6 (phrase that merely "expresses the intended result of a process step positively recited" is non-limiting); *Minton*, 336 F.3d at 1381.[74]

Separately, this element represents nothing more than the natural result flowing from the prior art method of administration disclosed in the VIEW References, using a measure (BCVA) which had already been disclosed in the prior art as a clinical trial measurement and/or endpoint, including in the VEGF Trap-Eye Phase 1, Phase 2, and Phase 3 AMD trials. In addition, the prior art disclosures of the results of those trials provide further support for the inherency of the subject matter of claim 30. For example, 29% of the patients receiving monthly 2.0 mg doses for three months, followed by as-needed dosing in the VEGF Trap-Eye Phase 2 AMD trial exhibited an increase in BCVA of ≥ 15 letters; and 30.6% of the patients receiving three monthly doses followed by every-8-week dosing in the Phase 3 VIEW1 trial gained ≥ 15 letters. (*See, e.g.*, Dixon; Retina Society Meeting Presentation; 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release; Heier 2012). Accordingly, claim 30 is anticipated

[74] Mylan incorporates fully herein the arguments set forth in its claim construction briefs, served on November 29, 2022 and December 15, 2022.

at least by each of the references disclosing the VIEW dosing regimen, including, but not limited to, Dixon, Adis, NCT 795, NCT 377, 4-28-2008 Regeneron Press Release, 5-8-2008 Regeneron Press Release, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release, 11-22-2010 Regeneron Press Release, 2009 Regeneron 10-K, 3-31-2009 Regeneron 10-Q, 6-30-2009 Regeneron 10-Q, 9-30-2009 Regeneron 10-Q, 3-31-2010 Regeneron 10-Q, 6-30-2010 Regeneron 10-Q, 9-30-2010 Regeneron 10-Q, 5-8-2008 Bayer Press Release, and 8-19-2008 Bayer Press Release.

To the extent this element is limiting, the element is expressly set forth in the prior art. For example, the VIEW References identify improvement by > 15 letters as a metric in assessing AMD treatment, including as a secondary outcome measure for the VIEW trials. (*See, e.g.*, Dixon; NCT-795; NCT-377; 5-8-2008 Regeneron Press Release; 9-14-2009 Regeneron Press Release; 5-8-2008 Bayer Press Release). Therefore, a person of ordinary skill in the art reading each of the VIEW References would have understood and been aware of the secondary endpoint identified for those trials.

Further, a person of ordinary skill in the art would have understood from the prior art that the BCVA letter measure is an obvious choice to use when assessing clinical trials relating to AMD treatments. (*See, e.g.*, Nguyen 2009a; Dixon; Adis; NCT-795; NCT-377; 9-14-2009 Regeneron Press Release; 11-22-2010 Regeneron Press Release; Heier 2009; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-

Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q; Brown 2006; Rosenfeld 2006; Lucentis Medical Review; Fung 2007; Lalwani 2009; Avila 2009; Bashshur 2008; Wu 2009). Further a person of ordinary skill in the art would have had a reasonable expectation of success at meeting the BCVA criteria set forth in claim 30 when using the recited regimen, in light of the positive Phase 1 and Phase 2 results discussed above and reported in the prior art. (*See, e.g.*, Nguyen 2009a; Heier 2009; Dixon; Adis; Retina Society Meeting Presentation; 3-27-2007 Regeneron Press Release; 8-2-2007 Regeneron Press Release; 4-28-2008 Regeneron Press Release; 5-8-2008 Regeneron Press Release; 8-19-2008 Regeneron Press Release; 9-28-2008 Regeneron Press Release; 4-30-2009 Regeneron Press Release; 11-03-2009 Regeneron Press Release; 2008 Regeneron 10-K; 3-31-2008 Regeneron 10-Q; 6-30-2008 Regeneron 10-Q; 9-30-2008 Regeneron 10-Q; 2009 Regeneron 10-K; 3-31-2009 Regeneron 10-Q; 6-30-2009 Regeneron 10-Q; 9-30-2009 Regeneron 10-Q). Further, the results from the VIEW trials provide further evidence of the reasonable expectation of success that a person of ordinary skill in the art would have had in meeting the criteria set forth in claim 30 when using the recited regimen. (*See, e.g.*, 11-22-2010 Regeneron Press Release; 12-20-2010 Regeneron Press Release; 1-18-2011 Regeneron Press Release).

Accordingly, claim 30 of the 572 patent is anticipated and rendered obvious by each of the VIEW References, and obvious in view of each of the prior art combinations set forth above for claim 29, including combinations incorporating one or more references disclosing the use of BCVA in assessing AMD, and/or results of the Phase 1, Phase 2, or Phase 3 trials, in view of the knowledge of a person of ordinary skill in the art.

30. Secondary Considerations.

Mylan is unaware of any evidence of secondary considerations that would render non-obvious the particular combination of elements claimed in the 572 patent, as described above and incorporated herein by reference.

Mylan is aware that the applicant argued during prosecution of related applications that "there was a need in the art for alternative treatment protocols" and that "applicants have demonstrated improved and unexpected results." (681 patent PH, 6/25/2018 Applicant Remarks at 8). Identical arguments made by the applicant in traversing rejections during prosecution of related patent claims have been refuted. (*See, e.g.*, IPR2021-00880, Petition for *Inter Partes* Review of U.S. Patent 9,669,069 at 69-72; IPR2021-00880, Declaration of T. Albini, M.D. ¶¶ 217-24; IPR2021-00881, Petition for *Inter Partes* Review of U.S. Patent 9,254,338 at 66-69; IPR2021-00881, Declaration of T. Albini, M.D. ¶¶ 404-11). For the same reasons presented in the IPR filings, that discussion incorporated by reference herein, there are no secondary considerations that would be sufficient to render non-obvious the claimed subject matter of the 572 patent.

Additionally, the patentee must prove the required nexus before relying on any secondary considerations of alleged non-obviousness. Mylan is not aware of any evidence that would establish the required nexus for any of the claims of the 572 patent, nor has Regeneron presented any evidence that would establish the required nexus for any of the claims of the 572 patent despite Mylan's requests for such discovery.

Further, even if there were any evidence of such secondary considerations[75] and the required nexus, the *prima facie* evidence of obviousness is sufficiently strong that it cannot be rebutted by evidence relevant to secondary considerations of non-obviousness.

As a result, all claims of the 572 patent are anticipated and obvious in view of at least the references and combinations set forth above, and in view of the knowledge of a person of ordinary skill in the art.

D. Obviousness-Type Double Patenting.

The 572 patent Asserted Claims are invalid for OTDP over at least each of the 746 patent, 747 patent, 799 patent, and 049 patent.

1. Claim 1.

The language of claim 1 of the 572 patent is set forth above.

Claim 1 of the 572 patent is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent. Each patent discloses VEGF Trap-Eye (i.e., aflibercept), and methods of treating AMD. (*See, e.g.*, 746 patent at SEQ ID NO:16, 2:48-49, 2:53-59, 6:39-50, claims 1-5; *see also, e.g.*, 747 patent at SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-63; 20:15-67, 21:1-22:42, claims 1-6; 049 patent (same); 799 patent (same)). Further, the patents disclose dosing regimens for AMD that comprise an initial dose, and subsequent doses between 1-6 months apart. For at least these reasons, claim 1 of the 572 patent represents nothing more than an obvious species within the genus disclosed, and/or an obvious variation of the subject matter disclosed, in the 746 patent, the 747 patent, the 799 patent, and the 049 patent, and thus is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents. Arguments made by Regeneron

[75] Mylan reserves the right to address any evidence of secondary considerations that are raised in litigation by any entity, or entities, attempting to assert the 572 patent.

in contesting OTDP rejections during prosecution of related patent claims have been refuted. (*See, e.g.*, IPR2021-00880, Petition for *Inter Partes* Review of U.S. Patent 9,669,069 at 69-72; IPR2021-00880, Declaration of T. Albini, M.D. ¶¶ 217-24; IPR2021-00881, Petition for *Inter Partes* Review of U.S. Patent 9,254,338 at 66-69; IPR2021-00881, Declaration of T. Albini, M.D. ¶¶ 404-11). Accordingly, claim 1 is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

2. Claims 2-14.

The language of claims 2-14 of the 572 patent is set forth above. Claims 2-14 depend either directly or indirectly from claim 1 and thus incorporate the elements of claim 1. The reasons why claim 1 is invalid for OTDP are incorporated by reference. Claims 2-14 are invalid for OTDP for at least the additional reasons set forth below.

Claims 2-4, 8-10, and 14 do not require any active steps beyond those set forth in claim 1, and/or are drawn to inherent and/or obvious variations of the subject matter set forth in claim 1, and disclosed in the 746, 747, 799, and 049 patents. Thus, claims 2-4, 8-10, and 14 are not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Accordingly, for at least these additional reasons, claims 2-14 of the 572 patent are invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

3. Claim 15.

The language of claim 15 of the 572 patent is set forth above.

Claim 15 of the 572 patent is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent. Each patent discloses VEGF Trap-Eye (i.e., aflibercept), and methods of treating AMD, as well as DR and retinal edema. (*See, e.g.*, 746 patent at SEQ ID NO:16, 2:48-49, 2:53-59, 6:39-50, claims 1-5; 747 patent at SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-63; 20:15-67, 21:1-22:42, claims 1-6; 049 patent (same); 799 patent (same)). Further, the

patents disclose dosing regimens that comprise an initial dose, and subsequent doses between 1-6 months apart. For at least these reasons, claim 15 of the 572 patent represents nothing more than an obvious species within the genus disclosed, and/or an obvious variation of the subject matter disclosed, in the 746 patent, the 747 patent, the 799 patent, and the 049 patent, and thus is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents. Arguments made by Regeneron in contesting OTDP rejections during prosecution of related patent claims have been refuted. (*See, e.g.*, IPR2021-00880, Petition for *Inter Partes* Review of U.S. Patent 9,669,069 at 69-72; IPR2021-00880, Declaration of T. Albini, M.D. ¶¶ 217-24; IPR2021-00881, Petition for *Inter Partes* Review of U.S. Patent 9,254,338 at 66-69; IPR2021-00881, Declaration of T. Albini, M.D. ¶¶ 404-11). Accordingly, claim 15 is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

4. Claims 16-23 and 25.

The language of claims 16-23 and 25 of the 572 patent is set forth above. Claims 16-23 and 25 depend either directly or indirectly from claim 15 and thus incorporate the elements of claim 15. The reasons why claim 15 is invalid for OTDP are incorporated by reference. Claims 16-23 and 25 are invalid for OTDP for at least the additional reasons set forth below.

Claims 16-17 and 20-21 do not require any active steps beyond those set forth in claim 15, and/or are drawn to inherent and/or obvious variations of the subject matter set forth in claim 15, and disclosed in the 746, 747, 799, and 049 patents. Thus, claims 16-17 and 20-21 are not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Claim 25 claims four secondary doses, which is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Accordingly, for at least these additional reasons, claims 16-25 of the 572 patent are invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

5. Claim 26.

The language of claim 26 of the 572 patent is set forth above.

Claim 26 of the 572 patent is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent. Each patent discloses VEGF Trap-Eye (i.e., aflibercept), and methods of treating AMD, as well as DR and retinal edema. (*See, e.g.*, 746 patent at SEQ ID NO:16, 2:48-49, 2:53-59, 6:39-50, claims 1-5; 747 patent at SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-63; 20:15-67, 21:1-22:42, claims 1-6; 049 patent (same); 799 patent (same)). Further, the patents disclose dosing regimens that comprise an initial dose, and subsequent doses between 1-6 months apart. For at least these reasons, claim 26 of the 572 patent represents nothing more than an obvious species within the genus disclosed, and/or an obvious variation of the subject matter disclosed, in the 746 patent, the 747 patent, the 799 patent, and the 049 patent, and thus is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents. Arguments made by Regeneron in contesting OTDP rejections during prosecution of related patent claims have been refuted. (*See, e.g.*, IPR2021-00880, Petition for *Inter Partes* Review of U.S. Patent 9,669,069 at 69-72; IPR2021-00880, Declaration of T. Albini, M.D. ¶¶ 217-24; IPR2021-00881, Petition for *Inter Partes* Review of U.S. Patent 9,254,338 at 66-69; IPR2021-00881, Declaration of T. Albini, M.D. ¶¶ 404-11). Accordingly, claim 26 is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

6. Claims 27 and 28.

The language of claims 27 and 28 of the 572 patent is set forth above. Claims 27 and 28 depend from claim 26 and thus incorporate the elements of claim 26. The reasons why claim 26 is invalid for OTDP are incorporated by reference. Claims 27 and 28 are invalid for OTDP for at least the additional reasons set forth below.

Claim 27 claims two secondary doses, which is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Claim 28 merely clarifies what would have been widely understood by those of ordinary skill in the art, and thus is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Accordingly, for at least these additional reasons, claims 27 and 28 of the 572 patent are invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

7. Claim 29.

The language of claim 29 of the 572 patent is set forth above.

Claim 29 of the 572 patent is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent. Each patent discloses VEGF Trap-Eye (i.e., aflibercept), and methods of treating AMD, as well as DR and retinal edema. (*See, e.g.*, 746 patent at SEQ ID NO:16, 2:48-49, 2:53-59, 6:39-50, claims 1-5; *see also, e.g.*, 747 patent at SEQ ID NO:6, 2:1-2, 2:9-35, 5:28-51, 7:5-63; 20:15-67, 21:1-22:42, claims 1-6; 049 patent (same); 799 patent (same)). Further, the patents disclose dosing regimens that comprise an initial dose, and subsequent doses between 1-6 months apart. For at least these reasons, claim 29 of the 572 patent represents nothing more than an obvious species within the genus disclosed, and/or an obvious variation of the subject matter disclosed, in the 746 patent, the 747 patent, the 799 patent, and the 049 patent, and thus is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents. Arguments made by Regeneron in contesting OTDP rejections during prosecution of related patent claims have been refuted. (*See, e.g.*, IPR2021-00880, Petition for *Inter Partes* Review of U.S. Patent 9,669,069 at 69-72; IPR2021-00880, Declaration of T. Albini, M.D. ¶¶ 217-24; IPR2021-00881, Petition for *Inter Partes* Review of U.S. Patent 9,254,338 at 66-69; IPR2021-00881, Declaration

of T. Albini, M.D. ¶¶ 404-11). Accordingly, claim 29 is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

8. Claim 30.

The language of claim 30 of the 572 patent is set forth above. Claim 30 depends from claim 29 and thus incorporate the elements of claim 29. The reasons why claim 29 is invalid for OTDP are incorporated by reference. Claim 30 is invalid for OTDP for at least the additional reasons set forth below.

Claim 30 does not require any active steps beyond those set forth in claim 29, and/or are drawn to inherent and/or obvious variations of the subject matter set forth in claim 29, and disclosed in the 746, 747, 799, and 049 patents. Thus, claim 30 is not patentably distinct from one or more claims of the 746, 747, 799, and 049 patents.

Accordingly, for at least these additional reasons, claim 30 of the 572 patent is invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

* * *

For at least the reasons discussed above, the 572 patent Asserted Claims are invalid for OTDP over at least the 746 patent, the 747 patent, the 799 patent, and the 049 patent.

E. Enablement.

The 572 patent Asserted Claims are invalid for lack of enablement because the 572 patent fails to enable the full scope of the claims.

1. Claim 1.

The language of claim 1 of the 572 patent is set forth above.

Claim 1 of the 572 patent is invalid for lack of enablement for at least the reasons identified below.

To the extent claim 1 of the 572 patent is not anticipated or obvious, as discussed above, the 572 patent fails to provide sufficient support for the subject matter claimed in claim 1. For example, the specification does not describe or enable anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 1 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to enable a person of ordinary skill in the art to practice the claimed method without undue experimentation.

Claim 1 of the 572 patent describes administering aflibercept as "a single initial dose . . . followed by one or more secondary doses . . . followed by one or more tertiary doses" without an upper limit on the number of doses. In addition, claim 1 of the 572 patent does not enable a method for treating all angiogenic eye disorders. For example, the working examples are limited to AMD, RVO, and DME. Claim 1 is not limited to neovascular AMD, and thus the 572 patent specification does not include a disclosure sufficient to enable a person of ordinary skill in the art to practice the claimed method without undue experimentation.

Further, claim 1 is drawn to, among other things, the administration of "one or more secondary doses" without an upper limit on the number of secondary doses; the administration of "one or more tertiary doses" without an upper limit on the number of tertiary doses; and a method for treating any "angiogenic eye disorder." The breadth of each of the aforementioned claim elements renders the claims open to a substantial number of inoperative embodiments and/or methods not sufficiently described in the specification, particularly in view of any Regeneron argument that the claims require particular levels of efficacy. In addition, claim 1 is not expressly limited to any specific angiogenic eye disorders. The working examples are limited to a very narrow subset of angiogenic eye disorders, and, to the extent that Regeneron argues that the claims

require particular levels of efficacy, the specification provides insufficient information and disclosures indicating how to extrapolate data and regimen design from those disorders that are disclosed in the working examples, to those that are not (e.g., branch retinal vein occlusion, choroidal neovascularization, iris neovascularization, neovascular glaucoma, etc.). (*See, e.g.*, 572 patent at 5:31-47). Accordingly, the claims would require undue experimentation to practice, and are not enabled by the specification.

The 572 patent specification fails to enable a person of ordinary skill in the art to practice the claimed method without undue experimentation with respect to "wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose," as properly construed in accordance with the intrinsic and extrinsic evidence. For example, the 572 patent specification provides no guidance or metric as to what constitutes a "gain in visual acuity" within the scope and context of the claimed method. Accordingly, the claims would require undue experimentation to practice, and are not enabled by the specification.

The 572 patent specification also fails to enable a person of ordinary skill in the art to obtain the "aflibercept" formulations for the claimed method. The 572 patent provides no guidance as to the manufacturing and process steps needed to produce aflibercept formulations. Regeneron's own expert, Dr. Klibanov, declared that "Sanofi is a major, sophisticated, international biopharmaceutical company; yet despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881 Declaration of A. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that "Sanofi observed that the aflibercept substance made in its Vitry, France, manufacturing facility degraded faster than Regeneron's drug substance

and drug product." (*Id.* ¶ 94). As such, the 572 patent's limited disclosure fails to enable the full scope of the claimed method.

Given the breadth of the claim, the lack of guidance in the specification, and the quantity of experimentation required, the 572 patent does not enable one skilled in the art to practice the full scope of claim 1 without undue experimentation.

Accordingly, for at least these reasons, claim 1 of the 572 patent is invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

2. Claims 2-14.

The language of claims 2-14 of the 572 patent is set forth above.

Claims 2-14 of the 572 patent depend either directly or indirectly from claim 1, and thus incorporate the elements of claim 1. For at least the same reasons set forth above with respect to claim 1, said discussion incorporated herein by reference, and because the limitations of claims 2-14 do not suffice to cure the failures of claim 1 to meet the requirements of § 112, the 572 patent does not enable one skilled in the art to practice the full scope of claims 2-14 without undue experimentation.

Accordingly, claims 2-14 of the 572 patent are invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

3. Claim 15.

The language of claim 15 of the 572 patent is set forth above.

Claim 15 of the 572 patent is invalid for lack of enablement for at least the reasons identified below.

To the extent claim 15 of the 572 patent is not anticipated or obvious, as discussed above, the 572 patent fails to provide sufficient support for the subject matter claimed in claim 15. For example, the specification does not describe or enable anything more than was taught in the prior

art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 15 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to enable a person of ordinary skill in the art to practice the claimed method without undue experimentation.

Claim 15 of the 572 patent describes administering aflibercept as "a single initial dose . . . followed by one or more secondary doses . . . followed by one or more tertiary doses" without an upper limit on the number of doses. Given the breadth of the claim, the lack of guidance in the specification, and the quantity of experimentation required, the 572 patent does not enable one skilled in the art to practice the full scope of claim 15 without undue experimentation.

The 572 patent specification also fails to enable a person of ordinary skill in the art to obtain the "aflibercept" formulations for the claimed method. The 572 patent provides no guidance as to the manufacturing and process steps needed to produce aflibercept formulations. Regeneron's own expert, Dr. Klibanov, declared that "Sanofi is a major, sophisticated, international biopharmaceutical company; yet despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881 Declaration of A. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that "Sanofi observed that the aflibercept substance made in its Vitry, France, manufacturing facility degraded faster than Regeneron's drug substance and drug product." (*Id.* ¶ 94). As such, the 572 patent's limited disclosure fails to enable the full scope of the claimed method.

Accordingly, for at least these reasons, claim 15 of the 572 patent is invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

4. Claims 16-23 and 25.

The language of claims 16-23 and 25 of the 572 patent is set forth above.

Claims 16-23 and 25 of the 572 patent depend either directly or indirectly from claim 15, and thus incorporate the elements of claim 15. For at least the same reasons set forth above with respect to claim 15, said discussion incorporated herein by reference, and because the limitations of claims 16-23 and 25 do not suffice to cure the failures of claim 15 to meet the requirements of § 112, the 572 patent does not enable one skilled in the art to practice the full scope of claims 16-23 and 25 without undue experimentation.

In addition, claims 17, 20, and 21 are not enabled because the specification does not provide disclosure sufficient for a person of ordinary skill in the art to practice the full scope of the claims without undue experimentation. The specification fails to disclose DME patients gaining at least 9 letters BCVA according to ETDRS letter score, in visual acuity within 24 weeks following the initial dose, or at least 8 letters BCVA according to ETDRS, and fails to identify a method to achieve said gain that was not disclosed in the prior art, and therefore does not enable one skilled in the art to practice the full scope of claims 17 and 20-21 without undue experimentation.

Accordingly, claims 16-23 and 25 of the 572 patent are invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

5. Claim 26.

The language of claim 26 of the 572 patent is set forth above.

Claim 26 of the 572 patent is invalid for lack of enablement for at least the reasons identified below.

To the extent claim 26 of the 572 patent is not anticipated or obvious, as discussed above, the 572 patent fails to provide sufficient support for the subject matter claimed in claim 26. For example, the specification does not describe or enable anything more than was taught in the prior

art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 26 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to enable a person of ordinary skill in the art to practice the claimed method without undue experimentation.

Claim 26 of the 572 patent describes administering aflibercept as "a single initial dose . . . followed by one or more secondary doses . . . followed by one or more tertiary doses" without an upper limit on the number of doses. Given the breadth of the claim, the lack of guidance in the specification, and the quantity of experimentation required, the 572 patent does not enable one skilled in the art to practice the full scope of claim 26 without undue experimentation.

Each of the aforementioned claim elements render the claims open to a substantial number of inoperative embodiments, leading to the need for undue experimentation to practice the full scope of the invention.

The 572 patent specification fails to enable a person of ordinary skill in the art to practice the claimed method without undue experimentation with respect to "wherein the method is as effective in achieving a gain in visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with [AMD] at 52 weeks following the initial dose," as properly construed in accordance with the intrinsic and extrinsic evidence. For example, the 572 patent specification provides no guidance or metric as to what constitutes a "gain in visual acuity" within the scope and context of the claimed method. Accordingly, the claims would require undue experimentation to practice, and are not enabled by the specification.

The 572 patent specification also fails to enable a person of ordinary skill in the art to obtain the "aflibercept" formulations for the claimed method. The 572 patent provides no guidance as to the manufacturing and process steps needed to produce aflibercept formulations.

Regeneron's own expert, Dr. Klibanov, declared that "Sanofi is a major, sophisticated, international biopharmaceutical company; yet despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881 Declaration of A. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that "Sanofi observed that the aflibercept substance made in its Vitry, France, manufacturing facility degraded faster than Regeneron's drug substance and drug product." (*Id.* ¶ 94). As such, the 572 patent's limited disclosure fails to enable the full scope of the claimed method.

Accordingly, for at least these reasons, claim 26 of the 572 patent is invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

6. Claims 27 and 28.

The language of claims 27 and 28 of the 572 patent is set forth above.

Claims 27 and 28 of the 572 patent depend directly from claim 26, and thus incorporate the elements of claim 26. For at least the same reasons set forth above with respect to claim 26, said discussion incorporated herein by reference, and because the limitations of claims 27 and 28 do not suffice to cure the failures of claim 26 to meet the requirements of § 112, the 572 patent does not enable one skilled in the art to practice the full scope of claims 27 and 28 without undue experimentation.

Accordingly, claims 27 and 28 of the 572 patent are invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

7. Claim 29.

The language of claim 29 of the 572 patent is set forth above.

Claim 29 of the 572 patent is invalid for lack of enablement for at least the reasons identified below.

To the extent claim 29 of the 572 patent is not anticipated or obvious, as discussed above, the 572 patent fails to provide sufficient support for the subject matter claimed in claim 29. For example, the specification does not describe or enable anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 29 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to enable a person of ordinary skill in the art to practice the claimed method without undue experimentation.

Claim 29 of the 572 patent describes administering aflibercept as "a single initial dose . . . followed by one or more secondary doses . . . followed by one or more tertiary doses" without an upper limit on the number of doses, thus lacking enablement. Given the breadth of the claim, the lack of guidance in the specification, and the quantity of experimentation required, the 572 patent does not enable one skilled in the art to practice the full scope of claim 29 without undue experimentation.

Each of the aforementioned claim elements render the claims open to a substantial number of inoperative embodiments, leading to the need for undue experimentation to practice the full scope of the invention.

The 572 patent specification fails to enable a person of ordinary skill in the art to practice the claimed method without undue experimentation with respect to "wherein the method is as effective in maintaining visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with [AMD] at 52 weeks following the initial dose," as properly construed in accordance with the intrinsic and extrinsic evidence. For example, the 572 patent

specification provides no guidance or metric as to what constitutes a "maintaining visual acuity" within the scope and context of the claimed method. Accordingly, the claims would require undue experimentation to practice, and are not enabled by the specification.

The 572 patent specification also fails to enable a person of ordinary skill in the art to obtain the "aflibercept" formulations for the claimed method. The 572 patent provides no guidance as to the manufacturing and process steps needed to produce aflibercept formulations. Regeneron's own expert, Dr. Klibanov, declared that "Sanofi is a major, sophisticated, international biopharmaceutical company; yet despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881 Declaration of A. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that "Sanofi observed that the aflibercept substance made in its Vitry, France, manufacturing facility degraded faster than Regeneron's drug substance and drug product." (*Id.* ¶ 94). As such, the 572 patent's limited disclosure fails to enable the full scope of the claimed method.

Accordingly, for at least these reasons, claim 29 of the 572 patent is invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

8. Claim 30.

The language of claim 30 of the 572 patent is set forth above.

Claims 30 of the 572 patent depends directly from claim 29, and thus incorporates the elements of claim 29. For at least the same reasons set forth above with respect to claim 29, said discussion incorporated herein by reference, and because the limitations of claim 30 do not suffice to cure the failures of claim 29 to meet the requirements of § 112, the 572 patent does not enable one skilled in the art to practice the full scope of claim 30 without undue experimentation.

Accordingly, claim 30 of the 572 patent is invalid for failing to meet the enablement requirements of 35 U.S.C. § 112.

* * *

For at least the reasons discussed above, the 572 patent Asserted Claims are not enabled such that one of ordinary skill in the art would understand how to practice the claimed invention without undue experimentation.

F. Written Description.

The 572 patent Asserted Claims are invalid for lack of written description because the 572 patent does not convey to those skilled in the art that the named inventors were in possession of the full scope of the claims.

1. Claim 1.

The language of claim 1 of the 572 patent is set forth above.

Claim 1 of the 572 patent is invalid for lack of written description for at least the reasons identified below.

To the extent claim 1 of the 572 patent is not anticipated or obvious, as discussed above, the 572 patent fails to provide sufficient support for the subject matter claimed in claim 1. For example, the specification does not describe or disclose anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 1 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 1.

Claim 1 of the 572 patent lacks written description support at least because the specification does not disclose administering aflibercept as "a single initial dose . . . followed by one or more secondary doses . . . followed by one or more tertiary doses" without an upper limit on the number

of doses. In addition, claim 1 of the 572 patent lacks written description support because the specification does not disclose a method for treating all angiogenic eye disorders. For example, the working examples are limited to AMD, RVO, and DME. Claim 1 is not so limited, and thus, the 572 patent specification does not include a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 1.

Further, claim 1 is drawn to, among other things, the administration of "one or more secondary doses" without an upper limit on the number of secondary doses; the administration of "one or more tertiary doses" without an upper limit on the number of tertiary doses; and a method for treating any "angiogenic eye disorder." The breadth of each of the aforementioned claim elements is not sufficiently disclosed in the specification, and therefore the specification fails to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 1.

The 572 patent specification also fails to disclose the "aflibercept" formulations for the claimed method. The 572 patent provides no description of the manufacturing and process steps needed to produce "aflibercept" formulations having the requisite stability, potency, and binding properties, to be administered under the claimed method. Regeneron's own expert, Dr. Klibanov, declared that "Sanofi is a major, sophisticated, international biopharmaceutical company; yet despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881 Declaration of A. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that "Sanofi observed that the aflibercept substance made in its Vitry, France, manufacturing facility

degraded faster than Regeneron's drug substance and drug product." (*Id.* ¶ 94). As such, the 572 patent's limited disclosure fails to describe the claimed method.

Accordingly, for at least these reasons, claim 1 of the 572 patent is invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

2. Claims 2-14.

The language of claims 2-14 of the 572 patent is set forth above.

Claims 2-14 of the 572 patent depend either directly or indirectly from claim 1, and thus incorporate the elements of claim 1. For at least the same reasons set forth above with respect to claim 1, said discussion incorporated herein by reference, and because the limitations of claims 2-14 do not suffice to cure the failures of claim 1 to meet the requirements of § 112, the 572 patent does not provide a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claims 2-14.

In addition, the subject matter of claim 14 is not sufficiently described in the specification, because exclusion criteria are mentioned only once in the 572 patent, and then only in the context of a Phase 3 clinical trial for AMD, along with 37 other exclusion criteria that were required to be applied. (572 patent at 10:63 – 12:10). Accordingly, there is no written description support for the application of "exclusion criteria" outside the context of an AMD clinical trial, and no written description support for applying only a subset of the 37 exclusion criteria.

Accordingly, claims 2-14 of the 572 patent are invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

3. Claim 15.

The language of claim 15 of the 572 patent is set forth above.

Claim 15 of the 572 patent is invalid for lack of written description for at least the reasons identified below.

To the extent claim 15 of the 572 patent is not anticipated or obvious, as discussed above, the 572 patent fails to provide sufficient support for the subject matter claimed in claim 15. For example, the specification does not describe or disclose anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 15 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 15.

In addition, claim 15 of the 572 patent lacks written description support at least because the specification does not disclose administering aflibercept as "a single initial dose . . . followed by one or more secondary doses . . . followed by one or more tertiary doses" without an upper limit on the number of doses.

The 572 patent specification also fails to disclose the "aflibercept" formulations for the claimed method. The 572 patent provides no description of the manufacturing and process steps needed to produce "aflibercept" formulations having the requisite stability, potency, and binding properties, to be administered under the claimed method. Regeneron's own expert, Dr. Klibanov, declared that "Sanofi is a major, sophisticated, international biopharmaceutical company; yet despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881 Declaration of A. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that "Sanofi observed that the aflibercept substance made in its Vitry, France, manufacturing facility degraded faster than Regeneron's drug substance and drug product." (*Id.* ¶ 94). As such, the 572 patent's limited disclosure fails to describe the claimed method.

Accordingly, for at least these reasons, claim 15 of the 572 patent is invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

4. Claims 16-23 and 25.

The language of claims 16-23 and 25 of the 572 patent is set forth above.

Claims 16-23 and 25 of the 572 patent depend either directly or indirectly from claim 15, and thus incorporate the elements of claim 15. For at least the same reasons set forth above with respect to claim 15, said discussion incorporated herein by reference, and because the limitations of claims 16-23 and 25 do not suffice to cure the failures of claim 15 to meet the requirements of § 112, the 572 patent does not provide a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claims 16-23 and 25.

In addition, claims 17, 20, and 21 lack written description support at least because the specification fails to disclose DME patients gaining at least 9 letters BCVA according to ETDRS letter score, in visual acuity within 24 weeks following the initial dose, or at least 8 letters BCVA according to ETDRS, and fails to identify a method to achieve said gain that was not disclosed in the prior art.

The 572 patent specification also fails to disclose the "aflibercept" formulations for the claimed method. The 572 patent provides no description of the manufacturing and process steps needed to produce "aflibercept" formulations having the requisite stability, potency, and binding properties, to be administered under the claimed method. Regeneron's own expert, Dr. Klibanov, declared that "Sanofi is a major, sophisticated, international biopharmaceutical company; yet despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881 Declaration of A. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that

"Sanofi observed that the aflibercept substance made in its Vitry, France, manufacturing facility degraded faster than Regeneron's drug substance and drug product." (*Id.* ¶ 94). As such, the 572 patent's limited disclosure fails to describe the claimed method.

Accordingly, claims 16-23 and 25 of the 572 patent are invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

5. Claim 26.

The language of claim 26 of the 572 patent is set forth above.

Claim 26 of the 572 patent is invalid for lack of written description for at least the reasons identified below.

To the extent claim 26 of the 572 patent is not anticipated or obvious, as discussed above, the 572 patent fails to provide sufficient support for the subject matter claimed in claim 26. For example, the specification does not describe or disclose anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 26 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 26.

Claim 26 of the 572 patent lacks written description support at least because the specification does not disclose administering aflibercept as "a single initial dose . . . followed by one or more secondary doses . . . followed by one or more tertiary doses" without an upper limit on the number of doses. Thus, the 572 patent specification does not include a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 26.

The 572 patent specification also fails to disclose the "aflibercept" formulations for the claimed method. The 572 patent provides no description of the manufacturing and process steps

needed to produce "aflibercept" formulations having the requisite stability, potency, and binding properties, to be administered under the claimed method. Regeneron's own expert, Dr. Klibanov, declared that "Sanofi is a major, sophisticated, international biopharmaceutical company; yet despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881 Declaration of A. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that "Sanofi observed that the aflibercept substance made in its Vitry, France, manufacturing facility degraded faster than Regeneron's drug substance and drug product." (*Id.* ¶ 94). As such, the 572 patent's limited disclosure fails to describe the claimed method.

Accordingly, for at least these reasons, claim 26 of the 572 patent is invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

6. Claims 27 and 28.

The language of claims 27 and 28 of the 572 patent is set forth above.

Claims 27 and 28 of the 572 patent depend directly from claim 26, and thus incorporate the elements of claim 26. For at least the same reasons set forth above with respect to claim 26, said discussion incorporated herein by reference, and because the limitations of claims 27 and 28 do not suffice to cure the failures of claim 26 to meet the requirements of § 112, the 572 patent does not provide a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claims 27 and 28.

Accordingly, claims 27 and 28 of the 572 patent are invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

7. Claim 29.

The language of claim 29 of the 572 patent is set forth above.

Claim 29 of the 572 patent is invalid for lack of written description for at least the reasons identified below.

To the extent claim 29 of the 572 patent is not anticipated or obvious, as discussed above, the 572 patent fails to provide sufficient support for the subject matter claimed in claim 29. For example, the specification does not describe or disclose anything more than was taught in the prior art or was known to a person of ordinary skill in the art at the time of the alleged invention. Accordingly, to the extent that claim 29 is not anticipated or obvious over the prior art, then the specification does not include a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 29.

Claim 29 of the 572 patent lacks written description support at least because the specification does not disclose administering aflibercept as "a single initial dose . . . followed by one or more secondary doses . . . followed by one or more tertiary doses" without an upper limit on the number of doses. Thus, the 572 patent specification does not include a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 29.

The 572 patent specification also fails to disclose the "aflibercept" formulations for the claimed method. The 572 patent provides no description of the manufacturing and process steps needed to produce "aflibercept" formulations having the requisite stability, potency, and binding properties, to be administered under the claimed method. Regeneron's own expert, Dr. Klibanov, declared that "Sanofi is a major, sophisticated, international biopharmaceutical company; yet despite receiving the amino acid sequence, host cells, culture media, and know-how that Regeneron uses to produce aflibercept, Sanofi could not successfully manufacture aflibercept drug substance with the same superior stability profile as Regeneron." (IPR2021-00881 Declaration of

A. Klibanov, Ph.D., Ex. 2049 ¶ 94; *see also id.* ¶¶ 90-105). Dr. Klibanov further declared that "Sanofi observed that the aflibercept substance made in its Vitry, France, manufacturing facility degraded faster than Regeneron's drug substance and drug product." (*Id.* ¶ 94). As such, the 572 patent's limited disclosure fails to describe the claimed method.

Accordingly, for at least these reasons, claim 29 of the 572 patent is invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

8. Claim 30.

The language of claim 30 of the 572 patent is set forth above.

Claim 30 of the 572 patent depends directly from claim 29, and thus incorporates the elements of claim 29. For at least the same reasons set forth above with respect to claim 29, said discussion incorporated herein by reference, and because the limitations of claim 30 do not suffice to cure the failures of claim 29 to meet the requirements of § 112, the 572 patent does not provide a disclosure sufficient to convey to a person of ordinary skill in the art that the inventors were in possession of the full scope of claim 30.

Accordingly, claim 30 of the 572 patent is invalid for failing to meet the written description requirements of 35 U.S.C. § 112.

* * *

For at least the reasons discussed above, the 572 patent Asserted Claims are invalid for failing to satisfy the written description requirement of 35 U.S.C. § 112.

G. Indefiniteness.

The 572 patent Asserted Claims are invalid for indefiniteness pursuant to 35 U.S.C. § 112.

1. Claim 1.

The language of claim 1 of the 572 patent is set forth above.

Claim 1 of the 572 patent is indefinite for the reasons described below.

For example, the term "one or more secondary doses" is indefinite. The term fails to place an upper limit on the number of secondary doses, placing the claim outside the scope of what is disclosed in the specification, and leaving persons of ordinary skill in the art unsure about when they may or may not be operating within the bounds of the claim. Likewise, the term "one or more tertiary doses" is indefinite for failing to place an upper limit on the number of tertiary doses. In addition, the term "angiogenic eye disorder" does not inform, with reasonable certainty, those skilled in the art about the scope of the invention, because a person of ordinary skill in the art would have understood there to be different types of angiogenic eye disorders.

To the extent Regeneron argues that a "method for treating" is a limitation and requires a demonstration of efficacy, then claim 1 is indefinite for failing to articulate or offer any guidance about how to assess any such efficacy, or what levels of efficacy would suffice to meet said limitation.

In addition, claim 1 of the 572 patent fails to particularly point out and distinctly claim the subject matter of the claimed method with respect to "wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose," as properly construed in accordance with the intrinsic and extrinsic evidence. For example, the claim term lacks a plain and ordinary meaning, and the 572 patent specification provides no definition informing a person of ordinary skill in the art as to what constitutes infringement, thus failing to adequately perform the function of notifying the public of the scope of the patentee's right to exclude. Accordingly, claim 1 is indefinite. Claim 1 is further indefinite with respect to "wherein the patient achieves a gain in visual acuity within 52 weeks following the initial dose," because differences in testing methods could result in a single embodiment infringing and not infringing simultaneously.

Accordingly, claim 1 of the 572 patent fails to inform, with reasonable certainty, a person of ordinary skill in the art about the scope of the invention, and is therefore invalid under 35 U.S.C. § 112 for being indefinite

2. Claims 2-14.

The language of claims 2-14 of the 572 patent is set forth above.

Claims 2-14 of the 572 patent depend either directly or indirectly from claim 1, and thus incorporate the elements of claim 1. For at least the same reasons set forth above with respect to claim 1, said discussion incorporated herein by reference, and because the limitations of claims 2-14 do not suffice to cure the failures of claim 1 to meet the requirements of § 112, claims 2-14 of the 572 patent fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.

In addition, claims 2, 3, 8, and 10 are indefinite, because the claims fail to articulate the testing method to be used in connection with the methods of said claims. In addition, under Regeneron's proposed construction for "best corrected visual acuity," assessing BCVA letter score, according to ETDRS, could be conducted in a variety of ways, each of which could affect the outcome of the assessment. The claims also provides no guidance as to whether the BCVA letter score is to be maintained at the claimed levels, and if so, for how long, or whether, if multiple assessments are contemplated, a single result in the claimed range is sufficient to fall within the claims.

Claim 14 is indefinite because the claim fails to specify whether the claim requires an active step of applying the claimed exclusion criteria, leaving a person of ordinary skill in the art uncertain as to what activities might or might not constitute infringement of claim 14.

Accordingly, claims 2-14 of the 572 patent fail to inform, with reasonable certainty, a person of ordinary skill in the art about the scope of the invention, and are therefore invalid under 35 U.S.C. § 112 for being indefinite.

3. Claim 15.

The language of claim 15 of the 572 patent is set forth above.

Claim 15 of the 572 patent is indefinite for the reasons described below.

For example, the term "one or more secondary doses" is indefinite. The term fails to place an upper limit on the number of secondary doses, placing the claim outside the scope of what is disclosed in the specification, and leaving persons of ordinary skill in the art unsure about when they may or may not be operating within the bounds of the claim. Likewise, the term "one or more tertiary doses" is indefinite for failing to place an upper limit on the number of tertiary doses.

To the extent Regeneron argues that a "method for treating" is a limitation and requires a demonstration of efficacy, then claim 15 is indefinite for failing to articulate or offer any guidance about how to assess any such efficacy, or what levels of efficacy would suffice to meet said limitation.

Accordingly, claim 15 of the 572 patent fails to inform, with reasonable certainty, a person of ordinary skill in the art about the scope of the invention, and is therefore invalid under 35 U.S.C. § 112 for being indefinite.

4. Claims 16-23 and 25.

The language of claims 16-23 and 25 of the 572 patent is set forth above.

Claims 16-23 and 25 of the 572 patent depend either directly or indirectly from claim 15, and thus incorporate the elements of claim 15. For at least the same reasons set forth above with respect to claim 15, said discussion incorporated herein by reference, and because the limitations of claims 16-23 and 25 do not suffice to cure the failures of claim 15 to meet the requirements of

§ 112, claims 16-23 and 25 of the 572 patent fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.

In addition, claims 17 and 21 are indefinite, because the claims fail to articulate the testing method to be used in connection with the methods of said claims. In addition, under Regeneron's proposed construction of "best corrected visual acuity," assessing BCVA letter score, according to ETDRS, could be conducted in a variety of ways, each of which could affect the outcome of the assessment, without requisite information in the claims themselves as to how or when the assessment is to be conducted. The claims also provide no guidance as to whether the BCVA letter score is to be maintained at the claimed levels, and if so, for how long, or whether, if multiple assessments are contemplated, a single result in the claimed range is sufficient to fall within the claims.

Accordingly, claims 16-23 and 25 of the 572 patent fail to inform, with reasonable certainty, a person of ordinary skill in the art about the scope of the invention, and are therefore invalid under 35 U.S.C. § 112 for being indefinite.

5. Claim 26.

The language of claim 26 of the 572 patent is set forth above.

Claim 26 of the 572 patent is indefinite for the reasons described below.

For example, the term "one or more secondary doses" is indefinite. The term fails to place an upper limit on the number of secondary doses, placing the claim outside the scope of what is disclosed in the specification, and leaving persons of ordinary skill in the art unsure about when they may or may not be operating within the bounds of the claim. Likewise, the term "one or more tertiary doses" is indefinite for failing to place an upper limit on the number of tertiary doses.

To the extent Regeneron argues that a "method for treating" is a limitation and requires a demonstration of efficacy, then claim 26 is indefinite for failing to articulate or offer any guidance

about how to assess any such efficacy, or what levels of efficacy would suffice to meet said limitation.

In addition, claim 26 of the 572 patent fails to particularly point out and distinctly claim the subject matter of the claimed method with respect to "wherein the method is as effective in achieving gains in visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with [AMD] at 52 weeks following the initial dose," as properly construed in accordance with the intrinsic and extrinsic evidence. For example, the claim term lacks a plain and ordinary meaning, and the 572 patent specification provides no definition informing a person of ordinary skill in the art as to what constitutes infringement, thus failing to adequately perform the function of notifying the public of the scope of the patentee's right to exclude. Accordingly, claim 26 is indefinite. Claim 26 is further indefinite with respect to "wherein the method is as effective in achieving gains in visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with [AMD] at 52 weeks following the initial dose," because differences in testing methods could result in a single embodiment infringing and not infringing simultaneously.

Accordingly, claim 26 of the 572 patent fails to inform, with reasonable certainty, a person of ordinary skill in the art about the scope of the invention, and is therefore invalid under 35 U.S.C. § 112 for being indefinite.

6. Claims 27 and 28.

The language of claims 27 and 28 of the 572 patent is set forth above.

Claims 27 and 28 of the 572 patent depend directly from claim 26, and thus incorporate the elements of claim 26. For at least the same reasons set forth above with respect to claim 26, said discussion incorporated herein by reference, and because the limitations of claims 27 and 28 do not suffice to cure the failures of claim 26 to meet the requirements of § 112, claims 27 and 28

of the 572 patent fail to inform, with reasonable certainty, those skilled in the art about the scope of the invention.

In addition, claim 28 is indefinite, because the claim fails to articulate the testing method to be used in connection with the method of said claim. In addition, under Regeneron's proposed construction, assessing BCVA letter score, including according to ETDRS, could be conducted in a variety of ways, each of which could affect the outcome of the assessment, without any information set forth in the claim itself as to how or when the assessment is to be conducted. The claim also provides no guidance as to whether the BCVA letter score is to be maintained at the claimed levels, and if so, for how long, or whether, if multiple assessments are contemplated, a single result in the claimed range is sufficient to fall within the claim.

Accordingly, claims 27 and 28 of the 572 patent fail to inform, with reasonable certainty, a person of ordinary skill in the art about the scope of the invention, and are therefore invalid under 35 U.S.C. § 112 for being indefinite.

7. Claim 29.

The language of claim 29 of the 572 patent is set forth above.

Claim 29 of the 572 patent is indefinite for the reasons described below.

For example, the term "one or more secondary doses" is indefinite. The term fails to place an upper limit on the number of secondary doses, placing the claim outside the scope of what is disclosed in the specification, and leaving persons of ordinary skill in the art unsure about when they may or may not be operating within the bounds of the claim. Likewise, the term "one or more tertiary doses" is indefinite for failing to place an upper limit on the number of tertiary doses.

To the extent Regeneron argues that a "method for treating" is a limitation and requires a demonstration of efficacy, then claim 29 is indefinite for failing to articulate or offer any guidance

about how to assess any such efficacy, or what levels of efficacy would suffice to meet said limitation.

In addition, claim 29 of the 572 patent fails to particularly point out and distinctly claim the subject matter of the claimed method with respect to "wherein the method is as effective in maintaining visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with [AMD] at 52 weeks following the initial dose," as properly construed in accordance with the intrinsic and extrinsic evidence. For example, the claim term lacks a plain and ordinary meaning, and the 572 patent specification provides no definition informing a person of ordinary skill in the art as to what constitutes infringement, thus failing to adequately perform the function of notifying the public of the scope of the patentee's right to exclude. Accordingly, claim 29 is indefinite. Claim 29 is further indefinite with respect to "wherein the method is as effective in maintaining visual acuity as monthly administration of 0.5 mg of ranibizumab by intravitreal injection in human subjects with [AMD] at 52 weeks following the initial dose," because differences in testing methods could result in a single embodiment infringing and not infringing simultaneously.

Accordingly, claim 29 of the 572 patent fails to inform, with reasonable certainty, a person of ordinary skill in the art about the scope of the invention, and is therefore invalid under 35 U.S.C. § 112 for being indefinite.

8. Claim 30.

The language of claim 30 of the 572 patent is set forth above.

Claim 30 of the 572 patent depends directly from claim 29, and thus incorporates the elements of claim 29. For at least the same reasons set forth above with respect to claim 29, said discussion incorporated herein by reference, and because the limitations of claim 30 do not suffice to cure the failures of claim 29 to meet the requirements of § 112, claim 30 of the 572 patent fails to inform, with reasonable certainty, those skilled in the art about the scope of the invention.

In addition, claim 30 is indefinite, because the claim fails to articulate the testing method to be used in connection with the method of said claim. In addition, under Regeneron's proposed construction, assessing BCVA letter score, including according to ETDRS, could be conducted in a variety of ways, each of which could affect the outcome of the assessment, without requisite information provided in the claim as to how or when the assessment is to be conducted. The claim also provides no guidance as to whether the BCVA letter score is to be maintained at the claimed levels, and if so, for how long, or whether, if multiple assessments are contemplated, a single result in the claimed range is sufficient to fall within the claim.

Accordingly, claim 30 of the 572 patent fails to inform, with reasonable certainty, a person of ordinary skill in the art about the scope of the invention, and is therefore invalid under 35 U.S.C. § 112 for being indefinite.

* * *

Accordingly, the 572 patent Asserted Claims are invalid for indefiniteness pursuant to 35 U.S.C. § 112.

H. Unpatentable Subject Matter.

The language of the 572 patent Asserted Claims is set forth above.

At least claims 2, 3, 8, 10, 17, 21, 28, and 30 patent are invalid for failure to claim patent eligible subject matter. The claims are directed to the mere observation of outcomes resulting from the prior art dosing regimens set forth in the independent claims. Claims 2, 3, 8, 10, 17, 21, 28, and 30 do not require any alteration of the dosing regimens as a result of the observed BCVA/ETDRS scores, nor do the claims contain any active steps (e.g., assessment or measurement). As a result, claims 2, 3, 8, 10, 17, 21, 28, and 30 are drawn to nothing more than the observation of a natural law.

Claim 14 is invalid for failure to claim patent eligible subject matter. The mere recitation of "exclusion criteria," without any instruction to alter the claimed dosing regimen, or any other active step, renders the subject matter of claim 14 patent ineligible for being drawn to pure mental steps and/or abstract ideas.

Accordingly, claims 2, 3, 8, 10, 14, 17, 21, 28, and 30 of the 572 patent are invalid for failure to claim patent eligible subject matter pursuant to 35 U.S.C. § 101.

I. Unenforceability.

For at least the following reasons, the 572 patent Asserted Claims are unenforceable due to Regeneron's inequitable conduct during prosecution of the application(s) that led to the 572 patent issuance and the positions that Regeneron has taken before the Board.[76]

For example, while arguing to the U.S.P.T.O. during prosecution of related applications that the disclosures of Heier 2012 supported the patentability of the pending claims, Regeneron knew that the VIEW dosing regimens were widely disclosed in the prior art, including in its own prior art press releases, (*e.g.*, 8-19-2008 Regeneron Press Release, 9-28-2008 Regeneron Press Release, 9-14-2009 Regeneron Press Release), 10-Q forms, and 10-K forms, which were withheld from the U.S.P.T.O. while making those arguments. Moreover, Regeneron made arguments to the U.S.P.T.O. that were, upon information and belief, intentionally misleading and inaccurate. (*See, e.g.*, 338 patent PH, 9/11/2015 Applicant Remarks; 069 patent PH, 1/30/2017 Applicant Remarks; 681 patent PH, 6/25/2018 Applicant Remarks; IPR2021-00880, Petition for *Inter Partes* Review of U.S. Patent 9,669,069 at 69-72; IPR2021-00880, Declaration of T. Albini, M.D. ¶¶ 217-24;

[76] Fact discovery in this case is ongoing; Mylan reserves the right to amend, supplement, and/or clarify any of the statements provided herein based on any documents, deposition testimony, and/or other discovery materials that have not yet been obtained by, produced, or provided to Mylan, and/or with respect to which Mylan has not yet had adequate opportunity to review and analyze.

IPR2021-00881, Petition for *Inter Partes* Review of U.S. Patent 9,254,338 at 66-69; IPR2021-00881, Declaration of T. Albini, M.D. ¶¶ 404-11).

Further, Regeneron was aware of the materiality of references disclosing the VIEW dosing regimen, which is evidenced by its representations to the U.S.P.T.O. during prosecution of related applications and its subsequent decisions to submit a subset of said references to the U.S.P.T.O. in connection with other pending related applications. (*See, e.g.*, 681 patent PH, 6/25/2018 Applicant Remarks; 601 patent PH, 6/30/2020 Information Disclosure Statement). Further, upon information and belief, Regeneron was aware of the materiality of the misleading and inaccurate statements made to the U.S.P.T.O. during prosecution of the earlier applications. (*See, e.g.*, 338 patent PH, 9/11/2015 Applicant Remarks; 069 patent PH, 1/30/2017 Applicant Remarks; 681 patent PH, 6/25/2018 Applicant Remarks; 681 patent PH, 7/26/2018 Notice of Allowability).

Continuing this pattern of deception, during prosecution of the 892 application, Regeneron, upon information and belief, in an attempt to obscure references that it knew to be relevant to the subject matter of the pending claims, submitted hundreds of references to the U.S.P.T.O., effectively burying the references that contained anticipatory disclosures. (*See, e.g.*, 572 patent at pp. 1-11).

In addition, during at least PGR2021-00117, IPR2021-00880, and IPR2021-00881, Regeneron has taken positions that it knows to be misleading, inaccurate, and without merit, including, but not limited to, with respect to the identity of the VEGF Trap-Eye and aflibercept molecule, and its amino acid sequence and nucleotide sequence. (*See, e.g.*, IPR2021-00881, Patent Owner Response, Paper 40 at 24-35). Further, Regeneron has obstructed the PTAB proceedings at least through its continued pursuit of the above arguments, meritless claim construction

arguments, and also by presenting expert witnesses that were unwilling to answer basic questions and provide full and truthful testimony.

The most reasonable inference to be drawn from Regeneron's withholding of the above references from the U.S.P.T.O. and making misleading and inaccurate statements to the U.S.P.T.O. during the prosecution of the earlier applications in the patent family, followed by flooding the U.S.P.T.O. with hundreds of references during the prosecution of the 892 application, is that the actions were done with the specific intent to deceive the U.S.P.T.O.

Further, given the applicant's failure to provide relevant disclosures to the Examiner, and the misleading and inaccurate statements made to the U.S.P.T.O., during at least the prosecutions of the applications leading to the 338 patent and the 069 patent; given Regeneron's knowledge of the materiality of those actions; given that the most reasonable inference to be drawn from those actions is that they were done with the specific intent to deceive; and given the close relation of the claims at issue in the 338 and 069 patents to the other issued claims in the patent family; each member of the patent family, including the 572 patent, is unenforceable for inequitable conduct. *See, e.g., eSpeed*, 417 F. Supp. 2d 580.

For at least these reasons, the 572 patent Asserted Claims are unenforceable for inequitable conduct.

Date: January 12, 2023

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Exhibit O

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

REGENERON PHARMACEUTICALS, INC., Plaintiff, v. MYLAN PHARMACEUTICALS INC., Defendant.	Case No. 1:22-cv-00061-TSK **CONFIDENTIAL:**

OPENING EXPERT REPORT OF GREGORY MACMICHAEL, PH.D. REGARDING THE INVALIDITY OF THE ASSERTED CLAIMS OF U.S. PATENT NO. 11,084,865 UNDER 35 U.S.C. § 112

ASSUMING MYLAN'S CONSTRUCTION OF THE CLAIM TERMS "ORGANIC CO-SOLVENT" AND "NATIVE CONFORMATION"

AND

REGARDING THE INVALIDITY OF CLAIMS 6, 7, 12, 13, 18, 19, 22, AND 23, OF U.S. PATENT NO. 11,253,572 UNDER 35 U.S.C. § 112

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XOLAIR® label.	MYL-AFL0093456-72	"XOLAIR®"
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I. INTRODUCTION.

1. I, Dr. Gregory MacMichael, submit this Opening Expert Report ("Report") in order to provide expert testimony on behalf of Mylan Pharmaceuticals Inc. ("Mylan") regarding the invalidity of the Asserted Claims[1] of U.S. Patent No. 11,084,865 (the "'865 patent") under 35 U.S.C. § 112, assuming the Court adopts Mylan's proposed constructions for the claim terms "organic co-solvent" and "native conformation."[2] I also submit this Report in order to provide expert testimony on behalf of Mylan regarding the invalidity of claims 6, 7, 12, 13, 18, 19, 22, and 23 of U.S. Patent No. 11,253,572 ("'572 patent") under 35 U.S.C. § 112.

II. PROFESSIONAL QUALIFICATIONS AND BACKGROUND.

2. I am an expert in the field of biopharmaceutical sciences and biopharmaceutical formulations and related fields. My qualifications and credentials are set forth in my curriculum vitae, attached as Exhibit 62. Briefly, I received a B.S. in Microbiology from Pennsylvania State University in 1978, an M.S. in Microbiology/Biochemistry from North Carolina State University in 1980, and a Ph.D. in Microbiology/Biochemistry in 1984 from Mississippi State University.

3. I have over thirty-eight years of experience in the development and manufacture of biotherapeutic proteins, vaccines, and cell and gene therapies where I have demonstrated ability in developing superior processes for the manufacture of bulk drug substances and final drug products. I have worked in the biopharmaceutical industry at various companies such as Techne, Centocor,

[1] Counsel has informed me that Regeneron is currently asserting claims 4, 7, 9, 11, and 14-18 of the '865 patent, which I collectively refer to herein as the "Asserted Claims."

[2] To the extent the Court does not adopt Mylan's proposed constructions—or submits its own construction—for either term, I reserve the right to amend and/or supplement this report accordingly. In addition, I have prepared and submitted a separate report presenting my opinions regarding the invalidity of the Asserted Claims under 35 U.S.C. § 112, assuming the Court adopts Regeneron's claim construction proposals for "organic co-solvent" and "native conformation."

Chiron, Eli Lilly, Wyeth, Cook Pharmica, Novartis Corporation, Rocket Pharma, Nantkwest Therapeutics, Axovant Gene Therapies, Castle Creek Biosciences, and Coya Therapeutics, where I was involved in formulation development and/or process development of over 30 products. I was the Global Head of Biologics Development at Novartis for five years.

4. I am currently President and Founder of CMC BioServices, LLC, where I assist innovator and biopharmaceutical companies with the successful development and licensure of cell and gene therapies, biologics, and vaccines. In the almost thirteen years in this position, I have a proven history in planning and execution of drug substance and drug product development and production, CDMO oversight, optimizing and troubleshooting manufacturing processes, maximizing production output and decreasing the cost of goods, CMC regulatory filings, technical due diligence, and facility and equipment design.

5. I have also served in management positions, including Assistant Director of Process Development at Centocor (monoclonal antibodies), Senior Director of Development and Manufacturing at Chiron (recombinant vaccines), Senior Director of Development at Eli Lilly (therapeutic proteins), Vice President of Vaccines Development at Wyeth (vaccines, including Prevnar 13 and Flumist), Senior VP of Development and Manufacturing at Cook Pharmica (CDMO, therapeutic proteins), Global Head of Biologics Development at Novartis, and various positions in Cell and Gene Therapies at the Senior VP and Chief Technology level.

6. I have authored or co-authored fourteen publications in the field of pharmaceutical development, and I am a co-inventor of two U.S. patents.

7. I am a member of numerous technical societies, including the American Society of Cell and Gene Therapy, and the Alliance of Regenerative Medicine.

8. I have over thirty-eight years of experience in pharmaceutical research and

development in industry. I have extensive experience in the development and manufacturing of a variety of types of formulations for biologics, vaccines, viral vectors, and cell therapies. For example, as Global Head of Biologics Process Research and Development at Novartis, I led the development of Novartis's drug substance and drug product processes for a diverse biologics portfolio of more than forty-five programs from Phase 1 through commercial launch, which included monoclonal antibodies, nanobodies, glycosylated and non-glycosylated therapeutic proteins produced with mammalian and prokaryotic platforms, therapeutic vaccines, cell therapies, and gene therapies. This included streamlining the technical development of CHO-derived monoclonal antibodies and improving formulation development for high dosage formulations that are compatible with conventional and novel drug delivery devices. While at Novartis, in close partnership with Discovery and Manufacturing, I also developed the next-generation vector platforms, novel advanced vector delivery and novel approaches for stem cell differentiation, including the breakthrough Chimeric Antigen Receptor (CART) technology, stem cell and *in vivo* gene therapies. As Head of Biologics Development at Novartis, the Biologics Development (TRD) department gave technical support for Lucentis (anti-VEGF), used for treating wet macular degeneration.

9. At Techne, I designed bench-scale animal cell culture bioreactors for batch, fed-batch, and perfusion processes that were used to maximize monoclonal antibody production. At Centocor, I improved the productivity of the manufacture processes for the monoclonal antibodies for Reopro, Remicade, Panorex and Centoxin by optimizing cell lines and maximizing biomass through improvements in the media formulations and bioreactor parameters. I also authored the cell origin through the fermentation process sections for IND's and BLA's at Centocor.

10. As Director of Production, Vaccines Division, at Chiron, I led the process

optimization and scale-up of bulk processes, and directed the technology transfer and cGMP manufacturing of recombinant vaccines produced in Chinese Hamster Ovarian (CHO) in large scale perfusion culture. As Senior Director of Bioprocess Commercialization at Eli Lilly, I directed the development, transfer and launch of therapeutic proteins derived from both *E. coli* and mammalian cell culture. Also, at Eli Lilly, I developed the Xigris (activated Protein C for sepsis) bulk processes and generated the CMC sections for the BLA as well as delivered the scale-up, transfer and commercialization of Forteo (parathyroid hormone for osteoporosis), a recombinant protein produced in *E. coli*, and directed and authored the CMC sections required for the Forteo NDA.

11. Further, as Vice President of Vaccines Development at Wyeth, I directed the development of vaccine bulk processes, assays, formulations, and drug products from pre-toxicology through technical transfer for commercial manufacturing and validation. More importantly, it was at Wyeth where I led the team that developed the Prevnar 13 valent vaccine (the most complex project in the history of the pharmaceutical industry). This project included developing the process for producing six new polysaccharide antigens, seven new conjugation processes, and improving the processes for the serotypes found in the original Prevnar 7 vaccine, introduced a new 13v drug product formulation which significantly improved product stability, and a new formulation-fill process which improved the efficiencies of the utilization of formulated bulk, and developed, transferred, and validated 390 assays for monitoring and release of the intermediates and final drug product. In my time at Wyeth, I also produced the first in class Meningococcal B rL2086 bivalent vaccine through the rapid development of two ubiquitous surface MnB proteins using recombinant *E. coli* fermentation and purification processes in conjunction with platformed-based formulation technologies.

12. As Vice President of Development and Manufacturing, Chief Scientific Officer at Cook Pharmica, I directed the development, technical transfer, and manufacture of animal cell-derived therapeutic proteins and recombinant vaccines. This work spanned from cell line construction through drug product formulations and included supporting scale-up in manufacturing of both drug substance and drug product at clinical and commercial scale. I also developed and scaled processes for animal cell derived therapeutic proteins and CHO and NSO-derived monoclonal antibodies, including the manufacture of bulk drug substance and drug product and the development of three biosimilar products in CHO and SP/20.

13. I also gained extensive experience writing, reviewing and analyzing FDA submissions for both BLA and NDA products. Throughout my entire career, I have continued to work on the development and testing of protein based pharmaceutical formulations.

14. My CV further describes my background and experience and is attached to this Report as Exhibit A.

15. My opinions are based on my personal knowledge, background, education and experience, and the materials I have considered in connection with this litigation. A list of materials that I have considered in connection with preparing this Report is attached as Exhibit B.

III. UNDERSTANDING OF THE LAW.

16. Counsel has provided me an understanding of certain principles concerning patent law that have guided me in arriving at my stated conclusions in this report. In addition, Counsel informed me of the legal standards as they relate to the invalidity of patent claims. While I am not a patent attorney, I understand and have applied the below principles in reaching my opinions.

A. Claim Construction.

17. Counsel has informed me that before any invalidity analysis can be properly

performed, the scope and meaning of the challenged claims must be determined by claim construction.

18. Counsel has informed me that a patent may include two types of claims, independent claims and dependent claims. Counsel has further informed me that an independent claim stands alone and includes only the limitations it recites and that a dependent claim depends from an independent claim or another dependent claim. Counsel has also informed me that a dependent claim includes all the limitations that it recites in addition to the limitations recited in the claim (or claims) from which it depends.

19. Counsel has informed me that to determine how a person of ordinary skill in the art (whom I also refer to herein as a "POSA" or "skilled artisan") would have understood a claim term, one should look to sources available at the time of the invention that show what a skilled artisan would have understood disputed claim language to mean. Counsel has further informed me that this may include what is called "intrinsic" evidence as well as "extrinsic" evidence.

20. Counsel has informed me that, in construing a claim term, one should primarily rely on intrinsic patent evidence, which includes the words of the claims themselves, the remainder of the patent specification, and the prosecution history. Counsel has further informed me that extrinsic evidence, which is evidence external to the patent and the prosecution history, may also be useful in interpreting patent claims when the intrinsic evidence itself is insufficient. Counsel has informed me that extrinsic evidence may include dictionaries and other resources available to those of skill in the art at the time of the invention.

21. Counsel has informed me that words or terms should be given their ordinary and accepted meaning unless it appears that the inventors were using them to mean something else or something more specific. Counsel has informed me that to determine whether a term has special

meaning, the claims, the patent specification, and the prosecution history are particularly important, and may show that the inventor gave a term a particular definition or intentionally disclaimed, disavowed, or surrendered claim scope.

22. Counsel has informed me that the claims of a patent define the scope of the rights conferred by the patent. Counsel has informed me that because the claims point out and distinctly claim the subject matter, which the inventors regard as their invention, the claim construction analysis must begin with, and is focused on, the claim language itself. Counsel has informed me that the context of the term within the claim as well as other claims of the patent can inform the meaning of a claim term. For example, because claim terms are normally used consistently throughout the patent, how a term is used in one claim can often inform the meaning of the same term in other claims. Differences among claims or claim terms can also be a useful guide in understanding the meaning of particular claim terms.

23. Counsel has informed me that a claim term should be construed not only in the context of the particular claim in which the disputed term appears, but also in the context of the entire patent, including the entire specification. Counsel has informed me that because the specification is a primary basis for construing the claims, a correct construction must align with the specification.

24. Counsel has informed me that the prosecution history of the patent as well as art incorporated by reference or otherwise cited during the prosecution history are also highly relevant in construing claim terms. For instance, art cited by or incorporated by reference may indicate how the inventor and others of skill in the art at the time of the invention understood certain terms and concepts. Additionally, the prosecution history may show that the inventors disclaimed or disavowed claim scope, or further explained the meaning of a claim term.

25. With regard to extrinsic evidence, Counsel has informed me that evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises, can also be considered. For example, technical dictionaries may indicate how one of skill in the art used or understood the claim terms. However, Counsel has informed me that extrinsic evidence is considered less reliable than intrinsic evidence, and for that reason is generally given less weight than intrinsic evidence.

26. Counsel has informed me that in general, a term or phrase found in the introductory words or preamble of the claim, should be construed as a limitation if it recites essential structure or steps, or is necessary to give meaning to the claim. For instance, Counsel has informed me that preamble language may limit claim scope: (i) if dependence on a preamble phrase for antecedent basis indicates a reliance on both the preamble and claim body to define the claimed invention; (ii) if reference to the preamble is necessary to understand limitations or terms in the claim body; or (iii) if the preamble recites additional structures or steps that the specification identifies as important.

27. On the other hand, Counsel has informed me that a preamble term or phrase is not limiting where a challenged claim defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention. Counsel has further informed me that to make this determination, one should review the entire patent to gain an understanding of what the inventors claim they invented and intended to encompass in the claims.

B. Written Description.

28. Counsel has informed me that a patent claim will be invalid under 35 U.S.C. § 112 if the patent specification does not contain a written description of the claimed invention. I understand that description is "the *quid pro quo* of the right to exclude."

29. Counsel has also informed me that satisfying the written description requirement requires each and every limitation of a patent claim to be described in the patent in sufficient detail that a person of ordinary skill would recognize, based on the "four corners" of the patent, that the inventor possessed the full scope of the invention at the time of filing. In other words, the written description of a patent must clearly allow persons of ordinary skill in the art to recognize that the inventor invented what is claimed. I have also been informed that "the hallmark of written description is disclosure and that silence is generally not a disclosure" and, that for negative claim limitations, an adequate written description is when "the specification describes a reason to exclude" the element.

30. Counsel has informed me that it is not necessary for the inventors to recite every detail of their invention in the specification or to use the exact words that appear in the claims. A patentee may also satisfy the written description requirement by an inherent disclosure. But the missing descriptive matter must necessarily be present in the patent's specification such that a person of skill in the art would recognize it.

31. Counsel has informed me that, for claims reciting a genus, the specification must provide adequate written description for the genus such that a person of ordinary skill would understand that the inventor was in possession of the genus. A sufficient description must generally disclose either a sufficient representative number of species within the scope of the genus or structural features common to members of the genus such that a person of ordinary skill could visualize or recognize the members of the genus.

32. Counsel has informed me that, while written description may be found in the claims or specification of the originally filed application, subject matter added during prosecution of an application cannot support the claims of the issued patent without those claims losing priority to

the originally filed application.

C. Enablement.

33. Counsel has informed me that to comply with the enablement requirement of 35 U.S.C. § 112, a patent must provide a sufficient description of the claimed invention(s) to enable a person of ordinary skill in the art to make and use the claimed invention(s). I have been informed that the enablement requirement is only satisfied when one of skill in the art, after reading the specification, could make and use the claimed invention(s) without undue experimentation.

34. Counsel has informed me that in assessing whether a disclosure requires "undue experimentation," a court must consider the "*Wands* Factors": (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims.

35. Counsel has informed me that it is not enough for the specification to allow a person of ordinary skill to practice some of the embodiments of the claimed invention. Instead, the full scope of a claim must be enabled.

D. Indefiniteness.

36. Counsel has informed me that patentees are required to distinctly claim the subject matter that is regarded as the invention. I understand that for a claim to be sufficiently definite, a person of ordinary skill must be able to understand the scope of what is claimed with reasonable certainty when the claim is read in light of the specification and the prosecution history. In other words, the scope of a patent's claims must be sufficiently definite to inform the public of the subject matter that is covered by the exclusive rights of the patent. Furthermore, it is my

understanding that where a person of ordinary skill in the art would be unable to determine the bounds of the claims, the claims are invalid for indefiniteness.

IV. LEVEL OF ORDINARY SKILL IN THE ART.

37. I have been asked to provide my opinion on the level of ordinary skill in the art as of June 16, 2006, which I understand is the "priority date." I have been informed and understand that prior art to the '865 patent includes at least patents and printed publications in the relevant art that predate June 16, 2006, which I understand represents the earliest date to which the '865 patent may claim any sort of priority.

38. I understand the person of ordinary skill in the art ("POSA") is a fictional person who is assumed to be working in the technical field to which the patent pertains at the time the purported invention was made and is aware of all relevant prior art. I understand that elements that may be important in defining the POSA include: (1) the type of problems encountered in the art; (2) prior art solutions to those problems; (3) the speed of innovation in the field; (4) the sophistication of the technology; and (5) the educational level. Further, I understand that the POSA is a person of ordinary creativity, not an automaton, that in many cases will be able to fit the teachings of multiple prior art references together like pieces of a puzzle. Moreover, I understand that the prior art teachings also include inferences and creative steps that a POSA would employ and are not limited to precise teachings of the subject matter covered by the claims at issue.

39. A POSA during the relevant time period would have a fairly high level of education and skill. Here, a POSA would have at least a Ph.D. in chemistry, chemical engineering, biochemistry, pharmacology, or a related field, along with one to two years of experience in the development and manufacture of formulations of therapeutic proteins (or a lower degree with more practical industrial experience). A POSA would have access to biologists, biochemists,

physicians, pharmaceutical formulators, and the like, with knowledge and experience in fields such as drug discovery and development and the treatment of ophthalmic conditions.

40. I understand that Regeneron has not offered a definition of a POSA with respect to the '865 patent. I therefore reserve the right to revise or supplement my opinions set forth in this report in the event the Court adopts (or Regeneron asserts) a definition of a POSA that is materially different than the one I present in paragraph 39 above.

41. I am—and was on June 16, 2006—at least a person with at least ordinary skill in the art and am qualified to render opinions from the perspective of a POSA.

V. TUTORIAL – BACKGROUND OF THE FIELD AND TECHNOLOGY.

A. The State of the Art.

42. The '865 patent is directed to stable formulations of VEGF-specific fusion proteins. As such, in order to frame my analysis and provide proper context for my opinions, I provide the following overview of relevant technology at issue.

1. VEGF Antagonist.

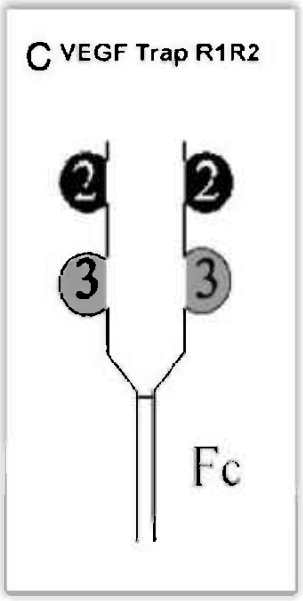
43. Vascular endothelial growth factor (VEGF) plays a critical role in angiogenesis, which is the growth of blood vessels, during normal development and in a number of diseases such as cancer and vascular eye disorders. (Rudge at 412). By 2005, various VEGF antagonists had been designed to block VEGF in disease models, including VEGF-blocking antibodies, soluble VEGF receptors, and small molecule inhibitors of VEGF receptors. (*Id.* at 413). Research identified the role for VEGF in tumor angiogenesis, with studies showing an upregulation of VEGF in various tumor types. (Ferrara-2005 at 968). As a result, anti-angiogenic VEGF inhibitors were identified as potential therapies, and were soon developed and entered clinical testing. (*Id.* at 971).

44. One of the first of these was bevacizumab, a humanized monoclonal antibody

approved for the treatment of metastatic colon cancer in combination with 5-fluoruracil (5FU). (Ferrara-2005 at 967, 971). In clinical trials, bevacizumab, an antibody blocking VEGF, and its derivative ranibizumab demonstrated efficacy of the VEGF antagonist approach in treating human patients suffering from cancers and eye diseases such as wet age-related macular degeneration (AMD). (Rudge at 411). VEGF has also been identified as a factor in the abnormal growth and fragility of new blood vessels in the eye, a condition associated with wet AMD. (*See* Ferrara-2005 at 971-72). Based on the recognition that neovascularization and vascular leakage are a major cause of vision loss in wet AMD, anti-VEGF agents were also developed for the specific purpose of treating AMD.

45. One of these, ranibizumab, is a humanized monoclonal Fab fragment capable of blocking the activity of VEGF-A, and is marketed under the name LUCENTIS®. Approved in 2006, LUCENTIS was originally indicated for the treatment of wet AMD via monthly intravitreal administration of 0.5 mg. (Shams at 31:21-32; Lucentis PI 2006 at 1).

46. Another is Regeneron's "VEGF Trap" (synonymously referred to in various references as "VEGF Trap_{R1R2}" or "VEGF TrapR1R2" and later as "aflibercept" or "VEGF Trap-Eye"). VEGF Trap-Eye is a fusion protein of Ig domain 2 of human VEGFRl and Ig domain 3 of human VEGFR2 combined with a human IgG Fc fragment, as depicted below:



(Wulff at 2798, Fig. 1). The VEGF Trap serves as a decoy to capture VEGF and prevent it from binding to VEGF receptors on the cell surfaces. (Rudge at 413).

47. Fc is also known as the "fragment crystallizable" region of an antibody, which was originally obtained by digesting an antibody with a protease known as papain. (Janeway at 3). As illustrated above, Fc of an IgG contains two identical polypeptide chains derived from the second and third constant domains of the antibody's two heavy chains. The two polypeptides are linked to each other via disulfide bonds formed between cysteine residues in the hinge region at the N-terminus of the second constant domains. (*Id.*) Fc-fusion proteins, also known as IgG-fusion proteins, are a well-known class of engineered protein drugs that take advantage of the dimerization capability of Fc. As such, Fc is a well-known multimerizing component in an engineered Fc-fusion protein.

48. In 2002, Regeneron published an article detailing VEGF Trap-Eye, a high-affinity VEGF blocker "that has prolonged *in vivo* pharmacokinetics and pharmacodynamics, lacks nonspecific toxicities, and can effectively suppress the growth and vascularization of a number of

different types of tumors *in vivo*," and was intended to treat disorders associated with increased angiogenesis. (Holash at 11393). Holash concluded that VEGF Trap may be useful in the treatment of retinopathies, given the contribution of pathological angiogenesis to such disorders. (*Id.* at 11397). Rudge also includes experimental work which indicated a role for VEGF in the pathology of other vascular eye disorders, including diabetic edema, DR, and AMD. (Rudge at 414).

49. In 2006, Rudge reported Regeneron's results of VEGF Trap clinical trials in human patients with AMD, diabetic edema, and diabetic retinopathy. (Rudge at 414-15).[3] Following the promising preclinical trials, VEGF Trap entered clinical trials assessing its effectiveness in treating these vascular eye diseases. The preliminary results showed that "VEGF Trap can rapidly and impressively decrease retinal swelling, and that these changes can be associated with improvement in visual acuity." (*Id.* at 414-15). Rudge also noted that the VEGF Trap was in the process of entering even more clinical trials related to vascular eye diseases. (*Id.* at 415).

2. Stable Protein Formulations.

50. Development of protein- and peptide-based therapeutic products for human use is growing steadily and they continue to receive an increasing rate of approval by the United States Food and Drugs Administration (US FDA). Because proteins are large and structurally complex molecules, they are susceptible to chemical and physical degradation. (Chi at 1325; Parkins at 129). As such, to achieve the benefits of therapeutic proteins for human health, stability of the protein in a formulation must be maintained.

[3] Rudge notably references prior, successful trials of LUCENTIS treating wet AMD. (*See* Rudge at 411 ("Efficacy in wet AMD has most notably been achieved using a modified fragment of the bevacizumab antibody, termed ranibizumab (Lucentis), delivered via monthly intraocular injections." (citing Brown 2006 and Heier 2006)).

51. Ensuring protein stability is a central part of developing pharmaceutical formulations because the full biological effects of the drug will not be realized if the protein becomes destabilized. As noted in Andya '326 in 2001:

> For a protein to remain biologically active, a formulation must preserve intact the conformational integrity of at least a core sequence of the protein's amino acids while at the same time protecting the protein's multiple functional groups from degradation. Degradation pathways for proteins can involve chemical instability (i.e. any process which involves modification of the protein by bond formation or cleavage resulting in a new chemical entity) or physical instability (i.e. changes in the higher order structure of the protein). Chemical instability can result from deamidation, racemization, hydrolysis, oxidation, beta elimination or disulfide exchange. Physical instability can result from denaturation, aggregation precipitation or adsorption, for example. The three most common protein degradation pathways are protein aggregation, deamidation and oxidation. Cleland et al. *Critical Reviews in Therapeutic Drug Carrier Systems* 10(4): 307-377 (1993).

(Andya '326 at [0005]).

52. Chemical degradation includes processes that make or break covalent bonds in proteins, which give rise to new chemical entities. (Chi at 1325; Parkins at 129). Examples of chemical degradation include deamidation, racemization, hydrolysis, oxidation, and disulfide exchange. (Parkins at 129). Deamidation is one of the most common ways of degradation in proteins and biopharmaceuticals that occurs when an amide group is lost from a glutamine or asparagine residue. (Parkins at 129-30; Bontempo at 103). Hydrolysis of the susceptible peptide bonds present in amino acids in the protein primary structure also disrupts the protein structure. (Parkins at 129-30; Bontempo at 103). Oxidation is another degradation mechanism and several amino acids on the protein chain, such as cysteine, methionine, tryptophan, tyrosine, phenylalanine, and histidine, are all prone to oxidation. (Parkins at 130; Bontempo at 102). Chemical degradation generates impurities that may trigger an immune response due to variations in the amino acid sequence or changes to the protein structure and contributes the loss of potency

of a therapeutic protein.

53. The biologically active state of most proteins is defined by a tightly folded conformational arrangement also known as its native conformation. When in the native conformation, polypeptide chains, consisting of amino acid chains, are folded into a tight 3-D structure. Physical degradation involves changes in the protein's native conformation, including denaturation (unfolding or misfolding), aggregation, precipitation, and surface adsorption. (Parkins at 131-32). Protein aggregation is a major problem for a protein formulation. (Bontempo at 104). Aggregation is one of the most common ways that lead to instability of a protein-based formulation and makes it therapeutically inactive. (Parkins at 131). Aggregation refers to a process by which native proteins in folded conformational arrangements associate with each other to form nonnative protein assemblies (i.e., aggregates). (Chi at 1325). The concentration of the protein drug directly affects the intermolecular interactions between protein molecules and thus its aggregation tendency. Protein aggregation is encountered throughout the lifetime of a therapeutic protein, including during refolding, purification, sterilization, shipping, and storage processes. (*Id.*). Aggregation leads to a decrease in protein activity, and also can lead to an increase in immunogenic reactions. (Parkins at 131).

54. Protein denaturation or unfolding is a process that involves conformational changes in protein structure that further leads to loss of activity although the chemical composition of the protein remains the same. Therefore, it is always desirable to obtain a chemically and physically stable protein formulation for efficacy, safety, and commercial reasons.

55. The '865 specification similarly discloses the stability problems associated with protein formulations:

> Proteins possess unique chemical and physical properties that present

> stability problems: a variety of degradation pathways exist for proteins, implicating both chemical and physical instability. Chemical instability includes deamination, aggregation, clipping of the peptide backbone, and oxidation of methionine residues. Physical instability encompasses many phenomena, including, for example, aggregation and/or precipitation.

('865 patent at 5:53-60).

56. Proteins are typically formulated as either a liquid formulation or a lyophilized formulation. A liquid formulation combines a protein with various excipients that stabilize the protein in a liquid solution. A lyophilized formulation can be created by freeze-drying a liquid protein solution having various excipients into a solid powder or cake. Before administration to a patient, a lyophilized formulation is reconstituted as a liquid solution. Both liquid and lyophilized formulations are typically stored in containers such as a vial. (Bontempo at 99).

57. By 2005, various conditions that influence protein stability in liquid or lyophilized formulations were well known in the field. For example, surfactants (i.e., surface active agents) may be used to avoid protein aggregation. Surfactants are amphiphilic molecules with both hydrophobic and hydrophilic portions, and they tend to orient so that the exposure of the hydrophobic portion to the aqueous solution is minimized. Surfactants prevent protein aggregation and unwanted adsorption during various processes of manufacture and storage. (Chi at 1328). Polysorbates such as polysorbate 20 ("Tween 20") and polysorbate 80 ("Tween 80") were among the most commonly used surfactants to reduce aggregation in protein formulations. (Randolph & Jones at 160-61; Parkins at 134).

58. Also, organic co-solvents may be used in some formulations. These typically include aqueous miscible solvents, for example polar protic or aprotic organic solvents, (*see* Strickley at 209, Table II), such as dimethyl sulfoxide (DMSO), dimethylacetamide (DMA),

ethanol, and low molecular weight polyethylene glycols (PEG) (e.g., PEG 200 and PEG 400), and glycerin. (*Id*.). An organic co-solvent increases the solubility of poorly soluble ingredients or excipients in a formulation. (Arakawa at 285; Strickley at 209).

59. Considerations for formulating a protein formulation to avoid aggregation typically also include choice of a stabilizing agent. Sucrose is a commonly used protein stabilizer and recommended for optimum long-term protein stability. (Parkins at 134.) Sucrose is well-suited to provide solution-state stabilization, as well as protection under frozen and lyophilization conditions. (*Id*.)

60. One parameter that is known to impact all the major degradation pathways is the solution pH of the formulation. (Cleland at 5). Protein stability against aggregation and other degradation mechanisms usually occurs over narrow pH ranges and a protein may degrade in solutions with pH outside these ranges. (*Id*. at 5-6). As a result, the desired pH range is a central concern to the choice of buffering agent that is used in the formulation as pH has a strong influence on aggregation rate. Various buffers are available to adjust the pH of protein formulations. Thus, another consideration for formulating a protein to avoid aggregation is choice of a buffer. It is desirable to keep the protein formulation within a narrow pH range to keep the formulation stable. (Chi at 1326). Phosphate buffer is one of the most used buffers, which can be easily made by mixing monobasic dihydrogen phosphate and dibasic monohydrogen phosphate. By varying the amount of each salt, a range of phosphate buffers can be prepared to provide robust buffering capacity at many possible pH levels (e.g., pH 5.8-8.0). (Phosphate buffer at 1). Thus, phosphate buffer is versatile for maintaining an optimal pH of many protein formulations.

61. In fact, as shown in the table below, at the time of filing of the application that became the '865 patent, many commercially available protein products, including AVASTIN®

(containing bevacizumab) and LUCENTIS® (containing ranibizumab), which target VEGF, use a buffer, an organic co-solvent[4] and a stabilizer in the marketed formulation (liquid or lyophilized). (*See also*, LUCENTIS®; AVASTIN®; REMICADE®; XOLAIR®; RAPTIVA®; SIMULECT®; HERCEPTIN®).

Product	Approval Date	Protein Active Ingredient	Buffer	Organic Co-solvent	Stabilizer	Type of Formulation
LUCENTIS®	2006	ranibizumab (anti-VEGF antibody)	histidine	polysorbate 20	trehalose	liquid
AVASTIN®	2004	bevacizumab (anti-VEGF antibody)	phosphate	polysorbate 20	trehalose	liquid
XOLAIR®	2003	omalizumab (anti-IgE antibody)	histidine	polysorbate 20	sucrose	lyophilized
RAPTIVA®	2003	efalizumab (anti-CD11a antibody)	histidine	polysorbate 20	sucrose	lyophilized
REMICADE®	1998	infliximab (anti-TNF-α antibody)	phosphate	polysorbate 80	sucrose	lyophilized
SIMULECT®	1998	basiliximab (anti-IL-2Rα antibody)	phosphate	polysorbate 80	sucrose	lyophilized
HERCEPTIN®	1998	trastuzumab (anti-HER2 antibody)	histidine	polysorbate 20	trehalose	lyophilized

62. Protein formulations, including the approved protein formulations listed above, are routinely stored under refrigerated conditions at 5° C ± 3° C (i.e., 2° C-8° C). (Guidance at 5;

[4] Herein, I am applying Regeneron's argument that polysorbate is an organic co-solvent.

LUCENTIS® at 2; AVASTIN® at 25; REMICADE® at 11; XOLAIR® at 15; RAPTIVA® at 20; SIMULECT® at 7; and HERCEPTIN® at 2). Therefore, to screen excipients for a stable protein formulation that can be developed into a viable drug product, it is industry standard to measure the stability of protein formulations upon storage for a period of time (e.g., 2 months, 6 months, 12 months, or 24 months) at 2° C-8° C. (Andya '801 at 8:22-38; Liu at [0063]).

63. Protein formulations are routinely optimized to improve stability of their active ingredients. For example, formulation design systems were available to assist in the selection of optimum parameters, such as optimal pH and protein concentration in a liquid formulation of an antibody. (Parkins at 132, and 134 (Fig. 7)). The optimization process further involves combining a therapeutic protein with excipients and then varying the concentrations of the excipients: "The formulation development approach is as follows: selecting the optimum solution pH, selecting buffer type and concentration, evaluating the effect of various excipients of the liquid and lyophilized stability, and optimizing the concentration of the screened excipients . . . ." (Kaisheva '316 at [0054]).

64. Many assays have been developed to assess the chemical and physical stability of protein formulations. Techniques were known long before 2006 for how to detect, measure, and elucidate the various types of degradation in protein samples. Some methods that were used included size exclusion chromatography, reverse phase liquid chromatography, hydrophobic interaction chromatography, a combination of native and SDS-PAGE analysis, laser light scattering analysis, circular dichroism, and gel electrophoresis.

65. One commonly used assay to analyze the physical stability of protein formulations is size exclusion chromatography. (Liu at [0278] (Table 1); Kaisheva '316 at [0038]). Size exclusion chromatography provides quantitative evaluation of molecules based on their sizes,

including percentages of monomers of a protein molecule (i.e., non-aggregate), and aggregates such as protein dimers and high molecular weight species in a protein formulation. Not all non-aggregate protein molecules under the same peak on size exclusion chromatography are in their native conformation. This is because certain chemical or physical degradation of protein, such as deamidation or disulfide shuffling, results in loss of the native conformation without changing or significantly changing the size of the protein molecule. In fact, size exclusion chromatography cannot be used to quantify amounts of different secondary or tertiary structural species of a protein molecule in a formulation. Nevertheless, the percentage of protein monomers on size exclusion chromatography is used as a proxy for assessing stability of protein formulations. The higher the percentage of protein monomers on the size exclusion chromatography, the more stable the protein formulation. It is common to expect a stable protein formulation to have at least 98% (including at least 99%) "native conformation" as measured by size exclusion chromatography upon storage at 5° C for a period of time (e.g., 2 months, 6 months, 12 months, or 24 months). In fact, before June 2006, many protein formulations containing similar excipients have shown at least 98% "native conformation" as measured by size exclusion chromatography upon storage at 5° C for two months or longer.

66. For example, Andya '801 reports in Table 2 that lyophilized protein formulations containing trehalose and polysorbate 20 (i.e., Tween 20) have >99% "intact protein" as measured by size exclusion chromatography after storage at 5° C for 2 weeks. (Andya '801 at 20:11 – 21:9). In addition, long-term stability was assessed for the 250 mM trehalose and 250 mM lactose formulations. After 12 months at 5° C, "there was no change in the % intact protein for the trehalose formulation." (*Id.* at 19:37-38.)

TABLE 2

Composition Prior to Lyophilization		% Intact Protein[a]		
[Protein][b] (mg/mL)	Formulation	Liquid (5° C)	Lyophilized (2 wk, 5° C)	Lyophilized (2wk, 40° C)
	10 mM sodium succinate pH 5.0			
5.0	275 mM trehalose, 0.01% Tween 20™	98.9	99.1	98.9
5.0	275 mM lactose, 0.01% Tween 20™	96.8	96.5	96.6
5.0	275 mM sorbitol, 0.01% Tween 20™	99.4	99.3	95.4
5.0	250 mM mannitol, 0.01% Tween 20™	100.0	99.9	98.8
5.0	250 mM trehalose, 0.01% Tween 20™	100.0	99.9	100.0
5.0	250 mM lactose, 0.01% Tween 20™	100.0	100.0	100.0
21.0	250 mM trehalose, 0.2% Tween 20™	99.3	99.1	99.1
21.0	250 mM sucrose, 0.2% Tween 20™	99.6	99.6	99.7
21.0	250 mM mannitol, 0.01% Tween 20™	100.0	94.6	94.0
21.0	188 mM mannitol/63 mM sorbitol, 0.01% Tween 20™	99.8	98.6	96.5
21.0	250 mM mannitol/25 mM glycine, 0.01% Tween 20™	99.5	96.5	96.4

a. The fraction of intact protein was measured by native size exclusion HPLC and the peak area of the native protein relative to the total peak area including aggregates (TSK3000 SW XL column, TosoHaas, with a flow rate of 1.0 mL/min; elution with phosphate buffered saline; detection at 214 and 280 nm). The protein formulations were analyzed before lyophilization (liquid, 5° C) and after lyophilization and storage at 5° C or 40° C for 2 weeks.
b. Formulations containing 5 mg/mL protein were reconstituted with distilled water (20 mL, 5.0 mg/mL protein), and formulations containing 21 mg/mL protein were reconstituted with bacteriostatic water for injection (BWFI, 0.9% benzyl alcohol; 20 mL, 20 mg/mL protein).

(Andya '801 at 20:11 – 21:9).

67. Dix reports in Table 9 the percentages of VEGF antagonist remaining in "native conformation" in a liquid formulation containing "5 mM phosphate, 5 mM citrate, 100 mM NaCl, 0.1 % polysorbate 20, 20% sucrose, and 25 mg/ml VEGF trap protein ... pH ranged from 6.0-6.1" after storage at 5 °C for up to 36 months. (Dix at 11:15-20). Table 9 is replicated below.

TABLE 9

Stability and Activity of Liquid Formulation (VGT-FS405)

Months	% Native Configuration	Bioassay	Binding Assay	Protein Content mg/ml
0	99.7	106	72	25.0
1	99.9	119	4.4 pM*	25.2
2	99.6	102	5.4 pM*	25.1
3	99.6	97	88	25.1
6	99.6	101	106	25.0
9	99.4	89	126	25.4
12	99.5	85	95	25.2
18	99.4	99	81	25.5
24	99.3	75	95	25.6
36	98.8	109	79	25.6

(*Id.* at 12:5-20).

68. Liu reports in Table 1 two liquid protein formulations having >98% monomer after storage at 5° C for 3 months (i.e., 99.3% and 98.8% respectively) or longer. Both protein formulations contain polysorbate 20, and one protein formulation further contains trehalose.

TABLE 1

Analytical Methods

Assay	Purpose
Color, Clarity, Appearance[a]	Visual inspection of liquid formulations
Size Exclusion Chromatography (SEC)[b]	Measures % monomer, soluble aggregates and low molecular weight components
Hydrophobic Interaction Chromatography (HIC)[c]	Measures level of Asp-32 isomerization and free thiol
UV Spec Scan (Gravimetric)[f]	Measures protein concentration
Turbidity (Mean OD 340–360 nm)[d]	Measures soluble and insoluble aggregates
Activity[e]	Determines binding activity of anti-IgE

[b]Size Exclusion Chromatography:

A TSK SUPER SW3000 (4.6 × 300 mm) column was used in an HP 1100 chromatography system. The column was loaded with 20 μg protein and eluted in 0.1 M potassium phosphate, pH 6.8. The sample was measured at 280 nm by a UV detector.

Summary of Liquid Formulations

Formulations	Protein Ranges	Buffer/Ranges	Excipients/Ranges
80 mg/ml E25 50 mM Histidine-HCl 150 mM Trehalose 0.05% Polysorbate 20 pH 6.0	40–150 mg/ml	His-HCl or His-Acetate Ranges: 10 mM–100 mM	Trehalose or Sucrose Sugar Ranges: 20 mM–350 mM Polysorbate: 0.01%–0.1%
150 mg/ml E25 20 mM Histidine-HCl 200 mM ArgHCl 0.02% Polsorbate 20 pH 6.0	40–260 mg/ml	His-HCl or His-Acetate Ranges: 10 mM–100 mM	ArgHCl Ranges: 50 mM–200 mM Polysorbate: 0.01%–0.1%

Temp (° C.)	Time (months)	Visual	pH	SEC[a] % Monomer	HIC[b] % of Main	Potency[c]	Turbidity[d]
		Stability Data for 150 mg/ml E25 in Histidine and ArgHCl formulation					
5	0	pass	6.2	99.0	64	106	0.25
	1	pass	6.0	99.2	63	100	0.27
	3	pass	6.0	99.3	63	111	0.25
	16	pass	6.0	98.9	62	83	0.27
30	1	pass	5.9	98.43	54	91	0.25
	3	Pass	6.1	97.53	42	65	0.30
	16	Pass	6.0	90.63	19	28	0.54
		Stability Data for 80 mg/ml E25 in Histidine and Trehalose formulation					
5	0	Pass	5.7	99.1	64	100	0.20
	1	Pass	5.8	98.7	63	92	0.20
	3	Pass	5.7	98.8	63	124	0.20
	6	Pass	5.7	99.1	63	97	0.21
	14	Pass	5.7	99.0	62	83	0.21
	24	Pass	5.7	98.8	62	84	0.20
30	1	Pass	5.8	98.7	55	77	0.20
	3	Pass	5.7	97.4	41	76	0.29

(Liu at [0278]-[0280]).

69. Kaisheva '417 also reports a number of liquid formulations having greater than 98% (including >99%) protein monomer after storage for three months (and longer) at 5° C, which was measured by size exclusion chromatography. The formulations contain Tween 80 (i.e., polysorbate 80). Table 5 is reproduced below. (*See also*, Tables 6 and 8-13).

> **[0070]** At each of the two time points, the samples were analyzed using various analytical techniques. Solution clarity was visually examined by holding the sample vials up against a black background under fluorescent lighting. The solution was inspected for insoluble species and color changes were recorded. Size exclusion chromatography was performed using a Perkin Elmer HPLC unit with diode array detection and two Tosohaas columns connected in series. The samples were diluted approximately 5 fold with the corresponding buffer to bring the concentration to about 1 mg/mL and 100 μL of the sample was injected onto the column. The sample concentration was measured by UV spectroscopy using the Perkin Elmer Lambda Bio 40 spectrophotometer.

> Example 4
>
> Stability Data of Two Daclizumab Antibody Formulations in Succinate Buffer

> **[0095]** Formulation 1: 100 mg/ml Daclizumab antibody, 30 mM sodium succinate (pH 6.0) 100 mM NaCl and 0.03% Tween –80.

TABLE 5

Stability results of Formulations 1 and 2.

Sample	Clarity	% Monomer	% Clip	% Aggregate	% Potency
T = 0					
F1	Clear	98.27	0.77	0.96	100
F2	Clear	98.27	0.77	0.96	90
T = 2 Weeks					
F1-5C	Clear	98.31	0.73	0.95	NA
F1-25C	Clear	98.03	0.82	1.14	NA
F1-37C	Clear	97.11	1.21	1.69	NA
F2-5C	Clear	98.20	0.92	0.90	NA
F2-25C	Clear	97.90	1.09	1.06	NA
T = 4 Weeks					
F1-5C	Clear	98.30	0.74	0.96	93
F1-25C	Clear	97.80	0.92	1.28	88
F1-37C	Clear	96.20	1.77	2.03	84
F2-5C	Clear	98.30	0.77	0.93	94
F2-25C	Clear	97.85	0.95	1.20	92
F2-37C	Clear	96.30	1.83	1.87	80
T = 8 Weeks					
F1-5C	Clear	98.24	0.73	0.95	96
F1-25C	Clear	97.51	0.82	1.14	96
F1-37C	Clear	94.76	1.21	1.69	90
F2-5C	Clear	98.34	0.78	0.88	90
F2-25C	Clear	97.42	1.20	1.38	90
F2-37C	Clear	94.63	3.06	2.31	85
T = 12 Weeks					
F1-5C	Clear	98.25	0.73	1.02	98
F1-25C	Clear	97.07	1.26	1.62	90
F1-37C	Clear	93.31	3.88	2.81	84
F2-5C	Clear	98.30	0.70	1.00	94
F2-25C	Clear	97.22	1.30	1.48	88
F2-37C	Clear	92.88	4.05	1.54	82

Example 7

Stability Data of Daclizumab Formulation at 5° C. for 18 Months

[0103] A liquid antibody formulation of 100 mg/ml Daclizumab in 30 mM sodium succinate, pH 6, 100 mM NaCl, and 0.03% Tween® 80 was incubated at 5° C. (2-8° C.) and tested for stability at different time points. The stability results indicate that the formulation is stable for at least 18 months at refrigerated temperature (Table 8).

TABLE 8

Stability Results of Daclizumab at 5° C.

Time (Month)	% Monomer	% Aggregate
0	99.0	N/A
3	99.1	0.2%
6	99.1	0.2%
9	98.8	0.2%
12	98.9	0.2%
18	98.6	0.2%

(Kaisheva '417 at 9-11 and [0070], [0094]-[0101], [0103]-[0107]).

70. Similarly, Lam reports stable liquid formulations of an antibody not subject to prior lyophilization comprising a surfactant and a polyol. (Lam at 2:25-30). A formulation containing polysorbate 20 as the surfactant and trehalose as the polyol had more than 98% monomer after storage at 2°-8° C for two years, which was measured by size exclusion chromatography.

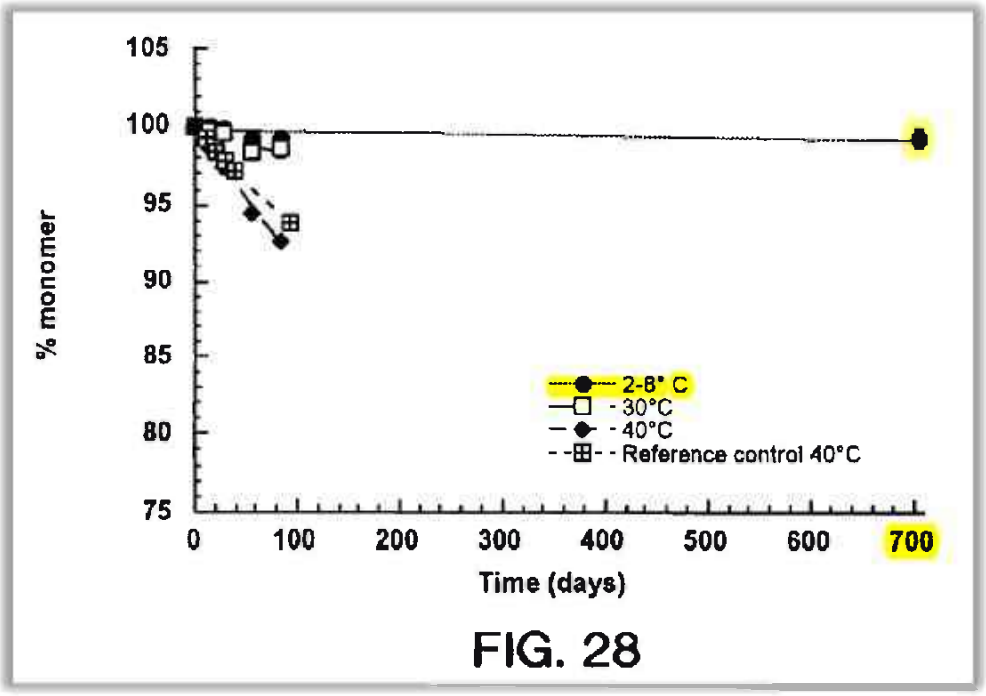


FIG. 28

FIG. 28 shows the stability profile of the prototype liquid rhuMAb CD20 multidose formulation stored at 2–8° C. for up to two years as measured by SEC HPLC. The formulation was composed of 40 mg/mL rhuMAb CD20, 150 mM trehalose, 0.9% benzyl alcohol and 0.02% polysorbate 20 at pH 5.0. The percent monomer at each timepoint was normalized to the percent monomer at T=0. The bioactivity of the formulation stored at 2–8° C. for two years was 99.2% relative to the reference control as measured by the CDC assay.

(*Id.* at Fig. 28 and 5:35-44);

SEC HPLC: Samples were diluted to 10 mg/mL with formulation buffer before being assayed. The method uses a TSK G3000 SWXL column (TosoHaas) with a mobile phase consisting of 0.2M potassium phosphate, 0.25M potassium chloride, pH.7. The socratic flow rate is 0.5 mLlmin with a total run time of 30 minutes. The amount of protein injected is 200 μp and the UV absorbance at 280 nm is used as the mode of detection.

(*Id.* at 41:60-67).

VI. THE ASSERTED '865 PATENT.

71. Based on my review of certain documents produced by Regeneron, as well as my review of the deposition testimony of Drs. Eric Furfine and Kenneth Graham, inventors of the asserted '865 patent, I provide below a summary of some of my observations concerning the development of the VEGF antagonist intravitreal injection formulation that was ultimately disclosed in the prior art as well as the '865 patent-in-suit.

A. Overview of the '865 Patent.

72. According to the '865 patent, the alleged "invention is directed to pharmaceutical formulations suitable for intravitreal administration comprising agents capable of inhibiting vascular endothelial growth factor (VEGF), and to methods for making and using such formulations. The invention includes liquid pharmaceutical formulations having increased stability, as well as formulations that may be lyophilize and reconstituted for intravitreal administration." ('865 patent at 1:45-52).

73. The specification of the '865 patent discloses "[i]n one aspect, a stable liquid ophthalmic formulation is provided that comprises 1-100 mg/ml VEGF-specific fusion protein antagonist, 0.01-5% of one or more organic cosolvent(s), 30-150 mM of one or more tonicity agent(s), 5-40 mM of a buffering agent, and optionally, 1.0-7.5% of a stabilizing agent, pH between about 5.8-7.0." ('865 patent at 2:33-38).

74. The specification of the '865 patent discloses "[i]n one or more specific embodiments, the organic co-solvent may be polysorbate, for example, polysorbate 20 or polysorbate 80, polyethylene glycol (PEG), for example, PEG 3350, or propylene glycol, or a combination thereof; the tonicity agent may be, for example, sodium chloride or potassium chloride; the stabilizing agent may be sucrose, sorbitol, glycerol, trehalose, or mannitol; and the

buffering agent may be, for example, phosphate buffer. In a specific embodiment, the phosphate buffer is a sodium phosphate buffer." ('865 patent at 2:39-48).

75. The specification of the '865 patent discloses "[i]n various embodiments, the organic co-solvent is polysorbate and/or PEG, the stabilizing agent is sucrose, the buffering agent is phosphate buffer, and the tonicity agent is sodium chloride." ('865 patent at 2:49-52).

76. The specification of the '865 patent discloses "[i]n another embodiment, the organic co-solvent is selected from one or more of polysorbate, for example, polysorbate 20 or polysorbate 80, polyethylene glycol (PEG), for example, PEG 3350, and propylene glycol." ('865 patent at 3:28-31).

77. The specification of the '865 patent discloses that "[p]roteins possess unique chemical and physical properties that present stability problems: a variety of degradation pathways exist for proteins, implicating both chemical and physical instability. Chemical instability includes deamination, aggregation, clipping of the peptide backbone, and oxidation of methionine residues. Physical instability encompasses many phenomena, including, for example, aggregation and/or precipitation. ('865 patent at 5:53-60).

78. Independent claim 1 of the '865 patent is directed to formulations containing a VEGF antagonist and broadly describes the excipients including a buffer, an organic co-solvent, and a stabilizing agent. (*See id*. at 19:29-41). The formulation under claim 1 is unlimited with respect to at least the following: (i) concentration of the required fusion protein, (ii) buffer type(s), (iii) buffer concentration(s), (iv) type(s) of organic co-solvent(s), (v) organic co-solvent concentration(s), (vi) type(s) of stabilizing agent(s), and (vii) stabilizing agent concentration(s).

79. Indeed, the claimed excipients encompass countless formulations. While it is impractical to consider the number of formulations encompassed by the scope of the claims

considering, for example, that the independent claim does not even provide any limitations on the concentration of the excipients, I have tried to provide a very conservative illustration as to the breadth of the claims in the table below. For example, I have set forth a conservative list of potential combinations of formulations encompassed by the claims below. In particular, the following table illustrates how the claims encompass at a minimum about 6 million formulations when simply accounting for a portion of the possible excipients encompassed by claim 1.

Independent Claim 1	Examples of Formulation Variables Within the Claim Scope	Number of Possibilities
A vial comprising an ophthalmic formulation suitable for intravitreal administration that comprises:	Type of formulation, e.g.: liquid or lyophilized (reconstituted).	**2**
a vascular endothelial growth factor (VEGF) antagonist … wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4	Concentration of VEGF TrapR1R2. Assuming the following concentrations, e.g.: 10 mg/ml, 20 mg/ml, 30 mg/ml, 40 mg/ml, 50 mg/ml, 60 mg/ml, 70 mg/ml, 80 mg/ml, 90 mg/ml, 100 mg/ml. ('865 patent at 2:33-38). I note there are numerous other potential concentrations that would further increase the number of possible formulations.	**10**
an organic co-solvent	These typically include, for example, dimethyl sulfoxide (DMSO), dimethylacetamide (DMA), ethanol, and low molecular weight polyethylene glycols (PEG) (e.g., PEG 200 and PEG 400), propylene glycol, and glycerin. (Strickley at 209, Table II; '865 patent at 2:33-38). Concentration, e.g.: 0.01%, 0.1%, 0.5%, 1%, 2%, 3%, 4%, 5%. ('865 patent at 2:33-38). My conservative estimate uses only the above possible variations of organic co-solvents. However, I note that there are numerous other potential organic solvents and concentrations that would further	7 (typical examples) x 8 (concentrations) = **56**

	increase the number of possible formulations.	
a buffer	These typically include, for example, acetate pH 3.8-5.8, succinate pH 3.2-6.6, citrate pH 2.1-6.2, phosphate pH 6.2-8.2, and triethanolamine pH 7.0-9.0. (Bontempo at 97). Concentration, e.g.: 5 mM, 10 mM, 20 mM, 30 mM, 40 mM. ('865 patent at 2:33-38). My conservative estimate uses only the above possible variations of buffers. However, I note that there are numerous other potential buffers and concentrations that would further increase the number of possible formulations.	5 (buffers) x 5 (concentrations) = **25**
a stabilizing agent	Sugars/sugar alcohols, e.g.: dextrose, ribose, fructose, sucrose, mannitol, inositol, sorbitol, trehalose, glycerol, and lactose. 20 natural amino acids. Concentration, e.g.: 1%, 2%, 3%, 4%, 5%, 6%, 7.5%. ('865 patent at 2:33-38). My conservative estimate uses only the above possible variations of stabilizing agents. However, I note that there are numerous other potential stabilizing agents and concentrations that would further increase the number of possible formulations.	10 (sugars) + 20 (amino acids) = 30 x 7 (concentrations) = **210**
TOTAL NUMBER OF FORMULATIONS:		2 x 10 x 56 x 25 x 210 = **5,880,000**

80. Example 1 of the '865 patent discloses that "[a]n ophthalmic liquid formulation containing 50 mg/ml VEGF Trap (SEQ ID NO:4), 10 mM phosphate, 50 mM NaCl, 0.1 % polysorbate 20, 5% sucrose, and pH 6.25, was stored at 5° C. in 3 ml glass vials and samples tested at 3, 6, 9, 12, 18 and 24 months." ('865 patent at 8:37-41).

81. Example 2 of the '865 patent discloses that "[a] liquid formulation containing 50

mg/ml VEGF Trap (SEQ ID NO:4), 10 mM phosphate, 50 mM NaCl, 3% polyethylene glycol 3350, 5% sucrose, and pH 6.25, was stored at 5° C. in 3 ml glass vials and samples tested at 3, 6, 9, 12, 18 and 24 months. ('865 patent at 8:64 – 9:1).

82. Example 3 of the '865 patent discloses that "[a] liquid formulation containing 40 mg/ml VEGF Trap above. (SEQ ID NO:4), 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, and pH 6.3, was stored at 5° C. in 3 ml glass vials and samples tested at 0.5, 1, 2, 3, and 4 months. ('865 patent at 9:24-28).

83. Example 4 of the '865 patent discloses that "[a] liquid formulation containing 40 mg/ml VEGF trap (SEQ ID NO:4), 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, and pH 6.3, was stored at 5° C. in 1 ml prefilled luer glass syringe with 4023/50 FluroTec coated plunger and samples tested at 0.5, 1, 2, 3, and 4 months. ('865 patent at 9:50-55).

84. Example 5 of the '865 patent discloses that "[a] liquid formulation containing 40 mg/ml VEGF trap (SEQ ID NO:4), 10 mM phosphate, 135 mM NaCl, 0.03% polysorbate 20, and pH 6.3, was stored at 5° C. in 3 ml glass vials and samples tested at 0.5, 1, 2, 3, and 4 months." ('865 patent at 10:18-21). The example 5 formulation does not include a stabilizing agent.

85. Example 6 of the '865 patent discloses that "[a] liquid formulation containing 40 mg/ml VEGF trap (SEQ ID NO:4), 10 mM phosphate, 135 mM NaCl, 0.03% polysorbate 20, and pH 6.3, was stored at 5° C. in 1 ml prefilled glass luer syringe with 4023/50 FluroTec coated plunger and samples tested at 0.5, 1, 2, 3, 4, and 5 months." ('865 patent at 10:45-49). The example 6 formulation does not include a stabilizing agent.

86. Example 7 of the '865 patent discloses that "0.8 ml of a liquid formulation containing 20 mg/ml VEGF trap (SEQ ID NO:4), 5 mM phosphate, 20 mM NaCl, 0.015% polysorbate 20, 2.5 % sucrose, and pH 6.3, were lyophilized in 3 ml glass vials. Samples were

stored at 5° C. and tested at 1, and 2 months. VEGF trap was reconstituted to a final concentration of 40 mg/ml VEGF Trap (final volume of 0.4 ml)." ('865 patent at 11:1-14).

87. Example 8 of the '865 patent discloses that "0.8 ml of a liquid formulation containing 20 mg/ml VEGF trap (SEQ ID NO:4), 5 mM phosphate, 67.5 mM NaCl, 0.015% polysorbate 20, and pH 6.3, were lyophilized in 3 ml glass vials. Samples were stored at 5° C. and tested at 1, 2, and 3 months. VEGF trap was reconstituted to a final concentration of 40 mg/ml VEGF trap (final volume of 0.4 ml)." ('865 patent at 12:1-13). The example 8 formulation does not include a stabilizing agent.

B. Summary of Portions of the '559 Application Prosecution History.

88. The '865 patent, titled *VEGF Antagonist Formulations Suitable for Intravitreal Administration*, issued on August 10, 2021, from U.S. Patent Application No. 16/739,559 ("the '559 application"), filed on January 10, 2020. In connection with the forming of my opinions in this matter, I have reviewed and considered the proceedings before the U.S. Patent Office ("PTO") which resulted in the issuance of the '865 patent—I understand this is commonly referred to as the prosecution history. I set forth below a brief summary of some of the more pertinent portions of the prosecution history.

89. On March 24, 2021, the U.S. PTO Examiner issued a non-final Office Action, rejecting all the pending claims 12-20 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims of U.S. Patent Nos. 8,092,803, 7,608,261, 9,340,594, and 9,914,763. ('865 patent file history, 3/24/2021 Office Action).

90. Applicants responded to the 3/24/2021 Office Action on May 5, 2021. Applicants amended claim 12, cancelled claims 13-20, and newly presented claims 21-83. ('865 patent file history, 5/5/2021 Office Action Response at 3-9). Amended claim 12 is shown below:

12 (Currently amended). A ~~pre-filled syringe~~ 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 the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein compriving an immunoglobin like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and~~

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.

('865 patent file history, 5/5/2021 Office Action Response at 3). Applicants supported the claim amendments stating that "[c]laims [sic] 12 is amended to recite a 'vial comprising an ophthalmic formulation suitable for intravitreal administration.' Support for the amended claims can be found throughout the originally filed application, such as, for example, at ¶¶[0002], [0037], and [0048]," and "[c]laim 12 is further amended to specify that the 'VEGF antagonist fusion protein is glycosylated and comprises amino acids 27-457 of SEQ ID NO:4.' Support for the amended claims can be found throughout the originally filed application, such as, for example, at ¶[0046]." (*Id*. at 10). Applicants filed a terminal disclaimer with respect to U.S. Patent 8,092,803. (*Id*. at 11).

91. Applicants argued that with the claim amendments, the rejection based on U.S. Patent 7,608,261 is traversed as "[a]ll the independent claims include an element relating to the stability of the protein conformation in storage over a period of time. This element is not contained within any of the claims of the '261 patent." (*Id*. at 12). Also, Applicants argued that the rejection based on U.S. Patent 9,340,594 is traversed as the claims of the "'594 patent do not include

elements relating to the percentage of the VEGF antagonist which maintains its conformation following storage over a given period of time. All the independent claims include an element relating to the stability of the protein conformation in storage over a period of time." (*Id.*). Finally, Applicants argued that the rejection based on U.S. Patent 9,914,763 is traversed as the claims of the "'763 patent do not include elements relating to the stability of the VEGF antagonist over time when stored which element is included in the claims of the present application by amendment. All the independent claims include an element relating to the stability of the protein conformation in storage over a period of time." (*Id.*).

92. On June 9, 2021, the Examiner issued a Notice of Allowability. ('865 patent file history, 6/9/2021 Notice of Allowability).

C. The Priority Date for the '865 Patent.

93. I understand that the content of the prior art is dictated by the priority date for the claimed invention. Here, I understand from Counsel that the earliest priority date to which the '865 patent is entitled is June 16, 2006. Therefore, for the purposes of this report, I have been instructed by Counsel that any teachings known to those of ordinary skill in the art as of June 16, 2006, at the earliest, make up the content of the prior art.

D. The Asserted Claims.

94. I have duplicated the Asserted Claims[5] below (along with certain unasserted claims from which an asserted claim depends):

[5] As stated above, I understand that Regeneron is currently asserting claims 4, 7, 9, 11, and 14-18 (i.e., the "Asserted Claims").

Claim 1 [UNASSERTED]	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.
Claim 2 [UNASSERTED]	The vial of claim 1, wherein the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate
Claim 4	The vial of **claim 2**, wherein said organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20.
Claim 5 [UNASSERTED]	The vial of claim 2, wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20.
Claim 7	The vial of **claim 5**, wherein said buffer comprises 5-25 mM buffer.
Claim 9	The vial of **claim 5**, wherein said buffer comprises a pH about 6.2-6.3.
Claim 10 [UNASSERTED]	The vial of claim 5, wherein said stabilizing agent comprises a sugar.
Claim 11	The vial of **claim 10**, wherein said sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.
Claim 14	The vial of **claim 5**, 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.
Claim 15	The vial of **claim 5**, wherein said formulation is capable of providing a turbidity of 0.01 or lower at OD_{405} after 2 month storage at 5° C.

Claim 16	The vial of **claim 5**, wherein at least 99% of said VEGF antagonist fusion protein is present in native conformation after 2 month storage at 5° C. as measured by size exclusion chromatography.
Claim 17	The vial of **claim 5**, wherein at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography.
Claim 18	The vial of **claim 5**, wherein said formulation does not contain phosphate.

(RGN-EYLEA-MYLAN-00028418, '865 patent at claims).

E. Claim Construction.

95. Counsel has informed me that the parties dispute the meaning of the terms "[present in] native conformation" and "organic co-solvent" recited in the Asserted Claims. My understanding of the parties' claim construction proposals is set forth in the following chart:

Claim Term	Regeneron's Claim Construction Proposal	Mylan's Proposed Construction
"[present in] native conformation"	This term does not need to be construed outside of the context of the limitations in which it appears (e.g., "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."). Within that context, it should be given its plain and ordinary meaning in view of the claims and the specification	Plain and ordinary meaning: *[present in] a form that does not exhibit chemical or physical instability*

"organic co-solvent"	Plain and ordinary meaning in view of the claims and specification; to the extent there is a dispute as to claim scope, "organic co-solvent" includes polysorbate 20, polysorbate 80, polyethylene glycol, or propylene glycol, or a combination thereof	Plain and ordinary meaning: *an organic substance added to a primary solvent to increase the solubility of said VEGF antagonist*

96. For this report, I was told to assume Mylan's proposed constructions.

VII. SUMMARY OF INVALIDITY POSITIONS.

97. I understand that Dr. Barrett E. Rabinow submitted a report in order to provide expert testimony on behalf of Mylan regarding the invalidity of the asserted claims of the '865 patent under 35 U.S.C. § 102/103. I have read his report and agree with his opinions that the asserted claims of the '865 patent are invalid as anticipated and/or obvious.

98. It is my opinion that (if not anticipated and/or obvious)[6] all of the Asserted Claims are invalid for (i) lacking sufficient written description, (ii) lacking enablement and/or (iii) indefiniteness. My opinions are based on my review of the Asserted Claims, the specification of the '865 patent and its prosecution history, the prior art, and the documents cited in this report and/or listed in Exhibit B.

[6] To the extent the prior art does not render the Asserted Claims invalid (in accordance with Dr. Rabinow's analyses), it is my opinion that the claims lack sufficient written description, enablement, and definiteness. As I explain further herein (and as Dr. Rabinow explained in his expert report), the '865 patent specification does not provide any formulation information that was not already known to a POSA prior to June 16, 2006.

VIII. THE ASSERTED CLAIMS ARE INVALID UNDER 35 U.S.C § 112.

99. It is my opinion that the Asserted Claims are invalid under 35 U.S.C. § 112, first paragraph, for lack of written description support, lack of enablement and/or indefiniteness. The following sections provide my opinion.

A. The Asserted Claims Are Invalid For Lack of Enablement.

100. The '865 patent Asserted Claims are invalid for lack of enablement because the '865 patent fails to enable the full scope of the claims. It is my understanding that a claimed invention is not patentable for lack of enablement if the specification does not contain a sufficient description of how to make and use the full scope of the claimed invention without undue experimentation. The '865 patent does not even disclose the full scope of the claimed formulations, let alone teach a POSA how to make and use the claimed formulations without undue experimentation. It is my opinion that the '865 patent specification fails to provide sufficient guidance for a POSA to practice the full scope of the claimed formulations.

1. *Wands* Factor[7] No. 8: The Breadth of the Claims.

101. Claim 1 of the '865 patent is broad and covers a large genera of formulations defined by their function—that is, the formulation's ability to maintain "at least 98% of the VEGF antagonist" in "native conformation" after the formulation is "stor[ed] at 5° C. for two months." Claim 1 of the '865 patent encompasses formulations comprising: (1) any amount of the VEGF antagonist fusion protein that is glycosylated and comprises amino acids 27-457 of SEQ ID NO: 4, (2) any buffer in any amount, (3) any organic co-solvent in any amount, and (4) any stabilizing agent in any amount. As set forth above in paragraph 79, these claimed excipients encompass a-

[7] The "*Wands* Factors" are found above in ¶ 34.

near infinite number of formulations. I address the breadth of each claim feature below:

102. ***Type of Formulation***: Claim 1 of the '865 patent encompasses any type of formulation that can be administered by intravitreal administration. The '865 patent expressly contemplates liquid and lyophilized formulations. Further, the '865 patent provides as exemplary formulations, lyophilized formulations that can be reconstituted as solutions, suspensions, or emulsions. ('865 patent at 7:32-34). Thus, a POSA would have understood that claim 1 encompasses many different types of formulations.

103. ***Amount of VEGF Antagonist Fusion Protein***: Claim 1 encompasses formulations comprising any concentration of the specific VEGF antagonist fusion protein that is required.

104. ***Type and Amount of Buffer***: Claim 1 includes formulations comprising any buffer at any concentration, including buffers in the free base or salt form, a racemate, or enantiomerically pure. Claim 1 also contemplates the use of one or more buffers. (*See, e.g.*, '865 patent at 6:67 – 7:2 ("The formulation can also comprise one or more pharmaceutically acceptable carriers, buffers, tonicity agents, stabilizers, and/or excipients.")).

105. ***Type and Amount of Organic Co-Solvent***: Claim 1 encompass formulations comprising any concentration of any organic co-solvent. A POSA would have recognized that "organic co-solvent" includes a wide range of aqueous miscible solvents, for example polar protic or aprotic organic solvents. (Strickley at 209, Table II). These typically include, for example, dimethyl sulfoxide (DMSO), dimethylformamide (DMF), dimethylacetamide (DMA), methanol, ethanol, and low molecular weight polyethylene glycols (PEG) (e.g., PEG 200 and PEG 400), and glycerin. *Id*. An organic co-solvent increases the solubility of poorly soluble ingredients or excipients in a formulation. (Arakawa at 285; Strickley at 209).

106. As I discussed above (and in my expert declaration submitted in support of Mylan's

proposed claim constructions), a POSA would have understood polysorbate in the context of the '865 patent claims to act as a surface-active agent, i.e., a surfactant, which has a different function than that of an organic co-solvent in protein formulations. In this report under Mylan's construction of "organic co-solvent," a POSA would not have understood a polysorbate to be an organic co-solvent (or a component thereof).

107. Claim 1 also contemplates the use of one or more "organic co-solvents." (*See, e.g.*, '865 patent at 6:67 – 7:2 ("The formulation can also comprise one or more pharmaceutically acceptable carriers, buffers, tonicity agents, stabilizers, and/or excipients.")).

108. ***Type and Amount of Stabilizing Agent***: Finally, the claims encompass formulations comprising any "stabilizing agent" at any concentration. Further, each stabilizing agent, including for example each different sugar, has unique biochemical and biophysical properties that can affect its ability to work as a stabilizer. (*See*, *e.g.*, Back at 5191, Table II, Table III). Claim 1 also contemplates the use of one or more "stabilizing agents." (*See, e.g.*, '865 patent 6:67 – 7:2 ("The formulation can also comprise one or more pharmaceutically acceptable carriers, buffers, tonicity agents, stabilizers, and/or excipients.")).

109. ***Functional Properties***: Claim 1 recites, "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." As I discussed above (and in my expert declaration submitted in support of Mylan's proposed claim constructions), a POSA would have understood that this claim encompasses formulations that maintain the stability of the VEGF antagonist fusion protein from 0% to 2% degradation after the recited storage conditions. As I explain above in paragraphs 63-64 (as well as in my expert declaration submitted in support of Mylan's proposed claim constructions (MacMichael Declaration)), a POSA would have known that stability refers to more

than just the presence of aggregation, however, claim 1 limits this element by requiring the use of size exclusion chromatography to distinguish between aggregated and non-aggregated proteins.

2. *Wands* Factor No. 4: The Nature of the Invention.

110. Claim 1 of the '865 patent is broad and covers large genera formulations defined by their function—that is, the formulation's ability to maintain "at least 98% of the VEGF antagonist" in "native conformation" after the formulation is "stor[ed] at 5° C. for two months." While the claims identify several excipients in the genera of formulations, a person of ordinary skill in the art would have understood that not all of the formulations with the claimed excipients would exhibit the claimed stability. ('865 patent at 19:29-41).

3. *Wands* Factor No. 7: The Predictability or Unpredictability of the Art.

111. It is my understanding that Regeneron has characterized the art of protein formulation development as unpredictable. For example, during the prosecution of a related foreign European patent, one of the '865 patent inventors (Dr. Dix) stated that "[f]ormulation of pharmaceutical preparations and achieving a stable composition is not a simple or routine matter." (*See* EP459 Dix Declaration ¶ 10). Dr. Dix further referred to several other references as alleged support for his proposition. (*Id*.).

112. As I described above, claim 1 of the '865 patent is very broad, reciting only that the claimed formulation comprises a "stabilizing agent," "organic co-solvent," and "buffer." Each of these broad categories encompasses numerous specific excipients. Applying Dr. Dix's declaration statements to the European Patent Office, a POSA would understand that not all stabilizing agents, organic co-solvents, and buffers have the same effect on a formulation as other members within the same excipient class. To obtain issuance of another related patent, Dr. Dix also declared that certain PEG excipients (e.g., PEG 3500) were able to provide a stable formulation, whereas other

PEG excipients (PEG 300) were not. ('256 App Dix Declaration ¶¶ 5-10). Dr. Dix also declared that different combinations, ratios, and ranges can impact the stability profile of a formulation. (*Id*. ¶ 5). In my opinion, Dr. Dix's declaration statements stand in contradiction to a conclusion that the full scope of the '865 patent claims are fully enabled.

4. *Wands* Factor No. 2: The Amount of Direction or Guidance Presented.

113. The '865 patent provides essentially no direction or guidance on how to make and use the claimed formulations. The claimed genera of formulations are not even described anywhere in the specification.

114. ***Concentration of Fusion Protein***: As I explain above (¶ 103), claim 1 encompasses formulations comprising ***any*** concentration of the required VEGF antagonist fusion protein. A POSA would have understood that different concentrations of fusion protein may require formulations with different buffering capacities. (*See*, *e.g.*, Gokarn at 3:15-21). But, the '865 patent does not provide any guidance for preparing formulations—or how to prepare a sufficient buffer system—across the full VEGF antagonist fusion protein concentration range with the claimed excipients. Accordingly, in my opinion, a POSA would require undue experimentation to determine how to formulate VEGF antagonist fusion protein across the full scope of the Asserted Claims.

115. ***Organic Co-Solvent***: As I explain above (¶¶ 105-106), a POSA would have recognized that "organic co-solvent" includes a wide range of excipients that include a variety of well-known organic co-solvents (e.g., aqueous miscible solvents, such as polar protic or aprotic organic solvents). Accordingly, the universe of "organic co-solvents" (and concentrations thereof) that may be used in the claimed formulations is extremely broad and diverse. The '865 patent does not provide any guidance for preparing formulations across the full scope of "organic co-solvent"

excipients that may be used in the claimed formulations. Accordingly, in my opinion, a POSA would require undue experimentation to determine how to a prepare an "organic co-solvent"-containing formulation across the full scope of the Asserted Claims.

116. As I discussed above (as well as in my expert declaration submitted in support of Mylan's proposed claim constructions (MacMichael Declaration)), a POSA would have understood polysorbate to act as a surface-active agent, i.e., a surfactant, which has a different function than that of an organic co-solvent in protein formulations. In this report under Mylan's construction of "organic co-solvent," a POSA would not have understood a polysorbate to be a an organic cosolvent (or a component thereof).

117. ***Stabilizing Agent***: The '865 patent specification also fails to provide guidance for the broadly claimed genera of "a stabilizing agent" in the claimed formulation. Rather, the specification only discloses one stabilizing agent: sucrose. ('865 patent at 2:49 – 3:10; *id*. at 3:32 – 4:6; *id*. at 8:37-41 (Example 1); 8:64 – 9:1 (Example 2); 9:24-28 (Example 3); 9:50-52 (Example 4); 10:18-20 (Example 5); 10:45-47 (Example 6); 11:5-8 (Example 7); 12:5-8 (Example 8)). A POSA would have understood that different stabilizing agents can have different stabilizing effects on a formulation, yet the '865 patent fails to provide any guidance on how to formulate the required VEGF antagonist fusion protein with any stabilizing agent besides sucrose. Accordingly, in my opinion, a POSA would have required excessive, undue experimentation to develop working formulations using ***any*** stabilizing agent at ***any*** concentration as the claims purportedly cover.

118. ***Buffer***: The '865 patent specification also fails to provide guidance for the broadly claimed genera of a buffer. Rather, the specification only discloses one type of buffer: phosphate. ('865 patent at 2:49 – 3:10; *id*. at 3:32 – 4:6; *id*. at 8:37-41 (Example 1); 8:64 – 9:1 (Example 2); 9:24-28 (Example 3); 9:50-52 (Example 4); 10:18-20 (Example 5); 10:45-47 (Example 6); 11:5-8

(Example 7); 12:5-8 (Example 8)). A POSA would have understood that different buffers can have different effects on a formulation, yet the '865 patent fails to provide any guidance on how to formulate the required VEGF antagonist fusion protein with any buffer besides phosphate. Accordingly, in my opinion, a POSA would have required excessive, undue experimentation to develop working formulations using ***any*** buffer at ***any*** concentration as the claims purportedly cover.

119. For example, the '865 patent does not disclose, let alone teach a POSA how to make, a formulation comprising histidine as the "buffer" without undue experimentation. In fact, the '865 patent does even mention the use of histidine anywhere in the specification—I understand the complete absence of histidine, and histidine-buffered solutions, from the '865 patent to be consistent with Regeneron's refusal to use histidine in any of its liquid formulations prior to June 2006. (*See* Graham Dep Tr. at 118:4-23; *id.* at 107:5-16).

120. Moreover, it is my understanding that Regeneron disclaimed histidine-buffered formulations of the same VEGF antagonist fusion protein in U.S. Patent No. 10,857,231 ("the '231 patent"). (*See* Exhibit 3001, PGR2021-00117 ("[B]ased on very recently discovered information, Patent Owner has reason to question whether the data presented in Table 7 of the Dix '231 Patent corresponds to the formulation described in Example 4 at column 10, lines 27-38."); Exhibit 2048, PGR2021-00117 (copy of Regeneron's disclaimer of the '231 patent); Paper 16, PGR2021-00117 (order denying institution of Post-Grant Review based on Regeneron's disclaiming all claims of the '231 patent)). It is my understanding that the '231 patent has an earliest filing date of March 25, 2005 (over 1 year before the '865 patent) and shares two (2) of the same inventors as the '865 patent. In my opinion, Regeneron's disclaimer of histidine-buffered formulations in the '231 patent reflects the '865 patent's lack of disclosure, description or enablement of such formulations

in the '865 patent. In short, I have seen no evidence (nor does the '865 patent specification provide any) that Regeneron possessed a histidine-buffered solution prior to June 16, 2006.

'231 Patent, Claim 1 *[DISCLAIMED]*	'865 Patent, Asserted Claims
A formulation comprising:	A vial comprising an ophthalmic formulation suitable for intravitreal administration that comprises:
10-50 mg/ml of a vascular endothelial growth factor (VEGF) antagonist fusion protein comprising amino acids 27-457 of SEQ ID NO: 4,	a vascular endothelial growth factor (VEGF) antagonist [Claim 2: said VEGF antagonist fusion protein is 40 mg/ml]
a buffer comprising histidine,	a buffer, and [Claim 18: said formulation does not contain phosphate]
an organic co-solvent comprising polysorbate, and	an organic co-solvent, [Claim 2: said organic co-solvent comprises polysorbate]
a stabilizing agent comprising a sugar, an amino acid or both	a stabilizing agent [Claim 10: said stabilizing agent comprises a sugar]
wherein said VEGF antagonist fusion protein exhibits less than about 3% degradation after 15 months of storage at 5° C.	… 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.

121. Thus, in my opinion, the '865 patent does not disclose, describe or enable, formulations using histidine as a buffer.

122. ***Functional Properties***: The specification does not provide any guidance on how to make formulations with the claimed excipients that exhibit the claimed stability properties. The specification provides no guidance or discussion on commonalities in formulations within the

claimed genus that can accomplish the specific stability required by claim 1. The specification does not even discuss the claimed stability in the context of the claimed genus of formulations. The limited guidance provided with respect to this functional property is provided in the working examples, which I discuss below.

5. *Wands* Factor No. 1: The Quantity of Experimentation Necessary.

123. The quantity of experimentation necessary to make and use the full scope of formulations claimed in the '865 patent is undue and, indeed, excessive. The claims encompass an enormous number of formulations despite the limited disclosure in the specification—as I explain above (¶¶ 124-25), the Examples provide only one (1) formulation that falls within the scope of the Asserted Claims. It would require an enormous amount of experimentation to make the full scope of formulations encompassed by the '865 patent claims. As discussed above in paragraph 79, the claims encompass millions of different formulations.

124. Only the liquid formulation in Example 2 includes the excipients claimed in independent claim 1. ('865 patent at 8:64-67). The formulations in Examples 1, 3-8 do not include an organic co-solvent. Further, a POSA would have understood that polysorbate 20, in the context of the '865 patent claims, is not a component of an organic co-solvent. Rather, a POSA would have understood that polysorbate 20 was acting as a surfactant, not an organic co-solvent, in the formulation. (Strickley at 209, Table II; Kaisheva '316 at [0059]). Moreover, the '865 patent itself does not define an organic co-solvent anywhere nor teach a POSA how to use polysorbate 20 as an organic co-solvent or as a component of an organic co-solvent.

125. The '865 Patent also does not disclose any examples within the scope of the claims that necessarily exhibit the claimed stability. The specific examples in the specification only disclose the amount of degradation determined by SE-HPLC. (*See*, *e.g.*, '865 patent at 8:41-42).

As discussed above, a POSA would have understood that degradation includes both physical degradation and chemical degradation mechanisms. Further, the specification of the '865 patent includes both chemical and physical degradation among the forms of protein instability. (*Id*. at 5:53-60). A POSA would have been aware that, particularly for chemical degradation, the apparent size/molecular weight of the protein would not necessarily be affected by the degradation processes. Therefore, SE-HPLC is not a sufficient method for characterizing both physical and chemical forms of degradation. Thus, the reported values do not reflect the total degradation percentage of the protein that would be expected by a POSA. Therefore, it is not clear whether these examples demonstrate a formulation where "at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months" as required by claim 1.

126. Further, the claims encompass certain embodiments that are merely hinted at in the specification that would require an exorbitant amount of further research and development. For example, the '865 patent expressly contemplates lyophilized formulations that can be reconstituted as solutions, suspensions, or emulsions. ('865 patent at 7:31-33, 7:63-65). There, however, is no disclosure in the '865 patent as to how to make these formulations. It would have required substantial research and technological achievement to prepare lyophilized formulations that can be reconstituted as a suspension or emulsion with the claimed excipients.

127. Once all of the formulations were prepared, it would have required years of additional experimentation to assess whether the formulations exhibited the required stability properties. Stability testing is a lengthy endeavor, as evident by the fact that claim 1 requires the recited stability after 2 months and claim 17 recites the claimed stability after at least 24 months. Even assuming that the full scope of formulations could be prepared simultaneously (which would be impossible in view of the large number of formulations), it would have required years of

additional work to conduct the required stability testing.

6. *Wands* Factor No. 6: The Relative Skill of Those in the Art.

128. As discussed in Section IV, a POSA would be a person with an advanced degree along with one to two years of experience in the development and manufacture of formulations of therapeutic proteins (or a lower degree with more practical industrial experience). Even someone with this level of skill would still require excessive experimentation and trial-and-error to arrive at the claimed formulation. Regeneron has, in fact, acknowledged that a POSA would "expect to engage in significant non-routine experimentation to develop a successful formulation." (*See* '840 App Dec. 6, 2016 Response to Office Action at 11). Further, as stated by one of the inventors (Dr. Dix), "[f]ormulation of pharmaceutical preparations and achieving a stable composition is not a simple or routine matter." (*See* EP459 Dix Declaration ¶ 10). Moreover, if the experimentation needed to achieve a histidine-buffered formulation (for example) were routine, there would have been no need for Regeneron to disclaim the '231 patent claims over a mere "question" as to whether the Example data corresponded to the claimed histidine buffered-formulation.

7. *Wands* Factor No. 5: The State of the Art.

129. The art available at the time of the alleged invention relating to VEGF antagonist fusion protein formulations fails to remedy the deficiencies of the '865 patent in view of the incredibly broad scope of the claimed formulations.[8]

[8] My opinion in this regard assumes that Regeneron will argue, in response to Dr. Rabinow's expert opinions regarding the prior art to the '865 patent, that the "state of the art" was somehow insufficient to teach the formulations of the Asserted Claims. As I state above, the '865 patent specification offers no information or teaching that was not otherwise previously disclosed in the prior art. Accordingly, it is my opinion that, if the prior art does not render the claims invalid in accordance with Dr. Rabinow's opinions, the Asserted Claims are not (and cannot be) sufficiently enabled, and thus, are invalid.

130. A POSA would have recognized that this includes a wide range of organic co-solvents that may be used in formulations and typically include aqueous miscible solvents, for example polar protic or aprotic organic solvents. (Strickley at 209, Table II). These typically include, for example, dimethyl sulfoxide (DMSO), dimethylacetamide (DMA), ethanol, and low molecular weight polyethylene glycols (PEG) (e.g., PEG 200 and PEG 400), and glycerin. (*Id*.) An organic co-solvent increases the solubility of poorly soluble ingredients or excipients in a formulation. (Arakawa at 285; Strickley at 209). As discussed above, a POSA would have understood polysorbate to act as a surface-active agent, i.e., a surfactant, which has a different function than that of an organic co-solvent in protein formulations. In this report under Mylan's construction of "organic co-solvent," a POSA would not have understood a polysorbate to be an organic co-solvent (or a component thereof).

131. Further, the '865 patent fails to inform persons of ordinary skill in the art of the SEC parameters required to test a "vial" for a VEGF antagonist in "native conformation." For example, the '865 patent fails to provide any parameter for performing the SE-HPLC. A person of ordinary skill in the art, to determine the scope of the claim term "at least 98% [or 99%] of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography," would need to know the parameter of the SE-HPLC, such as column type, machine used, amount and concentration of sample loaded, mobile phase, flow rate, run time, and detector type. (*See*, *e.g.*, Andya '801 at 20-21; Liu at 26-27; Lam at 41:60-67). The '865 patent provides none of these parameters. Moreover, a person of ordinary skill in the art would have understood that using different parameters would have produced different results.

132. Given the breadth of the claims, the lack of guidance in the specification, and the

quantity of experimentation required, the '865 patent does not enable one skilled in the art to practice the full scope of claim 1 without undue experimentation. Thus, claim 1 is not enabled such that one of ordinary skill in the art would understand how to practice the claimed invention without undue experimentation.

B. Dependent Claims 4, 7, 9, 11, and 14-18 Are Not Enabled By the Specification.

133. Claims 4, 7, 9, 11, and 14-18 depend either directly or indirectly from claim 1, and thus incorporate the elements of claim 1. Claims 4, 7, 9, 11, and 14-18 do not substantially narrow the scope of claim 1, and the specification fails to provide sufficient guidance for the genera of formulations claimed therein. Therefore, for at least the same reasons set forth above with respect to claim 1, said discussion incorporated herein by reference, the '865 patent does not enable a person of ordinary skilled in the art to practice the full scope of claims 4, 7, 9, 11, and 14-18 without undue experimentation.

1. Claims 2 (unasserted) and 4 Are Not Enabled.

134. Claim 2 is dependent on claim 1 and specifies that "the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate." As discussed above (as well as in my expert declaration submitted in support of Mylan's proposed claim constructions (MacMichael Declaration)), a POSA would have understood polysorbate to be a surface-active agent, i.e., a surfactant, which has a different function than that of an organic co-solvent in protein formulations. In this report under Mylan's proposed construction of "organic co-solvent," a POSA would not have understood the polysorbate of claim 2 to be an organic co-solvent (or a component thereof) unless it was present in sufficient concentration to increase the solubility of the VEGF antagonist in the formulation. Here, none of the Examples contain both a concentration of a VEGF antagonist fusion protein of 40 mg/ml and

an organic co-solvent comprising polysorbate.[9] Further, there is no teaching in the specification on how to use a polysorbate as an organic co-solvent (e.g., at what concentration does the polysorbate increase the solubility of the VEGF antagonist fusion protein). Therefore, the specification fails to provide sufficient guidance for the genera of formulations where "the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate."

135. Claim 2 also allows for any type and concentration of buffer, any type and concentration of a stabilizing agent, and any concentration of polysorbate. It would have required undue experimentation in view of this complete absence of guidance to make and use formulations across the entire scope of the claims, even where the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate, let alone formulations having the claimed stability. Therefore, for at least the same reasons set forth above with respect to claim 1, said discussion incorporated herein by reference, the '865 patent does not enable a person of ordinary skilled in the art to practice the full scope of claim 2 without undue experimentation.

136. Claim 4 depends from claim 2 and further specifies that the "organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20." In my opinion, a POSA would have understood "0.03% to about 0.1% polysorbate 20" to act as a surface-active agent, i.e., a surfactant, which has a different function than that of an organic co-solvent in protein formulations. In this report under Mylan's proposed construction of "organic co-solvent," a POSA would not have

[9] That said, as I previously explained (MacMichael Tr. at 135:3-6, 138:19 – 139:9), the formulation described in Example 2 of the '865 patent does comprise what a POSA may conclude is an organic co-solvent "polyethylene glycol 3350," and thus does fall within the scope of claim 1.

understood "0.03% to about 0.1% polysorbate 20," in the context of claim 4, to be a an organic cosolvent (or a component thereof), because, among other things, "0.03% to about 0.1% polysorbate 20" is unlikely sufficient concentration to increase the solubility of the VEGF antagonist. Accordingly, a POSA would have understood the claim 4 formulation to require a different organic co-solvent excipient, one that further comprises "0.03% to about 0.1% polysorbate 20." As I explain above, none of the Examples contain a concentration of a VEGF antagonist fusion protein of 40 mg/ml and an organic co-solvent comprising about 0.03% to about 0.1% polysorbate 20. Further, there is no teaching in the specification on how to use 0.03% to about 0.1% polysorbate 20 as the organic co-solvent. Therefore, in my opinion, the specification fails to enable claim 4.

137. Claims 2 and 4 also allow for any type and concentration of buffer and any type and concentration of a stabilizing agent. It would have required undue experimentation in view of this complete absence of guidance to make and use formulations across the entire scope of the claims, even where the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said "organic co-solvent" comprises about 0.03% to about 0.1% polysorbate 20, let alone formulations having the claimed stability. Therefore, in my opinion, the '865 patent does not enable a person of ordinary skilled in the art to practice the full scope of claims 2 and 4 without undue experimentation.

2. Claims 5 and 7 Are Not Enabled.

138. Claim 5 depends from claim 2 and specifies that the "organic co-solvent comprises 0.01% to 3% polysorbate 20." As discussed above (as well as in my expert declaration submitted in support of Mylan's proposed claim constructions (MacMichael Declaration)), a POSA would have understood polysorbate to be a surface-active agent, i.e., a surfactant, which has a different

function than that of an organic co-solvent in protein formulations. In this report under Mylan's proposed construction of "organic co-solvent," a POSA would not have understood the polysorbate of claim 5 to be an organic co-solvent (or a component thereof) unless it was present in sufficient concentration to increase the solubility of the VEGF antagonist in the formulation. Here, none of the Examples contain both a concentration of a VEGF antagonist fusion protein of 40 mg/ml and an organic co-solvent comprising more than ***0.1% polysorbate***. Consequently, there is no teaching in the specification on how to use a polysorbate as an organic co-solvent (e.g., at what concentration does the polysorbate increase the solubility of the VEGF antagonist fusion protein) or whether, e.g., 3% polysorbate 20 would act as an organic co-solvent in the claimed formulation. Therefore, the specification fails to provide sufficient guidance for the genera of formulations where the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20.

139. Claim 5 also allows for any type and concentration of buffer and any type and concentration of a stabilizing agent. It would have required undue experimentation in view of this complete absence of guidance to make and use formulations across the entire scope of the claims, even where the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said "organic co-solvent" comprises about 0.1% to about 3% polysorbate 20, let alone formulations having the claimed stability. Therefore, in my opinion, the '865 patent does not enable a person of ordinary skilled in the art to practice the full scope of claim 5 without undue experimentation.

140. Claim 7 depends from claim 5 and specifies that the "buffer comprises 5-25 mM buffer." There is not a single example of a working formulation with a buffer other than phosphate and the phosphate-buffered formulations disclosed and tested in Examples 1-6, contain 10 mM phosphate, and in Examples 7 and 8, contain 5 mM phosphate. ('865 patent at 8:37-41 (Example

1); 8:64 – 9:1 (Example 2); 9:24-28 (Example 3); 9:50-52 (Example 4); 10:18-20 (Example 5); 10:45-47 (Example 6); 11:5-8 (Example 7); 12:5-8 (Example 8)). Claim 7 also allows for any type of buffer having a concentration of 5-25 mM, and combined with any stabilizing agent at any concentration. There simply is no indication in the '865 patent that the inventors possessed anything but a phosphate-buffered / sucrose-stabilized formulation. It would have required undue experimentation in view of this complete absence of guidance to make and use formulations across the entire scope of the claims, even where the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20, and the buffer comprises 5-25 mM buffer, let alone formulations having the claimed stability.

3. Claim 9 Is Not Enabled.

141. Claim 9 depends from claim 5 and specifies that the "buffer comprises a pH about 6.2-6.3." The specification merely contemplates the use of a single buffer, phosphate. ('865 patent at 2:49 – 3:10; *id*. at 3:32 – 4:6; *id*. at Examples 1-8). There is not a single example of a working formulation with a buffer other than phosphate. (*See* '865 patent at 8:37-41 (Example 1); 8:64 – 9:1 (Example 2); 9:24-28 (Example 3); 9:50-52 (Example 4); 10:18-20 (Example 5); 10:45-47 (Example 6); 11:5-8 (Example 7); 12:5-8 (Example 8)). Claim 9 also allows for any type of buffer that comprises a pH about 6.2-6.3, and combined with any stabilizing agent at any concentration. There simply is no indication in the '865 patent that the inventors possessed anything but a phosphate-buffered / sucrose-stabilized formulation. It would have required undue experimentation in view of this complete absence of guidance to make and use formulations across the entire scope of the claims, even where the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20, and the buffer comprises a pH about 6.2-6.3, let alone formulations having the claimed stability.

4. Claims 10 and 11 Are Not Enabled.

142. Claim 10 depends from claim 5 and specifies that the "stabilizing agent comprises a sugar." The specification merely contemplates the use of a single stabilizing agent, sucrose. ('865 patent at 2:49 – 3:10; *id*. at 3:32 – 4:6; *id*. at Examples 1-8). There is not a single example of a working formulation with a stabilizing agent other than sucrose. (*See* '865 patent at 8:37-41 (Example 1); 8:64 – 9:1 (Example 2); 9:24-28 (Example 3); 9:50-52 (Example 4); 10:18-20 (Example 5); 10:45-47 (Example 6); 11:5-8 (Example 7); 12:5-8 (Example 8)). Claim 10 also allows for any buffer having any concentration, and combined with a sugar at any concentration.

143. Claim 11 depends from claim 10 and specifies that the "sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol." The specification merely contemplates the use of a single sugar stabilizing agent, sucrose. ('865 patent at 2:49 – 3:10; *id*. at 3:32 – 4:6; *id*. at Examples 1-8). There is not a single example of a working formulation with a sugar stabilizing agent other than sucrose. (*See* '865 patent at 8:37-41 (Example 1); 8:64 – 9:1 (Example 2); 9:24-28 (Example 3); 9:50-52 (Example 4); 10:18-20 (Example 5); 10:45-47 (Example 6); 11:5-8 (Example 7); 12:5-8 (Example 8)). There simply is no indication in the '865 patent that the inventors possessed anything but a phosphate-buffered / sucrose-stabilized formulation. Claim 11 also allows for any buffer having any concentration, and combined with a sugar selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol, at any concentration. It would have required undue experimentation in view of this complete absence of guidance to make and use formulations across the entire scope of the claims, even where the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20, and the stabilizing agent comprises a sugar selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol, let alone

formulations having the claimed stability.

5. Claims 14-17 Are Not Enabled.

144. Claims 14-17 depend from claim 5. Claim 5 depends from 2 and specifies that the "organic co-solvent comprises 0.01% to 3% polysorbate 20." For at least the same reasons set forth above with respect to claims 1, 2, and 5, said discussion incorporated herein by reference, the '865 patent does not enable a person of ordinary skilled in the art to practice the full scope of claims 14-17 without undue experimentation.

145. Claims 14-17 also allow for any buffer having any concentration, and combined with any stabilizing agent at any concentration. There simply is no indication in the '865 patent that the inventors possessed anything but a phosphate-buffered / sucrose-stabilized formulation. It would have required undue experimentation in view of this complete absence of guidance to make and use formulations across the entire scope of the claims, even where the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20, and any type and concentration of buffer and any type and concentration of a stabilizing agent, let alone formulations having the claimed stability.

146. In addition, claim 17 specifies that "at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography." It would have required undue experimentation in view of the complete absence of guidance to make and use formulations across the entire scope of the claims, even where the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20, and any type and concentration of buffer and any type and concentration of a stabilizing agent, let alone formulations having the claimed stability for 24 months

6. Claim 18 Is Not Enabled.

147. Claim 18 depends from claim 5 and specifies that the "formulation does not contain phosphate." The specification merely contemplates the use of a single buffer, phosphate. ('865 patent at 2:49 – 3:10; *id*. at 3:32 – 4:6; *id*. at Examples 1-8). There is not a single example of a working formulation with a buffer other than phosphate. (*See* '865 patent at 8:37-41 (Example 1); 8:64 – 9:1 (Example 2); 9:24-28 (Example 3); 9:50-52 (Example 4); 10:18-20 (Example 5); 10:45-47 (Example 6); 11:5-8 (Example 7); 12:5-8 (Example 8)). Claim 18 also allows for any buffer except phosphate at any concentration, combined with any stabilizing agent at any concentration. There simply is no indication in the '865 patent that the inventors possessed anything but a phosphate-buffered / sucrose-stabilized formulation. It would have required undue experimentation in view of this complete absence of guidance to make and use formulations across the entire scope of the claims, even where the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises 0.01% to 3% polysorbate 20, and any type and concentration of buffer, except phosphate, and any type and concentration of a stabilizing agent, let alone formulations having the claimed stability.

148. For at least the reasons discussed above, the '865 patent Asserted Claims are not enabled such that one of ordinary skill in the art would understand how to practice the claimed invention without undue experimentation.

C. The Asserted Claims Are Invalid For Lack of Written Description.

149. In my opinion, the Asserted Claims are invalid for lack of written description. To the extent the Asserted Claims are not anticipated or obvious (in accordance with Dr. Rabinow's opinions), the '865 patent fails to provide sufficient support for the subject matter claimed. For example, the specification does not describe anything more than was taught in the prior art or was

known to a POSA at the time of the alleged invention, June 16, 2006. Accordingly, to the extent that the Asserted Claims are not anticipated or obvious over the prior art, in my opinion, the specification does not include a disclosure sufficient to convey to a POSA that the '865 patent inventors possessed the full scope of the claimed subject matter.

1. The '865 Patent Claims Are Directed to a Broad Genus of VEGF Antagonist Fusion Protein Formulations.

150. The '865 patent specification fails to provide written description support for the Asserted Claims, which cover a near-unlimited combination of excipients and concentrations. Further, the claims encompass broad, functionally-defined genera of formulations requiring stability properties. Despite claiming genera of formulations using functional language to define desired results (i.e., maintaining "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"), the '865 patent specification provides no guidance or common structural features for use in a formulation to obtain the claimed functionalities or desired result. The '865 patent also does not disclose a sufficient number of species to demonstrate the patentee invented the claimed genera of formulations. For example, as I describe in more detail above (¶¶ 124-25), the Examples provide only one (1) formulation that falls within the scope of the Asserted Claims. Likewise, every example in the specification uses phosphate as the buffer and sucrose as the stabilizing agent. There simply is no indication in the '865 patent that the inventors possessed anything but a phosphate-buffered / sucrose-stabilized formulation. The specification does not convey possession of the claimed genera of formulations comprising the claimed (near-unlimited) combination of excipients that achieve the claimed functionalities and desired results.

2. The '865 Patent Fails to Provide Written Description Support for the Claimed Genera of Formulations.

151. Claim 1 is directed to broad genera of formulations that comprise in several cases, genera of excipients in any concentration, including: (1) any type and amount of any buffer, (2) any type and amount of any stabilizing agent, (3) any type and amount of any "organic co-solvent"; (4) any amount of the required VEGF antagonist fusion protein that is glycosylated and comprises amino acids 27-457 of SEQ ID NO: 4, and (4) at any pH. ('865 patent at claim 1). These broad genera of formulations are not described anywhere in the '865 patent specification, and, in my opinion, a POSA would have understood that the claimed genera were different from, and not supported by, those discussed in the specification.

152. First, the '865 patent specification does not describe all buffers encompassed in the claim term "a buffer." Instead, the specification examples use a single buffer, phosphate. (*See*, *e.g.*, '865 patent at 2:49 – 3:10; *id*. at 3:32 – 4:6; *id*. at '865 patent at 8:37-41 (Example 1); 8:64 – 9:1 (Example 2); 9:24-28 (Example 3); 9:50-52 (Example 4); 10:18-20 (Example 5); 10:45-47 (Example 6); 11:5-8 (Example 7); 12:5-8 (Example 8)). As such, the specification fails to describe, at least, histidine containing formulations (falling within the scope of the claims) that possess the claimed functionalities.

153. Second, the '865 patent also does not describe all stabilizing agents encompassed in the claim term "a stabilizing agent." Instead, the specification examples use a single stabilizing agent, sucrose. (*See*, *e.g.*, '865 patent at 2:49 – 3:10; *id*. at 3:32 – 4:6; *id*. at '865 patent at 8:37-41 (Example 1); 8:64 – 9:1 (Example 2); 9:24-28 (Example 3); 9:50-52 (Example 4); 10:18-20 (Example 5); 10:45-47 (Example 6); 11:5-8 (Example 7); 12:5-8 (Example 8)). The specification does not demonstrate that a person of ordinary skill in the art would have recognized that the

patentee was in possession of the entire range of working formulations with any stabilizing agent having any concentration, and combined with any buffer at any concentration, or any organic co-solvent at any concentration.

154. Third, the '865 patent does not describe all organic co-solvents encompassed in the claim term "an organic co-solvent." Instead, the specification demonstrates the use of a single organic co-solvent, polyethylene glycol 3350. (*See*, *e.g.*, '865 patent at 2:49-57; *id*. at 2:63-67; *id*. at 3:36-40; *id*. at 8:64 – 9:1 (Example 2)). The specification does not demonstrate that a person of ordinary skill in the art would have recognized that the named inventors were in possession of the entire range of working formulations with ***any*** organic co-solvent (or "organic co-solvent compris[ing] polysorbate") at ***any*** concentration, combined with ***any*** buffer at ***any*** concentration, and ***any*** stabilizing agent at ***any*** concentration.

3. Dependent Claims 4, 7, 9, 11, and 14-18 Are Invalid For Lack of Written Description.

155. Claims 4, 7, 9, 11, and 14-18 depend either directly or indirectly from claim 1, and thus incorporate the elements of claim 1. Claims 4, 7, 9, 11, and 14-18 do not substantially narrow the scope of claim 1, and the specification fails to provide sufficient description for the genera of formulations claimed therein. Therefore, for at least the same reasons set forth above with respect to claim 1, said discussion incorporated herein by reference, the '865 patent does not convey to those skilled in the art that the named inventors were in possession of the full scope of claims 4, 7, 9, 11, and 14-18.

a. Claims 2 and 4 Are Not Adequately Described.

156. Claim 2 depends directly from claim 1 and specifies that "the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate." As discussed above, none of the Examples contain a concentration of a VEGF

antagonist fusion protein of 40 mg/ml and an organic co-solvent comprising polysorbate. Further, there is no description in the specification of how to use a polysorbate as an organic co-solvent (e.g., at what concentration does the polysorbate increase the solubility of the VEGF antagonist fusion protein). Therefore, the specification fails to provide sufficient description for the genera of formulations where "the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said organic co-solvent comprises polysorbate." As such, the specification does not demonstrate that a POSA would have recognized that the patentee was in possession of the entire range of working formulations with any buffer having any concentration, and combined with any stabilizing agent at any concentration, or any claimed concentration range of an "organic co-solvent" comprising polysorbate. In other words, in my opinion, the specification does not convey to a POSA that the patentee possessed the entire range of working formulations under claim 2—i.e., formulations with ***any*** buffer at ***any*** concentration, combined with ***any*** stabilizing agent at ***any*** concentration and ***any*** concentration of ***any*** organic co-solvent that comprises polysorbate.

157. Claim 4 depends from claim 2 and therefore, I understand that claim 4 requires the limitations of claim 2, notably, 40 mg/ml of the required VEGF antagonist fusion protein. Claim 4 further specifies that the "organic co-solvent ***comprises*** about 0.03% to about 0.1% polysorbate 20." First, I understand that "comprises" means "includes" (which I further understand leaves the "organic co-solvent" claim term open-ended) and therefore a POSA would understand the scope of claim 4 encompasses formulations with an "organic co-solvent" (so long as it includes 0.03% to about 0.1% polysorbate 20). As discussed above for claim 2, none of the Examples contain a concentration of a VEGF antagonist fusion protein of 40 mg/ml and an organic co-solvent comprising about 0.03% to about 0.1% polysorbate 20. Further, there is no description in the specification of a formulation using 0.03% to about 0.1% polysorbate 20 as the organic co-solvent.

Therefore, the specification fails to provide sufficient description for the genera of formulations where the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said "organic co-solvent comprises about 0.03% to about 0.1% polysorbate 20." A POSA therefore would not have understood the inventors to be in possession of formulations comprising the entire scope of claim 4. Likewise, the specification does not convey to a POSA that the patentee possessed the entire range of working formulations under claim 4—i.e., formulations with ***any*** buffer at ***any*** concentration, combined with ***any*** stabilizing agent at ***any*** concentration and ***any*** concentration of ***any*** "organic co-solvent" that comprises 0.03% to about 0.1% polysorbate 20.

b. Claims 5 and 7 Are Not Adequately Described.

158. Claim 5 depends from claim 2 and therefore, I understand that claim 5 requires the limitations of claim 2, notably, 40 mg/ml of the required VEGF antagonist fusion protein. Claim 5 further specifies that the "organic co-solvent ***comprises*** 0.01% to 3% polysorbate 20." First, I understand that "comprises" here is open-ended and means "includes," and therefore, a POSA would understand the scope of claim 5 encompasses formulations with an "organic co-solvent" (so long as it includes the recited 0.01% to 3% polysorbate 20). As discussed above for claim 2, none of the Examples contain a concentration of a VEGF antagonist fusion protein of 40 mg/ml and an organic co-solvent comprising about 0.01% to 3% polysorbate 20. Further, there is no description in the specification of a formulation using 0.01% to 3% polysorbate 20 as the organic co-solvent. Therefore, the specification fails to provide sufficient description for the genera of formulations where the concentration of said VEGF antagonist fusion protein is 40 mg/ml, and wherein said "organic co-solvent comprises about 0.01% to 3% polysorbate 20." A POSA therefore would not have understood the inventors to be in possession of formulations comprising the entire scope of claim 5. Likewise, the specification does not convey to a POSA that the patentee possessed the

entire range of working formulations under claim 5—i.e., formulations with ***any*** buffer at ***any*** concentration, combined with ***any*** stabilizing agent at ***any*** concentration and ***any*** concentration of ***any*** "organic co-solvent" that comprises 0.01% to 3% polysorbate 20.

159. Claim 7 depends from claim 5 and specifies that the "buffer comprises 5-25 mM buffer." The '865 patent does not provide adequate written description support for the full scope of "wherein said buffer comprises 5-25 mM buffer." First, the specification only contemplates the use of phosphate buffer. (*See*, *e.g.*, '865 patent at 2:49 – 3:10; *id*. at 3:32 – 4:6; *id*. at Examples 1-8). There is not a single example of a working formulation with a buffer other than phosphate. (*See*, *e.g.*, '865 patent at 8:37-41 (Example 1); 8:64 – 9:1 (Example 2); 9:24-28 (Example 3); 9:50-52 (Example 4); 10:18-20 (Example 5); 10:45-47 (Example 6); 11:5-8 (Example 7); 12:5-8 (Example 8)).

160. Second, there is not a single example of a working formulation with a buffer above 10 mM. The phosphate-buffered formulations disclosed and tested in Examples 1-6, contain 10 mM phosphate, and in Examples 7 and 8, contain 5 mM phosphate. (*See*, *e.g.*, '865 patent at 8:37-41 (Example 1); 8:64 – 9:1 (Example 2); 9:24-28 (Example 3); 9:50-52 (Example 4); 10:18-20 (Example 5); 10:45-47 (Example 6); 11:5-8 (Example 7); 12:5-8 (Example 8)). A POSA would not have understood the inventors to be in possession of formulations comprising the entire scope of this excipient in view of the limited teachings of the '865 patent. Third, the specification does not demonstrate that a POSA would have recognized that the patentee was in possession of the entire range of 40 mg/ml VEGF antagonist fusion protein formulations with ***any*** organic co-solvent that comprises 0.01% to 3% polysorbate 20 plus ***any*** buffer (or combination of buffers) having a concentration of 5-25 mM, combined with ***any*** stabilizing agent at ***any*** concentration.

c. Claim 9 Is Not Adequately Described.

161. Claim 9 depends from claim 5 and specifies that the "buffer comprises a pH about 6.2-6.3." The '865 patent does not provide adequate written description support for the full scope of "wherein said buffer comprises a pH about 6.2-6.3." First, I understand that "comprises" here is open-ended and means "includes," and therefore, a POSA would understand the scope of claim 9 (which depends from claim 5, which depends from claim 2) encompasses formulations with an "organic co-solvent" (so long as it includes the recited 0.01% to 3% polysorbate 20). Second, the specification only contemplates the use of phosphate buffer. (*See*, *e.g.*, '865 patent at 2:49 – 3:10; *id*. at 3:32 – 4:6; *id*. at Examples 1-8). There is not a single example of a working formulation with a buffer other than phosphate. (*See* '865 patent at 8:37-41 (Example 1); 8:64 – 9:1 (Example 2); 9:24-28 (Example 3); 9:50-52 (Example 4); 10:18-20 (Example 5); 10:45-47 (Example 6); 11:5-8 (Example 7); 12:5-8 (Example 8)). A POSA therefore would not have understood the inventors to be in possession of formulations comprising the entire scope of claim 9. In other words, the specification does not convey to a POSA that the patentee possessed the entire range of working 40 mg/ml VEGF antagonist fusion protein formulations under claim 9—i.e., formulations with ***any*** buffer comprising a pH about 6.2-6.3, combined with ***any*** stabilizing agent at ***any*** concentration and ***any*** concentration of ***any*** "organic co-solvent" that comprises 0.01% to 3% polysorbate 20.

d. Claims 10 and 11 Are Not Adequately Described.

162. Claim 10 depends from claim 5 and specifies that the "stabilizing agent comprises a sugar." Claim 11 depends from claim 10 and specifies that the "sugar is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol." The '865 patent does not provide adequate written description support for the full scope of claims 10 or 11.

163. First, I understand that "comprises" here is open-ended and means "includes," and therefore, a POSA would understand the scope of claims 10 and 11 (which both depend from claim 5, which depends from claim 2) encompasses formulations with an "organic co-solvent" (so long as it includes the recited 0.01% to 3% polysorbate 20). Likewise, the added limitations of claims 10 and 11 only require that the "stabilizing agent" ***includes*** a sugar (claim 10) or, more specifically sucrose, sorbitol, glycerol, trehalose, or mannitol (claim 11)—in other words, non-sugar stabilizing agents may also be included in the claimed formulation. Second, the specification contemplates the use of only sucrose as a sugar stabilizing agent. (*See*, *e.g.*, '865 patent at 2:49 – 3:10; *id*. at 3:32 – 4:6; *id*. at Examples 1-8). There is not a single example of a working formulation with a sugar stabilizing agent other than sucrose anywhere in the patent. (*See*, *e.g.*, '865 patent at 8:37-41 (Example 1); 8:64 – 9:1 (Example 2); 9:24-28 (Example 3); 9:50-52 (Example 4); 10:18-20 (Example 5); 10:45-47 (Example 6); 11:5-8 (Example 7); 12:5-8 (Example 8)). A POSA therefore would not have understood the inventors to be in possession of formulations comprising the entire scope of claims 10 or 11. In other words, the specification does not convey to a POSA that the patentee possessed the entire range of working 40 mg/ml VEGF antagonist fusion protein formulations under claim 10—i.e., formulations with ***any*** buffer at ***any*** concentration, combined with ***any*** stabilizing agent that comprises ***any*** sugar (or, more specifically sucrose, sorbitol, glycerol, trehalose, or mannitol) at ***any*** concentration and ***any*** concentration of ***any*** "organic co-solvent" that comprises 0.01% to 3% polysorbate 20.

e. Claims 14-17 Are Not Adequately Described.

164. Claims 14-17 depend from claim 5. Claim 5 depends from claim 2 and specifies that the "organic co-solvent ***comprises*** 0.01% to 3% polysorbate 20." For the same reasons I provide above for Claims 5 and 2, it is my opinion that a POSA would not have understood the

inventors to be in possession of formulations comprising the entire scope of claims 14-17.

165. In addition, claim 17 specifies that "at least 98% of said VEGF antagonist fusion protein is present in native conformation following storage at 5° C. for 24 months as measured by size exclusion chromatography." The specification does not provide a description of a formulation meeting the elements of dependent claims 5 and 2 while also demonstrating the specific stability at 24 months of claim 17. Therefore, a person of ordinary skill in the art would not have understood the inventors to be in possession of formulations comprising the entire scope of this claim in view of the limited teachings of the '865 patent.

f. Claim 18 Is Not Adequately Described.

166. Claim 18 depends from claim 5 and specifies that the "formulation does not contain phosphate." The '865 patent does not provide adequate written description support for the full scope of "wherein said formulation does not contain phosphate." First, the specification only contemplates the use of a single buffer, phosphate. (*See*, *e.g.*, '865 patent at 2:49 – 3:10; *id*. at 3:32 – 4:6; *id*. at Examples 1-8). Second, there is not a single example of a working formulation with a buffer other than phosphate. (*See*, *e.g.*, '865 patent at 8:37-41 (Example 1); 8:64 – 9:1 (Example 2); 9:24-28 (Example 3); 9:50-52 (Example 4); 10:18-20 (Example 5); 10:45-47 (Example 6); 11:5-8 (Example 7); 12:5-8 (Example 8)). A POSA would not have understood the inventors to be in possession of formulations comprising the entire scope of this excipient in view of the limited teachings of the '865 patent. Third, the specification does not demonstrate that a POSA would have recognized that the patentee was in possession of the entire range of 40 mg/ml VEGF antagonist fusion protein formulations with ***any*** organic co-solvent that comprises 0.01% to 3% polysorbate 20 plus ***any*** buffer (or combination of buffers other than phosphate) at ***any*** concentration, combined with ***any*** stabilizing agent at ***any*** concentration.

167. Separately, I understand the added element of Claim 18 constitutes a "negative claim limitation." I have been informed by Counsel that, for a negative claim limitation, an adequate written description is when, for example, "the specification describes a reason to exclude" the element, such as disadvantages of using the element or to distinguish alternatives. In my opinion, the specification does not provide adequate written description for the negative limitation, "wherein said formulation does not contain phosphate." First, the specification does not identify any disadvantages to using phosphate—instead, phosphate is not only the preferred buffer of the claimed formulation, it is the only buffer expressly disclosed in the specification. (*See*, *e.g.*, '865 patent at 2:39-48). Second, the negative limitation does not distinguish phosphate-containing formulations from other alternatives because the specification does not provide any alternatives. As I've mentioned, phosphate-containing solutions are the only formulations disclosed or described in the '865 patent.

168. For at least the reasons discussed above, the '865 patent Asserted Claims are invalid for lack of written description because the '865 patent does not convey to those skilled in the art that the named inventors were in possession of the full scope of the claims.

D. The Asserted Claims of the '865 Patent Are Invalid As Being Indefinite.

1. "An Ophthalmic Formulation Suitable For Intravitreal Administration" is Indefinite."

169. The '865 patent specification provides absolutely no guidance as to what type of formulation (e.g., what type and amount of buffer, organic co-solvent and stabilizing agent) would be considered "suitable for intravitreal administration." The only limitation relating to suitability of the claimed formulation is that "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." Otherwise, this claim term is purely subjective and prone to multiple,

inconsistent interpretations. Moreover, the claims are unlimited with respect to whom (or what) the formulation must be suitable, furthering the uncertainty of the Asserted Claims' scope. Consequently, in my opinion, the Asserted Claims are indefinite for this additional reason because they do not notify a POSA as to the full scope of the claimed formulation and therefore there is a zone of uncertainty around what constitutes infringement under the Asserted Claims.

170. Accordingly, the '865 patent Asserted Claims are invalid for at least indefiniteness because they fail to inform, with reasonable certainty, those of ordinary skill in the art about the scope of the invention.

IX. CLAIMS 6, 7, 12, 13, 18, 19, 22, and 23 OF THE '572 PATENT ARE INVALID UNDER 35 U.S.C § 112.[10]

171. I understand that Regeneron has asserted claims 1-23 and 25-30 of the '572 patent. I was asked to provide expert testimony on behalf of Mylan regarding the invalidity of claims 6, 7, 12, 13, 18, 19, 22, and 23 of the '572 patent under 35 U.S.C. § 112. In my opinion, for at least the reasons discussed below, these claims are invalid for lack of written description because the '572 patent does not convey to those skilled in the art that the named inventors were in possession of the full scope of the claims.

A. Claims 6, 12, 18, and 22 Are Invalid For Lack of Written Description.

172. In my opinion, claims 6, 12, 18, and 22 are invalid at least for lack of written description. To the extent these claims are not anticipated or obvious, the '572 patent fails to provide sufficient support for the subject matter claimed. For example, the specification does not

[10] I reserve the right to supplement my opinions in this regard in reply to any argument or opinion Regeneron and/or its experts assert regarding the meaning of the '572 patent terms ("isotonic solution" and "nonionic surfactant") and/or the presence or obviousness of those elements in the prior art, including whether those terms comply with other patentability requirements under 35 U.S.C. § 112, such as enablement and definiteness.

describe anything more than was taught in the prior art or was known to a POSA at the time of the alleged invention, January 13, 2011. Accordingly, to the extent that these claims are not anticipated or obvious over the prior art, in my opinion, the specification does not include a disclosure sufficient to convey to a POSA that the '572 patent inventors possessed the full scope of the claimed subject matter.

173. Claims 6, 12, 18, and 22 all state "wherein the aflibercept is formulated as an isotonic solution." There is no indication in the '572 patent that the inventors possessed an isotonic solution of aflibercept. The only mention in the '572 specification of "an isotonic solution" is in an exemplary statement that "[a]s the aqueous medium for injections, there are, *for example*, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc." ('572 patent at 6:22-25 (emphasis added)). A POSA therefore would not have understood the inventors to be in possession of formulations comprising the entire scope of claims 6, 12, 18, and 22. Further, there are many types of isotonic solutions, and as the specification lacks ***any*** examples or description of ***any*** isotonic solutions in ***any*** concentrations, the specification does not convey to a POSA that the patentee possessed the entire range of working formulations under claims 6, 12, 18, and 22.

174. For at least the reasons discussed above, claims 6, 12, 18, and 22 of the '572 patent are invalid for lack of written description because the '572 patent does not convey to those skilled in the art that the named inventors were in possession of the full scope of the claims.

B. Claims 7, 13, 19, and 23 Are Invalid For Lack of Written Description.

175. In my opinion, claims 7, 13, 19, and 23 are invalid at least for lack of written description. To the extent these claims are not anticipated or obvious, the '572 patent fails to provide sufficient support for the subject matter claimed. For example, the specification does not

describe anything more than was taught in the prior art or was known to a POSA at the time of the alleged invention, January 13, 2011. Accordingly, to the extent that these claims are not anticipated or obvious over the prior art, in my opinion, the specification does not include a disclosure sufficient to convey to a POSA that the '572 patent inventors possessed the full scope of the claimed subject matter.

176. Claims 7, 13, 19, and 23 all state "wherein the aflibercept is formulated with a nonionic surfactant." There is no indication in the '572 patent that the inventors possessed an aflibercept formulation containing a nonionic surfactant. The only mention in the '572 specification of "a nonionic surfactant" is in an exemplary and prophetic statement that:

> [a]s the aqueous medium for injections, there are, *for example*, physiological saline, an isotonic solution containing glucose and other auxiliary agents, etc., *which may be used in combination with an appropriate solubilizing agent* such as an alcohol (e.g., ethanol), a polyalcohol (e.g., propylene glycol, polyethylene glycol), *a nonionic surfactant* [e.g., polysorbate 80, HCO-50 (polyoxyethylene (50 mol) adduct of hydrogenated castor oil)], etc.

('572 patent at 6:22-30 (emphasis added)). A POSA therefore would not have understood the inventors to be in possession of formulations comprising the entire scope of claims 7, 13, 19, and 23. Further, there are many types of nonionic surfactants, and as the specification only gives two examples of nonionic surfactants and lacks any specific description of using ***any*** nonionic surfactant in ***any*** concentration in a formulation, the specification does not convey to a POSA that the patentee possessed the entire range of working formulations under claims 7, 13, 19, and 23.

177. For at least the reasons discussed above, claims 7, 13, 19, and 23 of the '572 patent are invalid for lack of written description because the '572 patent does not convey to those skilled in the art that the named inventors were in possession of the full scope of the claims.

X. FUTURE OPINIONS.

178. This Report sets forth the opinions I have formed based on information available as of the date of this report. Because other as yet unknown and unidentified material may be introduced during this litigation, which may fall within my area of expertise, I may have relevant and important opinions regarding such as yet unknown and unidentified material. I reserve the right to be able to offer such opinions if they may become relevant or important as such material becomes known. I further reserve the right and intend to testify and offer additional opinions in response to any opinions offered by Regeneron or its purported experts.

179. I further reserve the right to supplement or amend this Report based on additional information made available to me, including in light of ongoing fact discovery (including third party discovery) and any expert reports submitted on behalf of Regeneron, or in order to clarify the information provided herein. I also reserve the right to supplement or amend this Report in light of any claim interpretations (or changes or supplements thereto) made by the Court.

XI. TRIAL EXHIBITS/TUTORIAL.

180. If I testify at trial in this case, I may rely on exhibits and/or visual aids to demonstrate the basis for my opinions. I have not yet prepared any such exhibits or visual aids. I also reserve the right to provide a tutorial relating to the general topics contained in this report, including a discussion of the prior art references discussed herein.

XII. COMPENSATION.

181. I am being compensated for the time I have spent on this litigation at [redacted] per hour for work and [redacted] per hour for live testimony performed, plus reasonable expenses for all time spent working on this matter. My compensation is not at all dependent upon the substance of my opinions or testimony, or the outcome of this case.

XIII. PRIOR TESTIMONY.

182. In the last four years, I have testified in the following case: *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, 1-22-cv-00061-TSK (N.D.W. Va.) (deposition).

Dated: February 2, 2023

[redacted]
h.D.

Exhibit T

IN THE UNITED STATES DISTRICT COURT

FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

REGENERON PHARMACEUTICALS, INC.,

Plaintiff,

vs.

MYLAN PHARMACEUTICALS, INC.,

Defendant.

Case No. 1:22-cv-00061

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*** OUTSIDE COUNSEL EYES ONLY ***

REMOTE VIDEO DEPOSITION OF

KENNETH S. GRAHAM, Ph.D.

January 19, 2023

9:11 a.m. Eastern

Stenographically Reported By:

Deanna Amore - CRR, RPR, CSR - 084-003999
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ALSO PRESENT:
Tim Tupiak, Legal Videographer
Michael Toth, Concierge
James Evans, Regeneron, Senior Director, Assistant General Counsel, Dispute Resolution

I N D E X

EXHIBITS

THE VIDEOGRAPHER: Good morning. We are going on the record. The time is 9:11 a.m. Eastern time on January 19, 2023.

Quality of recording depends on quality of camera and Internet connection of participants. What is heard from the witness and seen on the screen is what will be recorded.

Audio and video recording will continue to take place unless all parties agree to go off the record.

This is Media Unit No. 1 in the video-recorded deposition of Kenneth Graham, taken in the matter of Regeneron Pharmaceuticals, Incorporated versus Mylan Pharmaceuticals, Incorporated filed in the United States District Court for the Northern District of West Virginia, Case No. 1:22-cv-00061-TSK.

My name is Tim Tupiak. I'm the videographer. The court reporter is Deanna Amore, and we are both with the firm Veritext Legal Solutions.

I am not related to any party in this action, nor am I financially interested in the outcome.

If counsel will now state their

appearances for the record, beginning with the noticing attorney, after which the reporter will administer the oath.

MR. SALMEN: Heinz Salmen, of RMMS, on behalf of defendant, Mylan Pharmaceuticals, Inc. With me today are Eric Hunt, also of RMMS, and Scott Beall, also of RMMS, on behalf of defendant, Mylan.

MR. FLETCHER: Thomas Fletcher, Williams & Connolly LLP, for the plaintiff, Regeneron Pharmaceuticals, Inc. With me is my colleague from Williams & Connolly, Arthur Argall. Also present from Regeneron Pharmaceuticals, Inc., are in-house counsel James Evans and Andrew Gesior from Weil Gotshal.

THE STENOGRAPHER: Good morning, Counsel. Do all parties agree to the remote swearing and that it will be admissible in this proceeding?

MR. SALMEN: Yes.

Do we have local counsel on? Do they need to --

MR. SPIKER: Yes. Good morning. This is Garrett Spiker, of Steptoe & Johnson, in Bridgeport, West Virginia, appearing on behalf of Mylan.

MR. POGUE: David Pogue, Carey Douglas

Kessler & Ruby, on behalf of Regeneron.

MR. FLETCHER: We also consent to the remote administration of the oath.

MR. SALMEN: Yes.

(Whereupon, the witness was duly sworn.)

THE WITNESS: Yes.

THE STENOGRAPHER: Thank you.

You may proceed.

KENNETH S. GRAHAM, Ph.D.,

called as a witness herein, having been first duly sworn, was examined and testified as follows:

EXAMINATION

BY MR. SALMEN:

Q. Good morning, Dr. Graham. My name is Heinz Salmen. As I said, I represent Mylan in this matter, and I'll be questioning you today.

Dr. Graham, can you please describe your educational background beginning after high school?

A. Beginning after high school?

Q. Yes, please.

A. What do you want me to detail?

Q. Did you go to undergraduate school?

A. I did an undergraduate degree at Penn State.

Q. And what was your -- the major for your degree?

A. It was animal bioscience.

Q. When did you graduate?

A. 1983.

Q. And what did you do after graduating Penn State in 1983?

A. Went in for knee surgery.

Q. Let me be more specific. Did you go into the workforce after graduating Penn State, or did you pursue an additional degree anywhere?

A. So I worked for a period of time at the university as a laboratory technician.

Q. What type of laboratory did you work in?

A. So when I was an undergrad, I started working in the laboratories in the veterinary science department. I was conducting studies on vitamin E lipid membrane peroxidation, looking at the role of certain enzymes in those pathways. So it was kind of a biochemical laboratory with a focus on animal research. So we were evaluating the impact of certain nutritional supplements on these parameters, so specifically looking at selenium and vitamin E.

Q. And do you recall what years you were

working in that lab?

A. So I started after my freshman year in the university. I think I first set foot in the lab in fall of 1980.

Q. And when did you stop working at the lab?

A. In 1986.

Q. Okay. Did I understand you correctly earlier? You said you graduated 1983?

A. I graduated in 1983 with my bachelor's, yes.

Q. Okay. And did you continue with an advanced degree after 1983?

A. Yes.

Q. Can you describe that, please?

A. So while I was at Penn State, the research that I was working on, I looked at it and thought, "Well, gee, you know, I can get a degree with this." So I enrolled in the graduate program and got a master's in veterinary science, specifically looking at the biochemistry involved in lipid membrane peroxidation, arachidonic acid metabolism with the taurines, glutathione peroxidases, roles of glutathione, and certain nutritional aspects as well.

Q. When did you obtain your master's degree?

What year?

A. So I defended my master's dissertation in the summer of 1986, and I believe the degree was conferred in December of '86.

Q. Did you go on to obtain a Ph.D. after that?

A. Yes.

Q. Can you describe that educational background?

A. Yes.

Q. Please describe your Ph.D. work.

A. Okay. So my Ph.D. program involved a number of different aspects. I was focused in on two or three major areas within the realm of protein DNA binding.

One aspect of my research involved looking for sequence-specific recognition of DNA, how specific a specific class of protein could delineate one DNA sequence for another.

Also, performed work looking at how and where a specific DNA binding protein interacted with the sequence of interest.

In addition to that, I did some work developing what I would describe as a synthetic enzyme that would cut DNA at a specific single

nucleotide point. I characterized that cleavage reaction studying the mechanism by which the hydrogen was extracted from the ribose backbone that comprised the DNA.

And also looked at the nature of the metal-mediated cleavage that was occurring in the molecule or produced by the molecule when it encountered DNA.

Q. Was your Ph.D. work also done at Penn State?

A. No.

Q. What entity were you at there, university?

A. I was at the California Institute of Technology.

Q. Can you tell me the years that you worked on your Ph.D. at the California Institute of Technology?

A. So September of 1986 I joined the university and defended my dissertation in 1982 in the fall.

Q. 1992?

A. 1992 in the fall. I think I may have said '82.

Q. It could have been the microphone. I wasn't sure either.

You -- I'm sorry. Just to clarify, you received your Ph.D. in the fall of 1992?

A. Well, that's when I defended my thesis.

Q. Okay. And when was it granted?

A. So I walked in 1993 when they had the next graduation.

Q. Any other degrees that you obtained after graduating in 1993 with your Ph.D.?

A. No.

Q. And what was your first job after graduating Cal Institute of Technology in 1993?

A. Well, in fall of 1992, I joined the Beckman Research Institute of City of Hope, and I was in their department of molecular biology, I think was the appropriate term, at that point in time.

Q. So you started there in 1992?

A. In 1992 in the fall, yes.

Q. How long -- how many years were you at Beckman?

A. Well, I was at the Beckman Research Institute of City of Hope. That's different than Beckman, which is a company.

Q. Okay. Sorry. Yeah, I misunderstood. Let me ask the --

A. Go ahead.
Q. Let me ask the question.
How long were you at the Beckman Research Institute City of Hope in the department of molecular biology?
A. About nine years, almost ten.
Q. So through 2002 about?
A. Well, the end of 2001.
Q. Okay. Can you describe your roles and responsibilities -- well, let me first ask -- strike that last question.
What was your title when you first started -- can I just refer to it as "Beckman" for shorthand?
A. How about City of Hope?
Q. City of Hope. Okay.
What was your title when you started at City of Hope in 1992?
A. I believe it was research fellow.
Q. And then did you have any other titles after the nine to ten years that you were there?
A. When I left, I think I was considered a research scientist or possibly assistant professor I think is where we ended up with the description on that.

Q. Did you -- during those years, did you have classes that you oversaw?

A. So City of Hope was a research institute. At the time we did not offer coursework. During my tenure there, we did start a graduate program, and coursework was begun to be offered about the time that I left. But I did not teach formal courses. I did give seminars and lectures and had a small group of research associates or physicians that I did train over the course of the years.

Q. With regard to the seminars and lectures that you gave at City of Hope, what was the technical focus of those seminars or lectures?

A. Well, some of it involved characterization of proteins, specifically, antibodies.

Some of it involved chemistry involved with sequential degradation of proteins and peptides using chemical means for the purpose of determining the protein sequence.

I believe I did talk at least on one occasion about some mass spectral analyses and approaches to things.

Did some work on organic synthesis of some organophosphoreal compounds and characterization of those.

Q. At that time in your career, 2001, would you -- did you have an expertise in any technical area?

A. Yes.

Q. How would you describe that expertise in 2001?

A. So I would say I had expertise in a number of different areas at that point.

I was very skilled at performing metabolite analysis in animals.

I was exceptionally skilled at the analysis of tocopherols and tocopherol oxidation products as well as characterizing the enzyme kinetics of glutathione peroxidases and transferases.

I had expertise in the area of DNA synthesis or DNA expression as well as DNA purification and sequencing and characterization by multiple methods.

I had done work looking at the impact of deuterium in conducting kinetic isotope effects, quantifying those.

Had expertise in quantitative gel analysis using both radiolabel DNA and via other mechanisms such as staining.

I was experienced with handling multiple types of radionucleotides and utilizing them either for the purpose of metabolism tracer studies or other types of visualization.

I had done protein conjugation and knew how to conjugate reactive species or species capable of producing reaction to a specific protein in a specific location for the purpose of either mapping the position or location of the protein when it bound to another substance or substrate.

I was skilled in protein sequencing, amino acid analysis, mass spec, HPLC, NMR.

So I had a fairly wide repertoire of things. I was an expert on analysis of certain aspects of proteins, particularly their sequence and characterization of that.

Q. During those years, 1992 to 2001, at City of Hope, did you do any expert consulting work outside of your work for City of Hope?

A. I did.

Q. And can you generally describe your expert consulting experience during that time?

A. Well, I did a couple of different things.

One aspect of what I did was worked with a middle school in Los Angeles and helped them

develop a science curriculum. It was a hands-on science curriculum for the students, and actually, that won a blue ribbon from the U.S. Department of Education for being a novel way to train young individuals on science.

Other consulting that I performed was with primarily two companies. One was Hewlett Packard Instruments, now Agilent Technologies, and the other was Applied Biosystems.

Q. Applied -- I'm sorry. Applied Bio?

A. Systems. ABI.

Q. Okay. Systems.

A. Yeah.

Q. For the -- for your consulting work with HP and ABI, were you ever involved in any litigation as an expert consultant for those companies?

A. No, I was not.

Q. Can you describe your work experience after you left City of Hope in 2001?

A. Well, I left City of Hope in the fall of 2001 and pretty much immediately started working for Regeneron in January of 2002. We had a little bit of time. We had to move across country and do some stuff. So I had a month or two of downtime in

there, but my next job really was Regeneron Pharmaceuticals.

Q. And what was your first title at Regeneron?

A. I think it was supervisor of process sciences. I'm not sure to be honest with you.

Q. So before we go to the first exhibit, Dr. Graham, let me ask you a couple other background questions.

Have you been deposed before?

A. Yes.

Q. How many times have you been deposed?

A. I think this is the fourth time.

Q. Okay. You seem to have a good comfort with the process. So...

A. Well --

Q. When was the last time --

A. I'm as comfortable with this as I can be with anything like this. So...

Q. When was the last time you were deposed?

A. Well, I can't give you an exact date. I want to say earlier this year. It might have been the end of last year. Well, wait a minute. We are in 2023. So it was at some point in 2022, I think.

Q. So we are all on the same page, that was -- were you testifying as a fact witness for Regeneron in that deposition?

A. Yes.

Q. And do you recall the parties of that litigation?

A. I do.

Q. Who were the parties?

A. It was Regeneron and Novartis.

Q. And did that have to deal with a patent infringement litigation?

A. It did.

Q. Was Novartis the plaintiff in that litigation?

A. What do you mean by the "plaintiff"?

Q. Was Novartis the patentee or the patent owner in that litigation?

A. Yeah, I do believe the patent was owned by Novartis, yes.

Q. And what was the subject matter of the patent that Novartis owned in that litigation?

A. So are you asking me for the details of the patent in question?

Q. Yes.

A. All right. To the best of my

recollection -- and I apologize -- I don't have the patent in front of me -- the question involved a patent on a prefilled syringe that was produced using a bait silicone technology, and it specifically was talking about using this bait silicone technology which had been developed by a company named Vetter Pharmaceuticals in conjunction with an anti-VEGF product for intravitreal injection.

Q. Was that anti-VEGF product that the syringe was developed in conjunction with Lucentis or ranibizumab?

A. So the syringe that was the subject of the patent?

Q. Yeah.

A. No, actually, the syringe had been developed quite some time before. It was a standard offering by the Vetter Pharmaceutics, and they had used it in other areas. We actually had purchased the syringe from Vetter Pharmaceutics and used it some years prior to Novartis during some development work we had performed on Eylea.

Q. Just so I understand that correctly, the Vetter syringe is the prefilled syringe that you used during some of your work in developing the

Eylea formulation?

A. It was what we used during development of an Eylea drug product that was contained in the prefilled syringe.

Q. And were you testifying -- I may have asked this. Were you testifying as a fact witness or an expert in that case?

A. All right. Could you please define the difference for me as to what a fact witness and what an expert is?

Q. Sure.

Were you testifying with respect to Regeneron's development of its own prefilled syringe in that matter?

A. And that would be what type of a witness?

Q. That would be a fact witness.

A. Okay. And what is the definition of an expert witness?

Q. Well, can you answer the first question first, please?

Were you testifying with respect to Regeneron's development of a PFS or prefilled syringe or prefilled syringe formulation?

A. Okay. You've just said a whole bunch of stuff there. I'm sorry. You kind of lost me. Can

you take a step backwards, please?

Q. Sure.

Were you separately retained by Regeneron in that matter as an expert consultant outside of your normal roles and activities as an employee of Regeneron?

A. What do you mean by "separately retained"?

Q. Okay. Why don't we strike the question. We'll try to get back to it later.

When you started at Regeneron in January 2002, what was your title again?

A. I think I was a supervisor of process sciences, and I would have to go back and look. I mean, in all honesty, it's 20 years ago. So...

Q. If you look at, in the binder that we provided, Exhibit 704. This appears to be an organizational chart. Would you agree with that?

A. Hang on.

It does appear to be an organizational chart, yes.

Q. Can you tell me where your first role and title as supervisor of process science would fall in this organizational chart?

A. Well, it's -- so the organization that I was part of, I believe, at the time, reported

through Len Schleifer.

Q. Can you spell that name, please?

A. Len Schleifer?

Q. Oh, he's at the top. I see.

Were you part of the formulations and stability group that Dan Dix was the head of?

A. At what time?

Q. When you started in 2002?

A. No, I was not.

Q. So your initial department, does it appear on this organizational chart?

A. Well, so this is not an organizational chart of departments. This seems to be -- potentially have some departments in it, but it has programs -- it has a slot that states "Clinical Supplies," which I'm not sure whether -- what you mean by that as a department. So it would be difficult for me to appropriately bin where I fall in because it's possible, depending on how you interpret things, I could be in one or more of these areas.

Q. Okay. Just so we are on the same page, Dr. Graham, do you see at the bottom right-hand corner of this document, there's what we call a Bates number there, RGN-EYLEA?

A. Yes.

Q. Do you understand from -- that that Bates numbers reflects that this document was produced by Regeneron to Mylan in this matter?

A. Okay. What about it defines that it was produced by Regeneron to Mylan?

Q. Well, here, let me show you a different document.

MR. SALMEN: Mike, can we bring up Tab 3, please, Bates No. 00518628?

BY MR. SALMEN:

Q. And, Dr. Graham, you'll have to look at the screen for this one.

(Stenographer clarification.)

THE WITNESS: So that's showing up -- I thought the exhibits were showing up on the right-hand computer.

THE TECHNICIAN: That's probably -- are you talking about Exhibit Share?

Heinz, what do you want to mark this as? What exhibit?

MR. SALMEN: Could we mark it as Exhibit 734, please?

(Whereupon, Exhibit 734 was marked for identification.)

THE TECHNICIAN: Okay. It will be up there in just a second.

THE WITNESS: For me to read that, I am either going to have to grab the computer and drag it closer to me.

THE TECHNICIAN: Okay. Mr. Graham, it is in the Marked Exhibits folder. Each time an exhibit is introduced into the Marked Exhibits folder, you'll have to refresh your browser to see it. The easiest way to do that is to click on the Marked Exhibits folder in the folder tree on the left. That will refresh your browser for you. When you go in, just click on the PDF, that will open it up. There will be a "Comment" section on the right. You can close that "Comment" section. You don't need it.

Then, also, as you hover over the page with your mouse, a black bar will appear at the bottom. That is your navigation bar to page up, page down, zoom in, zoom out, and rotate, any annotations like that.

THE WITNESS: So I should be clicking on this folder here?

THE TECHNICIAN: Yeah. We can't see what you're looking at in the Exhibit Share, so -- but it's the Marked Exhibits folder, and then you'll click on Exhibit 734, and it will open up. It is also appearing on your Zoom screen as well.

THE WITNESS: It's thinking about it.

MR. FLETCHER: We have the document up in Exhibit Share, and we've also just printed a copy. You can actually use this print copy.

THE WITNESS: Yeah, we are using the print copy, that is for sure.

MR. SALMEN: Okay. Thank you, Mr. Fletcher.

BY MR. SALMEN:

Q. So, Dr. Graham, do you see, on the bottom right-hand corner of this exhibit, it says "Regeneron"?

A. Are you talking about Regeneron in the box?

Q. Yes.

A. Yes, I see that.

Q. And on the bottom left-hand corner it says "Confidential"?

A. Yep.

Q. And if you want to -- I'm not going to ask you any specific questions about the contents of

the rest of this document other than the front page, but if you want to flip through this and just confirm for me that this is a Regeneron document.

Do you agree that this is a Regeneron document?

A. Hold on. I haven't made it all way through it yet.

It appears to be a Regeneron presentation, yes.

Q. And going back to my previous question, can you identify where you fit in this organizational chart?

A. Yes, on this one I can.

Q. And where would you fit in this chart?

A. Okay. So you have a gentleman by the name of Randall Rupp.

And to be clear, this is in 2002 when I joined Regeneron; correct?

Q. Yes.

A. So you have a gentleman named Randall Rupp. Mr. Rupp was the senior vice president of manufacturing. So at the time I joined Regeneron, I was part of the pilot manufacturing group or team, and I worked to make clinical drug supplies. My role was involved in both manufacturing aspects

and product quality aspects.

Q. So in 2002, when you started at Regeneron, were you reporting directly to Dr. Rupp?

A. You mean Dr. Rupp?

Q. Dr. Rupp. Sorry.

A. Okay. So he was my vice president. My direct boss was a gentleman by the name of John Mitschelen, and he reported directly to Randy, but we had somewhat of a matrix-based organization. So I did receive guidance directly from Randy.

Q. With respect to the role that you mentioned of making clinical drug supplies, can you describe what that entailed?

A. Sure.

So I joined the pilot manufacturing facility and the manufacturing group at Regeneron in January of 2002. At the time I was supposed to be splitting my time between the manufacturing site in Albany and the manufacturing site, the GMP facility, that we had down in Tarrytown. I did a number of different things for the manufacturing facility.

One was I directly managed and supervised the bioanalytical testing lab that was in Tarrytown. This lab performed in-process and QC

release testing of certain items.

Additionally, I worked with the folks on the manufacturing floor to define column cut criteria and pooling criteria which were used to define the characteristics of the ultimate product that was used for clinical dosing.

My role, over the course of the year or so, expanded, and I became also responsible for certain aspects of the manufacturing facility as well as involved in selection of equipment and things that were used in the manufacturing facility. My lab was responsible for testing and ensuring the quality of critical components like pharmaceutical air, any of the gases that were used in the bioreactors, the water for injection as well as the RODI that was used at certain points within the facility.

We also got involved in assessing some challenges with corrosion that occurred in a heat exchanger and bioreactor. Really kind of a neat story there. We had a new bioreactor, and it kept blowing out heat exchangers, and it really came down to that this bioreactor's heat exchanger was dual function. You know, it worked off of both clean steam, which was another utility that we

monitored the quality of, and the circulating glycol loop, and that circulating glycol loop was set up only to be a cooling loop and had a specific type of glycol in it that provided no corrosion protection at high temperatures.

So when we went to the heat exchanger that was dual function, both heating and cooling, for the bioreactor, after so many heat cycles, it would perforate because the glycol would not prevent corrosion. So we actually swapped out the glycol in the entire cooling system to correct the problem.

Q. Dr. Graham, what products were in manufacture at Regeneron at this time in your first year there, 2002?

A. So during the first year of 2002, we were working on or getting ready to work on two things.

When I initially joined in January, we were making campaigns of a recombinant protein that is called IL1 Trap. It's actually now a marketed product which is Arcalyst. It was the first product Regeneron got approved. So we worked on that about through the middle of the year. I couldn't give you the exact date when we finished the last lot of that material.

And then in -- somewhere in the middle of the year or the fall, we began the process of changing over and switched from manufacturing of Arcalyst to what I really like to refer to as the first product I really touched at Regeneron which was a molecule that we referred to at the time as VEGF Trap.

Q. All right. So before we get to VEGF Trap, the IL1 Trap, if I understand your testimony correctly, you were working in the manufacturing facility to prepare product that was going to be sold on the market?

A. No, not at that time.

Q. Okay. So it was for clinical trial product?

A. Yes.

Q. When was the Arcalyst product approved by FDA?

A. You know, I'd have to go look up the exact date. I don't know when it was approved. I want to say 2006, but to give you an accurate answer, I would really have to take time and look it up.

Q. With respect to the IL1 Trap product, did you have any involvement in developing the formulation for that product?

A. No, I did not. You know, we produced the formulation of that product. We tested it.

Q. Was it a liquid formulation?

A. So the marketed form of Arcalyst or IL1 Trap is a lyophilized formulation.

Q. What's a lyophilized formulation?

A. So lyophilization is a process whereby you take a solution, liquid formulation, you freeze it, and at temperatures that are below the collapse point of or melting point of that solution, you remove the liquid or moisture in this case from the product. It's also referred to as freeze-drying.

So basically what you do is, in the case of Arcalyst, you have an aqueous solution that contains the drug and the excipients. You fill that into a vial, and, you know, you put a series of these vials into what's called a lyophilizer or freeze-dryer. You cool it, cool it to the point that it's frozen. Once it's fully frozen, you set your shelf at a defined temperature, and you pull a vacuum on it. In response to the vacuum, the water sublimes. So without going through a liquid state, you remove the water, and you're left with a solid behind.

Q. And then is that solid reconstituted with

anything before it's administered to the patient?

A. In this case, yes.

Q. What is it reconstituted with?

A. For Arcalyst, we used water for injection.

Q. What was Arcalyst used to treat?

A. So it treats an orphan indication which is cold -- okay. So it's -- it's a cold-induced autoimmune response. It's sometimes referred to as CAPS or FCAS. What happens in this case is if somebody has the disease, if they were to go from a warm room into a cold room, so, like, say, the middle of summer in the northeast or in the south, walking into an air conditioned room, in the mild form, that patient would break out in hives. In the more severe form, the disease produces Muckle-Wells-type symptoms including joint disfiguration. I mean, it's really a very insidious disease.

I actually met a patient that takes our drug. She and both her children have the disease. We were waiting in line to go into a movie theater in the middle of summer, and, you know, she realized, from the course of the conversation that my wife and friends were having, that I work for Regeneron.

And she goes, "Wow. This is a lifesaving drug for me. It has completely altered my life" because she and her children could not go to a movie because it was too cold, and they would end up in severe pain or with hives. And it completely freed her up and gave her her life back is the description she used to me.

Q. How is Arcalyst administered?

A. It is a subcutaneous injection.

Q. So is it a sterile liquid formulation?

A. Yes.

Q. And you said it's reconstituted with water. Was that correct?

A. It's reconstituted with sterile water for injection.

Q. What were the other components of that formulation?

Let me ask, more specifically, was there a buffer in that formulation?

A. Yes, I believe so.

Q. What was the buffer?

A. I would have to look it up. Arcalyst is not one of my products. I can find the information for you.

Q. No. That's okay.

Do you recall if there's a stabilizing agent in that formulation?

A. So if we are going to go through the composition of Arcalyst, I'd really like to look it up, you know, before we continue.

Q. Okay. Do you recall if there was an organic cosolvent in the formulation?

A. If we are going to continue this way, can I please go to the FDA website, download the product insert, and then I can speak accurately to the product's composition?

Q. We'll try to get you that document maybe for the next session.

You said earlier that the first product you touched at Regeneron was VEGF Trap-Eye. Do you recall that testimony?

A. I said I'd like to refer to VEGF Trap as the first product I truly touched at Regeneron, yes.

Q. What was your first involvement with VEGF Trap-Eye at Regeneron?

A. Okay. So let's be clear. My first involvement was with VEGF Trap. At that time I did not know that it was going for an eye indication.

What I did -- you know, we were getting

ready to do a manufacturing campaign, and we had to do a series of tests in process on the product to ensure that we would ultimately have a product that was of desirable quality at the end of the manufacturing campaign.

Some of these assays, and the sentinel assay that we used, primarily required a very long time to perform, you know, on the order of 90 to 120 minutes, and, you know, we were being asked to analyze 30 to 60 samples and make pooling decisions on the product within less than 24 hours.

So the first thing that I did was optimize or produce new methods that were much faster and, you know, provided the same answer that the older, slower methods did. So that was around in-process testing to ensure product quality.

Q. And just so I'm clear, the in-process testing methods that you optimized, those were for VEGF Trap samples?

A. Yes.

Q. And so I'm still speaking within that first year time frame. When did you -- when were you informed that VEGF Trap was going to be seeking an eye indication?

A. I think I learned about that at some point

during 2002. I couldn't give you the exact date.

Q. What was the --

A. Or excuse me. 2003.

Q. 2003. Okay.

(Simultaneous speaking.)

THE WITNESS: -- I was at the company.

BY MR. SALMEN:

Q. What was the original indication that VEGF Trap was pursuing when you were running these optimizations of in-process testing?

A. So the indications that we were -- or the company was looking at, by my understanding and my recollection, involved oncology and were looking at diseases where there were tumors, and the idea was to stop tumor growth, if I have it correct.

Q. And was that indication, that oncology indication, that Regeneron was pursuing based on VEGF Trap being an antagonist of VEGF?

A. I believe so, yes.

Q. Okay. What does it mean to be a VEGF antagonist?

A. Okay. I'm somewhat dyslexic so I may have it backwards, but by my recollection, an antagonist prevents the action of the thing that you are blocking. So if VEGF produces blood vessels, a

VEGF antagonist would prevent the VEGF from producing blood vessels.

Q. Without going back to your optimization of in-process testing activities, what was the formulation of VEGF Trap at that time?

A. For what purpose?

Q. For the purposes that you were running analytical testing on those samples.

A. Okay. So --

Q. So let me ask a better question.

The samples of VEGF Trap that you were developing in-process testing for, what was the form of the sample? Was it a liquid?

A. Okay. So we kind of spun around in circles here. Let me make sure I understand what you're asking. You're asking me that were the in-process samples of VEGF Trap that I tested in a liquid form?

Q. Yeah. Let me clarify the question.

The in-process samples that you were testing, were those drug substance samples?

A. They would be what we would -- well, no, actually -- okay. This was -- these were in-process samples during the course of the manufacturing process. The first stopping point in

the manufacturing process is drug substance. So my in-process samples are not drug substance. They are intermediates that occur prior to drug substance.

Q. Okay. Let me direct your attention to the patent at issue here. So let's go to in your binder, you should have a copy of this Defendant's Exhibit 703. This was previously marked.

A. So that would be DX 703?

Q. Yes.

Do you recognize this patent?

A. Hang on a second. I'm still struggling with your binder here.

Q. Do you recognize this patent, Dr. Graham?

A. Give me a moment. I've seen a lot of patents recently, and I want to make sure that I know what I'm looking at.

Yes, I recognize the patent.

Q. And I'm going to refer to this as the '865 patent. Is that okay?

A. And that's based on what?

Q. If you look in the upper right-hand corner of the sheet that you're looking -- page that you're looking at, it says "US 11,084,865"; is that

correct?

A. Okay. 865 B2, yes.

Q. For shorthand I'm going to refer to this as the "'865 patent." Is that acceptable?

A. Okay.

Q. If you look on the left-hand column, there is a parenthetical (54) that reflects the title. Do you see that?

A. By parenthetical, do you mean in parenthesis?

Q. Yes. The number 54.

A. Yes.

Q. And the title here is "VEGF antagonist Formulation Suitable for Intravitreal Administration"?

A. Yes.

Q. And you're named as an inventor here; correct?

A. Yes.

Q. I'll direct you to the abstract on this page, which is in the bottom right-hand corner. It states, quote, "Ophthalmic formulations of a vascular endothelial growth factor (VEGF)-specific fusion protein antagonists are provided suitable for intravitreal administration to the eye. The

ophthalmic formulations include a stable liquid formulation, a lyophilizable formulation. Preferably the protein antagonist has an amino acid sequence of SEQ ID NO:4."

Do you see that?

A. I do.

Q. Now, just before I ask my first question, Dr. Graham, I want to give you more context. If you turn to the claims of this patent, which appear on the last two pages, columns 19, 20, 21, and 22?

A. I see the claims, yes.

Q. Okay. So looking at claim 1, Dr. Graham, can you tell me what your contribution was to this claim as an inventor?

MR. FLETCHER: Objection.

THE WITNESS: Okay. What do you mean by "my contribution"?

BY MR. SALMEN:

Q. Well, I mean that you're identified as an inventor on this patent. So I'd like to know if you -- if and what you contributed to the vial formulation that is described in claim 1.

A. Okay. At the simplest, I helped make it.

Q. Okay. How did you help make it?

A. What do you mean by "how did I help make

it"?

Q. I was using your description of your contribution.

A. I guess I'm at a loss for what additional information you're asking.

Q. What do you mean by "I helped make it"? First, what is "it"? What is "it" referring to?

A. It refers to the formulation.

Q. Okay. And what is the formulation under claim 1?

A. So it's a mixture of components that include the VEGF Trap protein, a buffer, an organic cosolvent, and a stabilizing agent, and its specific ratio that ensures we're 98 percent of the VEGF Trap or VEGF antagonist is in the native confirmation following storage at 5 degrees C for two months as measured by size excision chromatography.

Q. What were you referring to when you said the "components are in a specific ratio that ensures the native confirmation"? What's the "ratio" referring to?

A. So that refers to the concentration of the components.

Q. And what is the VEGF Trap that you were

referring to?

A. What is the VEGF Trap that I was referring to?

Q. Yes, in this formulation.

A. So that would be your amino acids 27 to 457 of Sequence ID NO:4.

Q. Does that equate to VEGF Trap-Eye?

A. What you do mean "does that equate to"?

Q. So where you were reading from, it says "wherein said VEGF antagonist fusion protein is glycosylated and comprises amino acids 27 to 457 of SEQ ID NO:4."

Does that element of the claim equate to VEGF Trap-Eye?

A. So in terms of the active ingredient, yes.

Q. What's afilbercept?

A. Afilbercept is the generic name that was assigned to VEGF Trap.

Q. Is it the same molecule as VEGF Trap-Eye?

A. Yes, it is the same molecule. It is the generic name for the molecule.

Q. Is VEGF Trap and afilbercept, are those terms synonymous?

A. I believe they are used interchangeably, yes.

Q. What is an organic cosolvent in the context of this claim?

A. Well, an organic cosolvent is a molecule that you add to a formulation that functions as a bridge between hydrophilic and hydrophobic aspects of the molecule in question and the solvent water in this case.

Q. What's a buffer in the context of this formulation?

A. A buffer is a mixture of an acid and its conjugate base at a defined ratio to achieve a desired pH.

(Stenographer clarification.)

BY MR. SALMEN:

Q. Yeah. We had a little glitch on our end, Dr. Graham. Can you repeat -- I'll ask the question again.

What is a buffer in the context of this claim of the '865 patent?

A. Okay. So a buffer is a mixture of an acid and its conjugate base or, you know, two molecules, one in the acidic and one in the basic form, at a specific ratio which gives you your target pH.

Q. Okay. And what is a stabilizing agent in the context of this claim in the '865 patent?

MR. FLETCHER: We had a glitch on our Exhibit Share.

THE WITNESS: I'm sorry. Can you repeat the question?

BY MR. SALMEN:

Q. Sure.

Your claim 1 is what I'm referring to in the '865 patent, column 19. One of the components that this formulation comprises is a stabilizing agent; is that correct?

A. Yes. Okay.

Q. Can you -- let me just ask the question, Dr. Graham.

A. Go ahead.

Q. What is a stabilizing agent in the context of this claim in the '865 patent?

A. Okay. So in the context of this patent, a stabilizing agent is typically the form -- some form of a polyol. It can be a molecule like sucrose or mannitol or even, you know, sorbitol that is added to the solution to help ensure that the molecule in question maintains its native confirmation and activity.

Q. Okay. You've referred to "native confirmation." Can you explain what that means?

MR. FLETCHER: Objection.

THE WITNESS: So in the context of this patent?

BY MR. SALMEN:

Q. We can start there.

In the context of claim 1 of the '865 patent, what is native confirmation?

A. That's 98 percent of the molecule being present as the -- or a minimum of 98 percent of the molecule being present as the native form as determined by size excision chromatography.

Q. What is the native form of the molecule?

A. The native form as determined by size exclusion chromatography is the intact molecule as an individual species.

Q. Do you call that a monomer?

A. You -- so define what you mean by a "monomer."

Q. Well, the individual species that you are describing, is that the protein as it's produced by and released by the cell?

A. Okay. So let me try to answer it this way: VEGF Trap or afilbercept is comprised of two arms that come together. So the molecule is a dimer. So if you mean by a monomer or a native monomer, that dimer, then, yes.

Q. That's what I was referring to, a monomer of the dimer.

A. Okay. That's fine.

Q. And is that -- can I refer to it as the monomer now?

A. As long as we don't change our meaning on --

Q. I'm not going to change the meaning on you.

So is that monomer produced by a cell?

A. In this case, yes.

Q. What type of cell produces that monomer?

A. To my knowledge, what's being used is a Chinese hamster ovary cell.

Q. Can we refer to that as a CHO cell?

A. If it makes you feel more comfortable, yes.

Q. Now, does the CHO cell -- strike that.

When the monomer is produced in the CHO cell, is it also glycosylated?

A. Okay. So you're asking is this cell glycosylated as it's produced by the CHO cell?

Q. Yes.

A. To the best of my understanding, yes, that is how the molecule comes out of the CHO cell.

Q. And when the molecule comes out of the CHO cell, it's in its native glycosylated form; correct?

A. Can you be a little more specific here? What --

Q. Sure. Sure.

When the VEGF Trap molecule, the monomer that we agreed to use that term for, comes out of the CHO cell glycosylated, that is the native form of the protein; correct?

A. Okay. So that's an oversimplification what you get because, you know, there is VEGF Trap in the native form that is glycosylated that comes out, but our manufacturing process relies on purification steps that get you to the molecule that we referred to as afilbercept in the native form. So we've removed the other stuff from it. So there's a lot of things that come out of that CHO cell.

Q. Okay. So the other stuff that you are referring to, that's just other stuff that came out of the CHO cell along with the native VEGF Trap glycosylated molecule; right?

A. Yes.

Q. And your purification process removes all

of that other stuff?

A. Okay. So that's something I would have to sit down and think about a little bit, but the intent of the purification process is to remove other things from the molecule, yes.

Q. Let me ask it this way, Dr. Graham: Is the intent of the purification process to change the form of the VEGF Trap glycosylated molecule that came out of the cell?

A. Please define what you mean by "change the form."

Q. In any way does the -- let me -- I'll try it this way: Is the intent of the purification process that you were referring to to change the structure of the VEGF Trap glycosylated molecule that comes out of the CHO cell?

A. What do you mean by "change the structure"?

Q. Do you have an understanding of what a protein structure refers to?

A. I have an understanding of what protein structure refers to.

Q. Okay.

A. But I want to know what your definition of "change the structure" is.

Q. So using your understanding of protein structure, does the purification process change the protein structure of the VEGF Trap glycosylated molecule after it comes out of the cell?

A. All right. I think we're back at the same point. What do you mean by "change"?

Q. Is there any structural -- is the intent of the process to inflict any structural change on the molecule during purification?

A. Are you trying to ask does the purification process refold the molecule? Is that what you're trying to ask?

Q. What do you understand primary structure of a protein to mean?

A. Well, the primary structure is the amino acid sequence.

Q. Okay. So that's where I want to start, the primary structure or amino acid sequence of the VGEF Trap protein. Is the intent of the purification process that you were referring to to change that primary structure?

A. So if I have an afilbercept molecule, a native afilbercept molecule, and I take it through the purification process, the intent is not to change that molecule. The intent is to have that

molecule at the end of purification process.

Q. So the intent of the purification process is to have the VEGF Trap molecule be in the same form at the end of the process as it was at the beginning of the purification process?

A. If, by your definition, "the same form" means that I have that primary sequence in its entirety, then, yes.

Q. Okay. Dr. Graham, I think this may be a good time for a break. We've been going for quite a while.

THE VIDEOGRAPHER: Sure. We can go off the record. The time is 10:40 a.m. This is the end of Media Unit No. 1.

(A short break was taken.)

THE VIDEOGRAPHER: We are going back on the video record. The time is 10:55 a.m., and this is Media Unit No. 2.

BY MR. SALMEN:

Q. Dr. Graham, I'd like to go back to the conversation we were having before the break. We were discussing the protein before and after the purification process. Okay?

A. Yes.

Q. Why do you -- why did you run a

purification process on the VEGF Trap protein that came out of the CHO cell?

A. Well, okay, so this is not my primary area of expertise. However, the purpose of a purification process, as I understand it, is to remove the unwanted or undesirable materials from the product and leave you with the desired product.

Q. What do you mean by "undesirable materials"?

A. These can be things like CHO host cell DNA, in this case, or CHO host cell proteins, potentially truncated forms of the protein of interest, as an example.

Q. And the in-process testing that you were developing and optimizing, was that in process for the purification?

A. So --

Q. I guess -- I'll ask a better question. I'm referring back to what you testified as your first involvement with the VEGF Trap molecule, and you testified that you were analyzing samples and there you were optimizing and developing the in-process testing that was in place at the time. So I just want -- I guess I want a better understanding of what in-process testing were you

working on at that time.

A. Okay. Do you want the purpose of this?

Q. Well, was the in-process testing done against the purification steps?

A. Yes.

Q. Okay. So in that testing, during the purification steps, were you analyzing the samples for the presence of host cell DNA?

A. No, that was not one of the assays that I was using.

Q. Okay. Were you -- during that in-process testing of the purification steps, were you analyzing the samples for the presence of host cell proteins?

A. That also was not one of the assays I was using.

Q. Okay. For that in-process testing against the purification samples, were you analyzing for truncated forms of VEGF Trap?

A. Yes.

Q. And how -- what types of methods were you using to analyze the in-process samples for truncated forms of VEGF Trap?

A. As I recall, at the time we were using SDS-PAGE gel electrophoresis as the primary assay

for truncated forms.

Q. Why were you using that method?

A. Why were we using that method?

Q. Yes.

A. So it was a relative quick and robust method that had a high throughput. So we could throw 20 samples on a gel and get an answer within, you know, 30, 40 minutes.

Q. Just so I understand this, what is a truncated form of VEGF Trap? What does that mean?

MR. FLETCHER: Objection.

BY MR. SALMEN:

Q. You used the phrase "truncated forms of protein of interest." I just want to know what you meant by a "truncated form."

A. Something that doesn't contain the entirety of the desired amino acid sequence.

Q. And the desired amino acid sequence we agreed to, that's the native form of the VEGF Trap molecule?

MR. FLETCHER: Objection.

THE WITNESS: In part that comprises an aspect of the native form. If your sequence is too short, you're missing amino acids. It's not native form.

BY MR. SALMEN:

Q. So that would be the truncated version that you're referring to, the version that would be too short or missing amino acids?

A. Yeah. Yes.

Q. And the truncated forms of the protein of interest are not native VEGF Trap; right?

MR. FLETCHER: Objection.

THE WITNESS: Truncated forms lack a part of molecule.

BY MR. SALMEN:

Q. And that would translate into the truncated form not being the native molecule; correct?

MR. FLETCHER: Objection.

THE WITNESS: My interpretation of this would be if I'm missing a piece of the molecule, I don't have the native molecule.

BY MR. SALMEN:

Q. Okay. Back to the SDS-PAGE gel electrophoresis, how does that -- how does that method work to analyze the in-process samples?

A. So it's a sizing method. So it separates based on the size of the molecule. So it relies on the protein binding sodium dodecyl sulfate, and you

create a consistent charge, and then you have -- the amount of SDS is proportionate to the size or sequence that's available. So shorter molecules have less SDS; longer molecules have more SDS. And then when you put a current through the gel, the smaller things migrate more rapidly and the larger things migrate more slowly.

Q. Okay. Other than the truncated forms of the VEGF Trap, were you analyzing the in-process samples for other types of degraded VEGF Trap protein?

A. Yes.

Q. What other types -- what other degrade -- strike that. Let me ask a better question.

What other degraded forms of VEGF Trap were you analyzing for -- the in-process samples for?

A. We were looking for aggregates, so things that were larger in size than the desired molecule.

Q. Anything else?

A. With respect to the size of the molecule?

Q. Just any other degraded form of the VEGF Trap molecule. Were you analyzing the in-process samples for something other than aggregated or truncated forms?

A. All right. I'm sorry. I feel like you have two questions there.

Are you asking was I analyzing for any other potential variations in the afilbercept, or are you asking am I analyzing for any other degraded forms of the afilbercept?

Q. Well, start with the first one. Are you -- were you analyzing the in-process samples for any other variants of the VEGF Trap molecule?

A. Okay. So -- and this is based on my recollection. We were also monitoring the sialylation of the molecule, and we would -- had an assay that would look at the sialic acid content. We would also follow the protein concentration of the desired molecule.

Q. With respect to the analysis -- the sialylation analysis, can you first explain what sialylation of the molecule is?

A. Okay. So the description of afilbercept says that it is glycosylated; correct?

Q. Sure.

A. Sure? Okay. I'll take that as a yes.

Q. In your patent in the -- let's stick within the context of your patent, in the '865, claim 1. Yes, it says it's glycosylated.

A. Okay. So at the end of the glycoforms, there can be sialic acid added, and the amount of sialic acid that is added can vary. Sometimes a glycoform can have one sialylation. Sometimes you can have glycoforms that have two, three, or four sialylations. So it's a measure of the presence of completed glycoforms in some manners.

But really it looks at, you know, how much of this sialic acid was put onto the molecule.

Q. Does the sialylation of the molecule affect the amino acid sequence?

A. No, not to my knowledge.

Q. Was there a specific sialylation of the molecule that you were looking for?

A. I mean, in all honesty, you would have to go back and look at what the targets were in the manufacturing level -- manufacturing record to see if there were specific levels that we were targeting.

Q. Was there a concern that the various sialylation levels of the molecule would affect efficacy of the protein?

A. By my recollection the sialylation could play a role in aspects of that.

Q. So what was the actual purpose, then, for

analyzing sialylation of the in-process samples?

A. So we were following the chromatographic step. We were looking at, you know, were we getting rid of certain sialylated species, were we enriching for certain sialylated species, you know, to follow on what was happening after one of the particular chromatographic steps that were being used. I don't recall if we had a specific target for what went into the product strength.

Q. You referred to whether or not you were getting rid of certain sialylated species. In the purification process, how would you have gotten rid of sialylated species?

A. One of the purification steps that we used in the pilot plant was a cation exchange column and that differentially binds charge.

Q. The sialylated variants, would those all be considered native VEGF Trap proteins?

MR. FLETCHER: Objection.

THE WITNESS: So are you asking me in this -- in the context of this patent?

BY MR. SALMEN:

Q. Yes.

A. Okay. So provided, when I analyzed those sialylated forms, they were in the native

confirmation as determined by size exclusion, then the answer would be yes.

Q. Is that because size exclusion wouldn't differentiate between the different sialylated forms?

A. Size exclusion in the context of this patent monitors what is native VEGF Trap.

Q. I guess I'm not following that, Dr. Graham. Does -- did the size exclusion analysis differentiate between the sialylated variants that you were analyzing for in the in-process steps?

A. That was not what we used that assay for, no.

Q. Okay. Why did you not use the assay, the size exclusion chromatography assay, to analyze the in-process samples for the presence of sialylated variants?

A. Because we had an assay specifically designed to look at sialylation.

Q. What assay was that?

A. I would have to go back and review the SOP we were following to give you a more detailed description of the sialic acid assay.

Q. Is it safe to say, though, that size

exclusion HPLC was not specifically designed to look at sialylation?

A. Size exclusion HPLC is designed to look at size variants primarily.

Q. And two different sialylated variants would not have a sufficient enough size difference to be separated by size exclusion HPLC?

A. Sialic acid is a very small molecule. In my experience, I would not expect a single sialic acid difference to impact VEGF Trap on a size exclusion column.

Q. Now, were there other degraded forms of VEGF Trap that you were analyzing process samples for such as -- sorry -- such as oxidized versions?

A. During the manufacturing process, no.

Q. What's deamination?

A. Deamidation.

Q. Deamination with an L? Deamination?

A. Spell the word for me, please.

Q. Here, I'll just direct you to it. It's in your patent. If we look at column 5, about three quarters of the way down line 56 reads, quote, "Chemical instability includes deamination, aggregation, clipping of the peptide backbone, and oxidation of methionine residues."

Do you see that?

A. Yep, I do.

Q. Do you now know what deamination means?

A. Well, I think it's a misspelling, but I think it's supposed to be deamidation.

Q. Okay. We'll refer to it as deamidation then. Let me -- just so the record is clear, Dr. Graham, let me ask my question.

What is deamidation?

A. All right. So there are specific structures that are called an amide or an amide, and it is a combination of an organic acid in an amine group. So that forms an amide.

In the context of a protein, there are two amino acids that have amides as their side chain. One of them is glutamine. The other one is asparagine. Both of those amino acids exist as the amide, those forms, or the respective acid forms, which would be glutamic or aspartic acid.

In this patent what deamidation refers to is the loss of that, in this case, it's really an ammonia group from either asparagine or glutamine converting the amino acid into the acidic form of the molecule which would be glutamic acid or aspartic acid.

Q. Turning back to the in-process testing that you were conducting to analyze the samples during the purification steps, were you analyzing for deamidation of the VEGF Trap molecule?

A. I'm sorry. But, I mean, in all honesty, I would have to go back and check the manufacturing records on that.

Q. Would the VEGF Trap that has been deamidated -- is that the right word?

A. Undergone deamidation.

Q. Let me state the question again.

Would the VEGF Trap-Eye molecule that has undergone deamidation be considered a native form of that molecule?

MR. FLETCHER: Objection.

THE WITNESS: You know, as defined in this patent, it would depend on how it appears when it was tested by size exclusion chromatography.

BY MR. SALMEN:

Q. And what different appearances of the molecule could occur when the VEGF Trap has gone -- undergone deamidation?

A. What different appearances of the VEGF Trap could occur when the molecule has undergone deamidation?

Q. Yes.
A. One molecule or multiple molecules?
Q. Start with one.
A. You've got a VEGF Trap molecule.
Q. Would it change the folding of the protein?
Let me state the question a little better.
Could deamidation of the VEGF Trap-Eye change the folding pattern of the molecule?
A. In my experience with afilbercept, I cannot think of an example where deamidation has altered the folding of the molecule.
Q. Would deamidation cause the molecule to aggregate?
A. That's a good question. To be able to answer it, I think I'd have to do some experiments. I can't think of an example of it causing aggregation at this point, but it would be something interesting to test.
Q. Okay. Why don't we shift gears, and you mentioned that this in-process testing was your first involvement with the VEGF Trap molecule. What was your next contribution to the development of the VEGF Trap-Eye product?
A. My next contribution?

Q. Yes.

A. Wow. Okay. So I stated that I worked in the pilot manufacturing facility; right?

Q. Yes.

Regeneron Protected Material

Regeneron Protected Material

Regeneron Protected Material

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Regeneron Protected Material

Regeneron Protected Material

Regeneron Protected Material

A. So what's your definition of "drug substance"?

Q. The VEGF Trap afilbercept molecule.

A. Okay. So the VEGF Trap afilbercept molecule?

Q. Yes.

A. So you're talking about the active

pharmaceutical ingredient then?

Q. Yes.

Regeneron Protected Material

Regeneron Protected Material

Q. Was the afilbercept molecule coming out of solution in that intermediate?

A. So by "coming out of solution," are you asking was it precipitating?

Q. Yes.

A. Okay. No, not to my knowledge.

Q. After you successfully developed this purification process, can you describe what your next major contribution was in the development of the VEGF Trap-Eye product?

A. Sure. Let me think of it here.

Well, so the next contributions or contribution really came after I joined the formulation development group.

Q. What year was that?

A. I want to say it was 2005, beginning of 2005.

So we had gotten to a point where we were experiencing some unexpected stability results for the GMP product that was being used to dose clinically. This was in a formulation that's not the Eylea formulation, but all of a sudden, our quality organization, QC group, was observing

particulates in the drug. And this was particulates after the drug had been passed through a syringe and needle.

And where my contribution to this came in was really an understanding that the formulation that we were using was susceptible to shear stress, and multiple passages through a syringe and needle could result in a formation of particles.

We were looking at this, and, I mean, quite honestly, as a group, we were fairly panicked because, you know, we're a startup company with no money, very limited resources, and now we're looking at potentially having to stop our clinical development on one of the, at the time, I think, two products that we were really actively working on.

So then began the work where we were trying to evaluate and understand what was causing these particles and how we could mitigate that. So I was involved in the design of or the execution of multiple different experiments, you know, probably on the order of 100 or more that were done, to understand why particles were forming, what were the key triggers, what we could do to mitigate it, and all this effort evaluated things that we

weren't sure that could be in eye formulations.

We started looking at alternative organic cosolvents, things like polysorbate. We started looking at stabilizers like mannitol or sucrose, again, which we were not sure we could use in the eye, you know, a whole host of things. So it was kind of a throw everything up against the wall that you can think of that might work and find something that was stable because, you know, we were really up against the ropes.

Q. Okay. So -- sorry. I didn't mean to interrupt. I thought you were done.

So this was in -- this started in 2005 when you moved to the formulation development group?

A. Very shortly thereafter, yes.

Q. Okay. So at that time were you reporting to Dan Dix and Eric Furfine?

A. I was reporting to Dan Dix. He was my immediate supervisor. Eric was Dan's boss.

Q. When you were in the formulation group, did you keep a literature file of published literature?

A. I mean, I had some files of published literature. I didn't, I don't think, really keep a

specific file of that, but --

Q. Were there --

A. -- and may have had an article or two. I don't know.

Q. Was there a literature file in your lab or in the department?

A. You know, in all honesty, I don't remember.

Q. Was there a library of any kind at Regeneron in the formulation department?

A. I mean, the closest thing to a library we have is if somebody subscribed to a journal. You know, Regeneron really did not have a library at the time. I don't even know that we had good Internet access to publications at the time.

Q. Did you have any handbooks or textbooks?

A. Sure. I had some textbooks and handbooks, yeah.

Q. Which -- what handbooks or textbooks do you recall having -- I'll narrow the question -- that were specific to pharmaceutical development and the work that you were doing to resolve this problem of particle formation?

A. That I had? I mean, I'm a bioorganic chemist. My handbooks were synthetic methodology,

protecting groups, analytical texts. You know, I had some compendia that had compendial methods for doing things like particle analysis. I mean, really, to my knowledge, in 2005, there was not a textbook that dealt with this.

I mean, this was a fusion protein, you know, recombinant protein, kind of chimeric, two things were put together that were never meant to be together, and it's really a species that's unlike any molecule that is out there previously or since.

Q. So there were other VEGF antagonists. I think you mentioned that you had some competitors out there already in 2005?

A. I did not mention any competitors that I recall.

Q. So in 2005 were you aware of Genentech's development of ranibizumab?

A. What is the trade name of ranibizumab?

Q. Lucentis.

Here. I'll help you out here. If you look at Exhibit 714 in your binder.

A. One sec.

THE TECHNICIAN: I'm sorry, Heinz. Can you say that number again?

MR. SALMEN: 714.

MR. FLETCHER: We don't have our Exhibit Share open at the moment, but we have the paper exhibit. So I think we'll be okay.

BY MR. SALMEN:

Q. Okay. This should be in the binders. Does he have it?

A. Yeah, I have it in front of me.

Q. Okay. So the cover of Exhibit 714 is an email, and there's an attachment with a paper. The first author's name is Gaudreault.

Do you see that?

A. Yes, I do.

Q. And if you look at the bottom of the first column, left-hand side, you'll see that Dr. Gaudreault is from Genentech?

A. Okay.

Q. And then the title is "Preclinical Pharmacokinetics of Ranibizumab"?

A. Yes.

Q. Okay. Does this help refresh your recollection that Lucentis is the brand name for ranibizumab?

A. Yes.

Q. Okay. There's a -- I'll direct your

attention, on the second page of this article, page number 727, in the top right-hand corner, on the left-hand column, the first few sentences there, there's a formulation described that says: "Ranibizumab was formulated as 10 millimolar sodium succinate, 10 percent trehalose, and 0.05 percent Tween."

Do you see that?

A. I do.

Q. Were you aware of this article when it came out and was circulated in January 2005 at Regeneron?

A. From what I can see, this email was sent to a series of people at the company, and I was not one of them, neither was my boss Dan Dix, I believe, if I'm reading this correctly.

I mean, I don't have a specific recollection of seeing this paper in 2005. I can't say that I've never seen it. I mean, in fact, I did look at it as part of my prep to talk with you, but I can't tell you yes or no I saw it in 2005.

Q. Okay. I'm going to mark another exhibit here.

MR. FLETCHER: Mr. Salmen, is this now a new

exhibit?

MR. SALMEN: Yes.

MR. FLETCHER: If you could give us a minute, we've lost the witness's exhibits share. We still have ours. We can print it.

MR. SALMEN: Mike, if you could pull it up on the screen, it's Bates number -- the first Bates number is 540303.

(Whereupon, Exhibit 735 was marked for identification.)

THE TECHNICIAN: Do you know what the tab number is?

MR. SALMEN: Tab No. 5.

BY MR. SALMEN:

Q. And maybe we can do this just on the screen, Dr. Graham. I'm only going to show you this for some context.

A. Okay.

MR. SALMEN: Just show it on the Zoom, please. Can we make that nice and big for him?

MR. FLETCHER: You're going to lose your video. I apologize. For the record, is this an exhibit or is this not being marked as an exhibit?

MR. SALMEN: This is being marked as -- are we up to 735, please?

THE TECHNICIAN: That's correct.

THE WITNESS: I can only see part of it. Can you shrink it down a little bit?

BY MR. SALMEN:

Q. I just want to direct your attention to Daniel Dix's name on this email.

And you'll see there's an attached paper?

A. Okay.

MR. SALMEN: Mike, I think we lost the --

THE TECHNICIAN: Yeah. Hold on one second.

MR. SALMEN: -- the exhibit on the screen.

BY MR. SALMEN:

Q. I only bring this up, Dr. Graham, because you had mentioned that Dr. Dix was not copied on the previous email.

A. Okay. That's fine.

Q. You see that he is copied on this one; correct?

A. I do.

Q. And do you see that there's an attachment here?

A. I do.

MR. SALMEN: Okay. And if -- I'm just going -- if we could scroll to the next page of this email, that's the attachment and can we blow up the top

title.

BY MR. SALMEN:

Q. And so do you recognize this as the same Gaudreault article; right, Dr. Graham?

The one that you have a paper copy of that was --

A. Can you go to the next page, please?

Can you blow up the header, please?

Okay. It appears to be the same article, yes.

Q. Okay. So let's refer back, then, to the paper version that you have in Exhibit 714.

A. Okay.

Q. Do you recall now if you saw this article in February when it was forwarded on to Dr. Dix, your supervisor?

A. In all honesty, I do not recall seeing it. I may have, but, you know, we're in 2023. So it's 18 years ago.

Q. Okay. Just to clarify the record, Dr. Graham, this is 2025 [sic] when this paper came out, and I believe this was around the time that you said you joined the development group; correct?

MR. FLETCHER: 2023.

BY MR. SALMEN:

Q. I'm sorry?

A. You just said it was 2025, sir.

Q. Sorry. Okay. I misunderstood, and then I misspoke. Let's strike that. I'm sorry.

The article here is -- was circulated in early 2005 when you joined the group; right?

A. So it was certainly circulated among some people in January 2005, yes.

Q. Is this an article that Dr. Dix would have passed on to you?

A. I mean he might have. I don't have a recollection of it, but he might have.

Q. When you joined the formulation group, was there a concern about using polysorbates in an intravitreal administration?

A. Yes, there was a concern about using polysorbates in an intravitreal administration.

Q. What was that concern?

A. To the best of my recollection, I thought or think there may have been some studies or something established that said polysorbate was toxic to the retina. At least that's what I'm remembering.

Q. And back to this Gaudreault article, the

title of this is "Preclinical Pharmacokinetics of Ranibizumab after a Single Intravitreal Administration."

Do you see that?

A. I do.

Q. Do you agree that this formulation had 0.05 percent Tween-20 in it?

A. I do agree, yes, that's what they published.

Q. And Tween-20 is a polysorbate; correct?

A. Well, I mean, all polysorbates are not Tween-20. Tween-20 is a specific brand of polysorbate. So it may or may not be equivalent to others.

Q. Okay. I may have asked a poor question there. I'm sorry.

Tween-20 is a type of polysorbate; correct?

A. Tween-20 is a brand name for a specific polysorbate, yes.

Q. And what specific polysorbate is Tween-20 a brand of?

A. I forget who the manufacturer of Tween is, but Tween-20 would be a polysorbate 20.

Q. Okay. So if I refer to polysorbate 20 or

Tween-20, are those terms synonymous to you?

A. No, they are not.

Q. Okay. What's the difference between polysorbate 20 and Tween-20?

A. All right. So polysorbates, by the inherent nature in which they're made, are not a single uniform structure. There can be variations in terms of the percentage of specific amino acids -- excuse me -- amino acids -- sorry. I misspoke -- in terms of specific fatty acids, and you know, the exact composition of a specific manufacturer's brand of polysorbate or a specific manufacturer's polysorbate can, in a large way, determine the characteristics of its behavior.

Q. When you were addressing the particle formation problem when you started at the formulation development group in 2005, did you consider adding polysorbate or Tween-20 to the formulation to resolve that issue?

A. We did, yes.

Q. And when you did make that decision to consider polysorbate, were you still concerned about the toxicity of polysorbate to the retina in an intravitreal administration?

A. Absolutely.

Q. So what concentration amounts were you considering of polysorbate to resolve the particle formation issue?

A. I mean, I don't recall all the specific amounts that we tested. I know we tested a range, and I know on the low end of the range we were probably 0.01 to 0.03, and the upper end of the range, I'm honestly not sure. 0.01 to 0.03 percent weight by volume.

Q. So after this Gaudreault article came out, did you continue to monitor Genentech's development of its ranibizumab product?

A. Myself, personally, no, I did not.

Q. Did the formulation development group monitor Genentech's developments of its ranibizumab product after this 2005 article?

A. I mean, I don't recall, you know, specifically looking at what Genentech was doing.

Q. When you came to that 0.1 percent -- let me ask a different question. Sorry.

How did you come to that 0.01 percent to 0.03 percent of polysorbate in the formulation to potentially resolve the particle formation issue with your concern that polysorbate might be toxic to the retina?

A. Okay.
Q. I'll try to break it down for you.
A. Yeah, please.
Q. So you stated that at this time, in 2005, when you entered the formulation group, your first task was to address this particle formation issue; correct?
A. That was one of my first tasks, yes. You asked first thing with the afilbercept, so, yes.
Q. And as a potential resolution of that issue, you testified that you considered polysorbate; correct?
A. Yes.
Q. And you also testified that at that time there was still a concern of toxicity to the retina using polysorbate; correct?
A. Yes.
Q. So my question is how did you land on the 0.01 percent to 0.03 percent range of polysorbate to use in the formulation to potentially resolve the particle formation issue?
A. Okay. So we tested it.
Q. How did you know that that percentage would not be toxic to the retina?
A. The way we determined that was through a

toxicology study.

Q. What type of study?

A. So we used nonhuman primates.

Q. Would this have been after the January 2005 circulation of the Genentech article where they administered ranibizumab intravitreally to nonhuman primates?

A. I believe, yes.

Q. So at the time that you conducted your studies, you already knew that Genentech had conducted an intravitreal administration of a VEGF antagonist in a formulation that comprised 0.05 percent Tween to a nonhuman primate?

A. Are you asking if I specifically knew that?

Q. We can start there, yes.

Did you specifically know that?

A. I'm not sure. I mean, I honestly did not recall this paper until, you know, it was brought forth to me as far as deposition prep.

Q. Did you suggest that specific 0.01 percent to 0.03 percent range of polysorbate in the formulation?

A. That was determined empirically.

Q. What do you mean by "determined

empirically"?

A. We tested it.

Q. So this was the result of a broader range of percentages that were tested?

A. Yes.

Q. And what was the broader range of percentages that were tested?

A. Okay. I don't remember what the upper end was. I know we went up at least to 0.1 percent, but to give you an answer beyond that, I would have to go back and review documents and lab notebooks.

MR. FLETCHER: Counsel, we've been going well over an hour.

MR. SALMEN: Sure. Hard to keep track of time.

THE VIDEOGRAPHER: Going off the record. The time is 12:12 p.m. This is the end of Media Unit No. 2.

(A short break was taken.)

THE VIDEOGRAPHER: We are going back on the video record. The time is 12:23 p.m., and this is Media Unit No. 3.

BY MR. SALMEN:

Q. Dr. Graham, I'd like to pick up where we left off when you were addressing, in 2005, the particle formation issue that you were experiencing

with the VEGF Trap formulation.

I just wanted to clarify one point there. Is that the intravitreal -- let me strike that.

Was that the drug product formulation that was experiencing the particle formation as opposed to the drug substance formulation?

A. So that was a drug product formulation, yes.

Q. Okay. Which drug product formulation was that that was experiencing the particle formation problem?

A. It was what we referred to as IVT 1.

Q. Do you recall the formulation of IVT 1?

A. I am not sure of the afilbercept concentration, but it was a PEG-based formulation. So I think it had 0.1 percent PEG 3350 and 135 millimolar sodium chloride as excipients.

Q. I'm going to show you a document to see if it confirms or helps recall your recollection. Look at 555211. Let me see if this is in your binder.

A. 555211.

MR. SALMEN: That's to Mike. It's Exhibit 719 in your binder.

THE WITNESS: Am I done with 714?

BY MR. SALMEN:

Q. Yes.

A. So I can put that away?

Q. Sure.

A. You said 719?

Q. Yes. Are you there?

A. I am there.

Q. Exhibit 719 is memorandum dated August 16, 2005. The subject line is, quote, "VEGF Trap Intravitreal Formulation Storage and Shipping Conditions," and I'm just directing this to try to refresh your recollection about that IVT 1 formulation, Dr. Graham.

If you look at the second full paragraph immediately above the bold header that says "Stability," the last sentence is, quote, "The current intravitreal formulation contains the following: 10 millimolar sodium phosphate pH 6.25, 135 millimolar sodium chloride, and 0.1 percent PEG 3350."

A. Yes.

Q. Is that the IVT 1 formulation you were referring to?

A. That's what I recall we used to refer to that as, yes.

Q. So going back to my initial question, was this the formulation that was experiencing a particle formation issue when you joined the formulation development group in 2005?

A. I believe it was, yes.

Q. And when you testified in the last section about the use of polysorbate to resolve this particle formation issue, was it -- was one of the approaches to add polysorbate to this IVT 1 formulation?

A. So are you saying did we use a combination of polysorbate and PEG 3350 in the same formulation? Is that your question?

Q. Yes.

A. I want to say, yes, we did.

Q. So taking a step further back, I was asking whether your first approach was to fix this formulation, this IVT 1 formulation, so that it didn't have the particle formation problem by adding polysorbate to it.

A. So, I'm sorry, but can you rephrase that for me, please?

Q. Sure.

So for context, again, the existing formulation when you started at the formulation

development group in 2005 was this IVT formulation; correct?

A. Yes.

Q. And your recollection is that the IVT formulation is what we just looked at in Exhibit 719 as comprising 10 millimolar sodium phosphate pH 6.25, 135 millimolar sodium chloride, and 0.1 percent polyethylene glycol 3350; correct?

A. Okay. That was what I referred to as IVT 1, yes.

Q. Okay. And this is the formulation that you recall experienced the particle formation problem; correct?

A. Correct.

Q. Was the particle formation being caused by shear stress? I think was the term you used earlier.

A. That's what we believe the ultimate cause was, yes --

Q. What is --

A. What precipitated it, yes.

Q. Can you tell me what shear stress is? What does that mean?

A. Well, so shear in the case of what we're talking about here is an impact of having a

solution stream move at a -- either a high speed or through a small pipe or orifice, and what the concern was we were using 30-gauge needles, which, at the time, were substantially smaller than what you would typically use for a protein product. And the act of ejecting or passing the protein product through that needle, you know, depending on how fast you go, creates a certain amount of shear.

I have to refresh my memory as to the equation, but I believe it goes up as the square of the reciprocal of the diameter of the tube. So the smaller you get, the much faster or much greater the shear becomes.

Q. So this particle formation that was caused by the shear stress, is that indicative of the VEGF Trap molecule coming out of the solution or precipitating?

A. It's indicative of something coming out of solution. I'm not 100 percent certain as to the actual identity of or composition of the particles that were present.

Q. Okay. Let me shift gears for a second here, Dr. Graham.

In Exhibit 719, the one that illustrates the IVT -- the components of the IVT 1 formulation.

A. Yes.
Q. On the first page there, you see "Stability of 5 milligrams per mL of VEGF Trap"?
A. I do.
Q. Does that mean that 5 milligrams per mL of the VEGF Trap active ingredient were used in the current IVT 1 formulation?
Let me rephrase that.
In these samples was the concentration of VEGF Trap 5 milligrams per mL?
A. In which samples?
Q. The samples that were being studied here in this stability study.
A. Okay. So you're referring to the document that we -- you just provided me, which is 719?
Q. Yes.
A. All right. You know, as I look at 719, there are a range of protein concentrations listed.
Q. Okay. What's the range of protein concentrations that you see?
A. All right. Give me a minute. I need to kind of look through the entirety of the document, and I'll tell you what I see as a range.
Q. Sure.
Dr. Graham, do you have an understanding

now of the range of protein concentrations that were being tested here?

A. Yes, I do.

Q. Okay. And I'm just going to flip to the last page of this, 10 of 10, Bates No. 555220. Do you see those tables at the bottom?

A. I do.

Q. It says -- the first column says "VEGF Trap Concentration"?

A. Yes.

Q. 5 milligrams per mL, 10 milligrams per mL, 20 milligrams per mL, 40 milligram per mL, and 80 milligrams per mL.

Do you see that?

A. I do.

Q. Is that the range of protein concentrations that were being evaluated here for stability?

MR. FLETCHER: Objection.

THE WITNESS: Actually, no, I don't believe it is.

BY MR. SALMEN:

Q. Well, let's start at the front of this document then, page 1, and under "Stability of 5 Milligrams Per ML VEGF Trap," in that first

paragraph, it states "...5 milligrams per mL VEGF Trap in the intravitreal formulation."

Do you see that?

A. I do.

Q. Does that reflect -- when it says "in the intravitreal formulation," is that the list of components and concentrations and pH that's described as the current intravitreal formulation or the IVT 1 formulation?

A. I mean, I believe that it is, but for me to be 100 percent certain, I would have to pull Study 138 and take a look at it. But for the sake of argument, we'll say yes.

Q. Okay. And turning to the third page of this, Document 3 of 10, under "Stability of 10 milligrams per mL VEGF Trap," there's a similar sentence in the first paragraph where it states "...10 milligrams per mL VEGF Trap in the intravitreal formulation."

Is that also referring to using the IVT 1 formulation with 10 milligrams per mL VEGF Trap?

A. Again, I do believe it is, yes.

Q. Okay. And if we look at page 6 and 7 of this document, the header there is "Stability of 40 milligrams per mL VEGF Trap and 80 milligrams

per mL VEGF Trap."

Do you see that?

A. I do.

Q. And there's a similar statement in that paragraph, about four lines down, where it says "in the intravitreal formulation." Is that, again, a reference to the IVT 1 formulation that's described in the first page here?

A. Okay. I mean, I would want to confirm by pulling the study numbers, but I believe the answer is yes.

Q. So in this IVT 1 intravitreal formulation, is there an organic cosolvent?

A. There is.

Q. What is it?

A. It's the PEG 3350.

Q. So that's 0.1 percent PEG 3350?

A. Yes.

Q. Was that same amount of PEG 3350 used in the 5 milligrams per mL formulation and the 10 milligrams per mL formulation?

A. I believe that it was, yes.

Q. Was that same amount of PEG 3350 0.1 percent used in the 40 milligram and 80 milligrams per mL solutions?

A. I believe the answer is yes.

Q. So you did not have to adjust the amount of PEG to -- for the changing concentrations of the VEGF Trap-Eye in these solutions?

A. No. The formulation was kept consistent.

Q. In addressing the particle formation problem you were having with the IVT 1 formulation, did you increase the amount of PEG in those solutions to try to address that problem?

A. I'm not sure if higher levels of PEG were used, PEG 3350. They may have been, but I'd have to go back and look at the studies.

Q. Can you explain to me why, in response to one of my earlier questions, you were able to -- or how you were able to conclude that PEG 3350 is an organic cosolvent in this solution, the IVT 1?

A. Okay. So in this case PEG 3350 has the ability to interact with both the protein and the aqueous solution, and I think I described a cosolvent as something that forms a bridge between the protein and the solution in which it is in. Sometimes that's between hydrophilic areas and sometimes that's between hydrophobic areas.

Q. Okay. Was there a problem with the solubility of VEGF Trap-Eye in the solution without

PEG?

A. Not that I'm aware of, no.

Q. Can you go to Exhibit 721 in your --

MR. SALMEN: How are we doing on time, Tom?

MR. FLETCHER: If you want to do one more exhibit, I think that's reasonable. If you want to take a break now, let's take a break now.

MR. SALMEN: I just want to ask some preliminary questions on this one, please.

MR. FLETCHER: Sure.

BY MR. SALMEN:

Q. Is that okay with you, Dr. Graham?

A. Sure.

Q. Maybe five or ten more minutes. Okay.

Do you have Defendant's Exhibit 721 in front of you? Dr. Graham?

A. I do.

Q. Okay. Okay. Do you see this is an email? Can you pronounce the author's name for me, please?

A. Leu-Fen Lin.

Q. And this is an email from Leu-Fen Lin to Kelly Frye, copying Daniel Dix and yourself; is that correct?

A. It is.

Q. And the title -- the subject line of this

email is "Lyo formulation for exploratory tox study." Do you see that?

A. Yes.

Q. What is a lyo formulation?

A. Okay. A lyo formulation is a lyophilized formulation. So what it is is it's a formulation that is specifically made to be put into a vial or other container system and taken through a freeze-dry process in which you remove the solvent which, in this case, would be water from the formulation leaving a solid cake behind.

Q. If you flip to the back of this exhibit, there is a formulation at the top of that email, and that one is dated November 30, 2005, from Kelly Frye.

Is that the lyo formulation that you were just describing as in the vial for freeze-drying?

Let me ask a better question, Dr. Graham.

Is this the pre-lyophilization formulation?

A. I need a minute to read through this. This is not exactly --

Q. Sure.

A. -- clear, and I haven't seen this.

Okay. What is your question?

Q. My question was: This formulation described on the second page, No. 556501, is that the pre-lyophilization formulation?

A. I mean, quite honestly, based on the content of the email, I'm not sure. I mean, there's a couple emails from Leu or at least one email from Leu that is somewhat confusing. So I would probably need to look at some other sources to confirm what exactly this is.

The description has 10 millimolar phosphate, 0.1 percent PEG 3350, 0.03 percent polysorbate 20, 2.5 percent sucrose, and 40 mg per mL VEGF Trap.

So as I'm reading the text below, the plan is to reconstitute the vials with placebo back to 40 mg per mL. They want to keep the concentration of the formulations the same but test the excipient level for doubling the excipients. So there's a lot of things here that I don't quite understand.

You know, if they're reconstituting it back with placebo, what is the placebo they're using? What's the composition of that? I don't know what that means.

They said to bring it back up to 40 mg per mL. That doesn't necessarily match with

our standard practice in the group at the time because, typically, we would lyophilize at half the targeted protein concentration for reconstitution. So, you know, we would have a liquid -- you know, you said the word pre-lyo liquid, you know. It would have 20 mg per mL, and then we would reconstitute it back up to 40 mg per mL.

So this is -- I'm sorry, but this is rather confusing to me, and, I mean, I would really need to or really want to look at the supporting documentation for this email to try and interpret this. I mean, I've got somebody using nonstandard abbreviations.

Q. Okay.

A. I don't know what EI is, which is kind of confusing me here.

Q. Well, if we look at Leu-Fen Lin's email at 5:23 p.m., her Item No. 2, it says "If recon" -- I assume that's reconstitution; right?

A. I would assume.

Q. "If recon with placebo, the final drug product will have 20 millimolar Pi, 0.2 percent PEG, 0.06 percent PS, 5 percent sucrose, and 40 mg per mL VEGF Trap. Is that the intention?"

Do you see that?

A. Yes.

Q. And Kelly responds, at 5:28 p.m., in No. 2, "That is exactly the intention."

Do you see that?

A. Okay. I do.

Q. Does that inform you as to whether or not the formulation as described on the back page is the lyophilized formulation or the pre-lyophilization formulation, or is there even a difference?

A. You know, if I stand solely on the content of this email, it would be an interpretation of what is being done.

Q. And you see that the excipients are, in fact, doubling after reconstitution; correct?

A. Yes, I do see that.

Q. Did you help contribute to the development of this lyophilized formulation and selecting the excipients used here?

A. I know at one point I did make a recommendation for a lyophilized formulation. I don't know that I recommended 40 mg per mL. I think I had recommended a 20 mg per mL solution, but I had made recommendations for lyophilized formulations.

Q. Did your recommendation for a lyophilized formulation use a phosphate buffer?

A. It did, yes.

Q. Did you ever make a recommendation for a lyophilized formulation that used a histidine buffer?

A. You know, I possibly did because phosphate is usually not a desirable buffer for lyophilized formulations because the acidic and basic forms of the phosphate crystallize out at different rates and -- on freezing, and you can get a pH shift. Histidine is generally a much better buffer for lyophilization. So we probably had some discussions around that, but I don't recall if we ever did.

Q. Would histidine have been a better buffer for the original intravitreal formulation than phosphate?

MR. FLETCHER: Objection.

BY MR. SALMEN:

Q. The non-lyophilized version.

A. Can you ask your question again, please? I'm sorry. I got distracted by the objection.

Q. So in the IVT 1 formulation, you used phosphate buffer; correct?

A. Yes.

Q. Would histidine have been a better buffer for that formulation?

A. I don't know. You know -- go ahead.

Q. In addressing the particle formation problems that you were experiencing with the IVT 1 formulation, did you recommend changing the buffer from phosphate to histidine?

A. I don't recall making such a recommendation. I mean, it may have been something that was discussed. You know, we're talking 2005. I know, you know, there were certain things that we now joke about that were "Dan Dix nevers," things that you would never do, and one was you would never have a liquid formulation with histidine as a buffer. I know he was resistant to that.

As to your question, if I had switched my buffer from phosphate to histidine, would I still have gotten particles in the formulation provided I kept the rest of the composition the same --

Q. That wasn't exactly my question, Dr. Graham. My question was --

A. What was your question?

Q. -- to address the particle formation problem that you were experiencing when -- let me

restate. Let me strike that.

To address the particle formulation problem that the IVT 1 formulation was experiencing when you started at the formulation development group, did you recommend using a histidine buffer instead of a phosphate buffer to resolve that issue?

A. Honestly, I'm not sure. I may have.

Q. Given that Dr. Dix had a "Dr. Dix nevers" that you wouldn't use a histidine, would that recommendation have even been well received?

MR. FLETCHER: Objection.

THE WITNESS: You know, it could be a conversation. Whether or not it was actuated, I don't know. You know, it was -- I don't know honestly.

BY MR. SALMEN:

Q. Other than histidine, were there other "Dr. Dix nevers" that you recall?

A. That you'll never need a formulation with a concentration higher than 10 mg per mL.

Q. Any other ones?

A. The only other one is you'll never use arginine in a formulation.

Q. Well, I think it's 1:00 your time. So why

don't we break for lunch?

THE VIDEOGRAPHER: Going off the record. The time is 1:01 p.m. This is the end of Media Unit No. 3.

(A lunch break was taken.)

THE VIDEOGRAPHER: We are going back on the video record. The time is 1:37 p.m., and this is Media Unit No. 4.

BY MR. SALMEN:

Q. Welcome back, Dr. Graham.

I'm going to ask you to look at what's been previously marked as Defendant's Exhibit 716. It should be in your binder.

A. Okay.

Q. Dr. Graham, have you seen this exhibit before?

A. I have.

Q. You reviewed it in preparing for your deposition?

A. I did.

Q. So 716 is an email with attachment. The email is dated April 12, 2005?

A. It is.

Q. And you're listed as a recipient of this email; correct?

A. Yep, I am.

Q. The list of recipients on this email from Dr. Eric Furfine, is that the formulation group -- I'm sorry -- the formulation development group?

A. It was part of it, yes.

Q. Okay. So everyone on this list was part of the formulation development group?

A. Dan was, I was, Kelly was, Katherine Bowers, and your favorite Leu-Fen Lin, yes.

Q. Okay. So can you explain why that -- let me strike that question first.

The attachment here is, as far as the email line for attachment reads, is "Avastin EMEA discussion." Do you see that?

A. I do.

Q. What do you understand "EMEA" to be referring to?

A. Well, EMEA is the European medical regulatory body that controls the approval of and sale of pharmaceuticals, I think also devices and other medical items, kind of like our version of the -- or their version of our FDA.

Q. Okay. And this particular EMEA discussion document involved Avastin; is that correct?

A. Yes, that appears to be correct.
Q. What is Avastin?
A. So Avastin or bevacizumab is a monoclonal antibody. It's actually a humanized monoclonal antibody.
Q. Avastin is the marketed formulation of the humanized monoclonal antibody named bevacizumab?
A. Well, Avastin is the trade name for the generic bevacizumab. So it's Genentech's product name.
Q. Okay. And in case I didn't say it, for context, the date on this is April 12, 2005; correct?
A. That appears to be correct, yes.
Q. Okay. Was this still around the time that you were working to resolve the particle formation issue in the IVT formulation?
A. Yes.
Q. And can you tell me why Dr. Furfine -- strike that.
Why was this information relevant to the formulation group?
A. So in my understanding of, or at least the takeaway I had from this, based on Eric's email, is that he wanted to have us be aware of the types of

things that they were doing to characterize their proteins. You know, Genentech, at the time, I think many people would consider was the preeminent biotech company in the world, you know, had state-of-the-art analytical capabilities, and, you know, was very effective at characterizing and understanding molecules.

Q. Okay. Now, referring to the second paragraph of Dr. Furfine's email, was he also conveying this information for you to be aware of the formulation issues that Genentech experienced with their development of Avastin?

A. Well, I'm -- I mean, I'm unaware of what formulation issues Genentech experienced with their development of Avastin. I'm not sure if it's disclosed in this document. I would have to read the document to understand and know if they were present and what they were.

Q. Okay. Let's take a look at some portions of the document here.

A. Okay.

Q. I'll first direct your attention to the -- what's -- I'm going to refer to the page numbers that are page 1 of 61 or 2 of 62 that's at the bottom middle of each page. Do you see that?

A. Okay. So then the actual page number for what was written as opposed to the legal exhibit?

Q. Yes.

A. Okay.

Q. So on page 3 of 61, there's a header there, "Part II: Chemical, Pharmaceutical, Biological Aspects."

Do you see that?

A. I do.

Q. And the second section down is "Composition." Do you see that?

A. Yes.

Q. And the first two sentences of this paragraph read: "Avastin is provided as a concentrate for solution for infusion in a single-use vial which contains a nominal amount of either 100 milligrams of bevacizumab in 4 milliliters or 400 mg grams of bevacizumab in 16 milliliters. Concentration of 25 milligrams per mL."

Do you see that?

A. I do.

Q. The next sentence reads: "Bevacizumab is formulated with 51 millimolar sodium phosphate pH 6.2, 60 milligrams per mL trehalose dihydrate,

and 0.04 percent polysorbate 20."

Do you see that?

A. I do.

Q. Okay. Now, for more context, I am going to direct your attention to page 8 of 61. The top of the page reads "Drug Product."

Are you there?

A. Give me a second. Yeah, I have 8.

Q. Do you see here the first sentence is "The goal was to develop a liquid" -- strike that.

"The goal was to develop a stable liquid intravenous formulation"; correct?

A. That's what the sentence says, yes.

Q. And then the last paragraph of this small section on pharmaceutical development, which is the one, two, three, fourth paragraph down, reads: "Due to physical instability of the liquid formulation used in Phase I and Phase II clinical studies, the formulation was changed by increasing the pH to 6.2, changing the histidine buffer for sodium phosphate, increasing the ionic strength by increasing the concentration of the buffering species, decreasing the trehalose concentration to modify the osmolality, and increasing the polysorbate 20 concentration."

Do you see that?

A. I do.

Q. Does that refresh your recollection on the formulation issues that Genentech was having in its development of the Avastin formulation?

A. Well, it lists what's contained in this document. I mean, I'm sorry, but I still don't have a recollection of the specific issues, but I can see them here. They are in print, yes.

Q. So referring back to Dr. Furfine's email in the second paragraph, he states, "As one point in support of our approaches, they started with a histidine buffer as a liquid formulation and switched to phosphate for later development work and marketing."

Do you see that?

A. I do.

Q. What approach did you understand Dr. Furfine to be referring to here?

A. As I read the email, I'm not entirely sure what he meant. You know, it might be best to ask him since he wrote it.

However, if I read through it, I think we had talked at one point or another about using an alternative buffer or buffers. I know we

considered that there might be multiple suitable buffers, but there were thoughts that phosphate is a native buffer in the body, and, therefore, we should use phosphate because it's native to the body. Histidine might not be a native buffer to the body. So that would be, to the best of my recollection, what he was referring to.

Q. So was your interpretation, then, that Genentech switched from a histidine buffer to a phosphate buffer justified your approach in using a phosphate buffer for the IVT formulation of VEGF Trap?

A. No. It merely says that if phosphate works out to be a suitable buffer for your molecule, somebody has used a phosphate buffer before. I mean, quite honestly, looking at bevacizumab and considering its formulation and looking at another molecule and considering its formulation, the suitable formulation is really something that is determined, in large part, by the molecule you're dealing with.

As I'm looking at what's going on here, they had a lot of things going on. They didn't just say, "Okay. We're going to switch to phosphate." Well, they changed pH. They changed

buffer. They changed the ionic strength of the solution. They changed the concentration of the buffer which, you know, has potentially multiple effects.

You know, it looked like they had one or more specific stability problem that they were trying to work their way through and made a whole bunch of changes because they found the sweet spot for that molecule, and just because it's the sweet spot for that molecule doesn't mean it's the sweet spot for any other molecule.

Q. Was phosphate buffer the sweet spot for the VEGF Trap molecule?

A. It was a sweet spot for the VEGF Trap molecule, yes, under certain conditions.

Q. Were there other buffers that you would describe as the sweet spot for the VEGF Trap molecule?

A. There were other suitable buffers, yes.

Q. What were those buffers?

A. Right now the only thing that really comes to my mind is histidine, but I think we used a phosphate and citrate buffer for the Zaltrap, which is a different but related formulation or use of afilbercept. I know that fairly extensive

screening studies were done, but I don't know that I could list all of the buffers that were tested at this point.

Q. Before we took a break, you said that Dr. Dix had a -- what would we call it? -- a belief that you would never use histidine in a formulation; is that correct?

A. He made the statement to us, "You would never use histidine in a liquid formulation," yes.

Q. What was Dr. Dix's disfavor for histidine in a liquid formulation?

A. He believed it would turn yellow.

Q. Any other problems that Dr. Dix had with using histidine in a liquid formulation?

A. Not that I recall at this time, no.

Q. And would the formulation turning yellow be an undesirable property for an intravitreal administration?

A. A change in color in a formulation is undesirable.

Q. Would a change in color -- would you describe that as an instability of the formulation?

A. You could, yes.

Q. And so to avoid a change in color of the -- of a histidine formulation, one solution

would be to use a different buffer; is that correct?

A. Well, it depends on what the cause of your change in color is.

Q. Well, if it's -- the cause is what Dr. Dix believed histidine to cause in liquid formulations, would a change of color to yellow in your histidine formulation motivate you to change the buffer to something non-histidine?

A. So if you were able to establish that the histidine was changing and forming a yellow compound, which it is known to do, yes, it would be logical to try a different buffer and see if that was suitable for the molecule.

Q. At this time in the formulation development group, April 2005, did you consider histidine a suitable formulation -- a suitable buffer for your IVT formulation?

MR. FLETCHER: Objection.

THE WITNESS: At this time, in 2005, I had too little information to make that assessment.

BY MR. SALMEN:

Q. Did you, as of this time, in April 2005, had you evaluated any histidine-buffered formulations for VEGF Trap in an intravitreal

solution?

A. I -- honestly, I don't recall. I'm sorry.

Q. Last question on this document.

At this time, in April 2005, were you aware of Avastin being used off-label to treat wet AMD?

A. Was I personally aware of it?

Q. Yes.

A. Actually, I don't believe so, but, I mean, I don't have a recollection of knowing that at this point in time.

Q. We're going to move on to another document, Dr. Graham, Defendant's Exhibit 723. It should be in your binder.

A. 723, you said?

Q. Yes, 723, Bates number -- the first page Bates number is 580273.

A. Okay.

Q. Dr. Graham, do you recognize Exhibit 723?

A. Give me a minute to look through it. Okay.

Q. The memo is from you and Dan Dix to Laura Pologe. Who is Laura Pologe?

A. It's Laura Pologe.

Q. Pologe.

And who is she?

A. So Laura Pologe was a Regeneron employee.

Q. What department?

A. She was in regulatory affairs.

Q. Okay. And can you describe what information this memorandum is providing to Laura Pologe --

A. Sure.

Q. -- in regulatory affairs?

A. I think so, yes.

Q. Please describe it.

A. Okay. So one aspect of drug development is called demonstration of acceptability or demonstration of acceptance under conditions of use. So what this is is this summarizes a syringe compatibility or a condition of use study is a more common term for it.

In this study you take drug product and you handle it in the same manner as you would expect a clinician to and assess the impact of the manipulations on the product quality.

So in this specific case, we looked at two different drug product images. One was an image that contained 40 mg per mL VEGF Trap and the other was an image that contained 30 mg per mL -- excuse

me -- 10 mg per mL VEGF Trap.

Both of these formulations or both of these images were in formulations that contained 10 millimolar phosphate, 135 millimolar sodium chloride, and 0.1 percent PEG 3350.

In the study, as was described, we removed material from a vial drug product into a disposable syringe. We used a 27-gauge needle, half-inch long, to withdraw the product from the vial. We then replaced that needle with a 30-gauge half-inch needle and assessed how the product performed in a disposable syringe over a span of about four hours.

This result was compared to a control vial in which drug was left in the original primary container and held under the same conditions for four hours.

Q. So do I understand correctly the control vial, the contents formulation in that control, did not go through a syringe?

A. That is correct.

Q. Now, you described the steps of loading the syringe and simulating the injection of the formulation through the syringe. Were those the types of steps that caused the shear stress that you were describing earlier today that was a

potential cause for the precipitation problems you were experiencing?

A. They were similar.

Q. Can you describe what the differences would have been?

A. Well, you know, based on my recollection when we were assessing the impact of shear stress, the rate at which the product was expelled from the needle was much, much greater. You know, we -- instead of going at a reasonable or what I would describe as a reasonable rate for ejection of the product, we went as fast as we could. So it was as rapidly as you could.

Q. Okay. This study that's in Exhibit 723, were these meant to simulate more of a clinical-style rate of injection?

A. Yes. I think I had indicated that earlier.

Q. I'm sorry if I missed it. I wasn't trying to be duplicative.

And --

A. "Duplicative."

Q. In my questioning or -- never mind. Strike it.

Looking at the subject line here,

Dr. Graham, you mentioned that there were two concentrations of the formulation being tested, 10 milligrams per mL and 40 milligrams per mL; is that correct?

A. Yes.

Q. And the components of the intravitreal formulation are listed in that first paragraph as 10 millimolar phosphate buffer pH 6.3, 135 millimolar sodium chloride, and 0.1 percent PEG 3350; correct?

A. That is correct.

Q. Is that the same formulation for both concentrations, 10 milligrams and 40 milligrams?

A. Yes, I believe so.

Q. Did you have to increase the concentration of any of the excipients to accommodate the 40-milligram sample?

A. What do you mean -- I'm sorry. You're confusing me here.

Q. So let's look at the 0.1 percent PEG 3350. Was 0.1 percent PEG 3350 used in the 10 milligrams per mL formulation?

A. Yes.

Q. And did you have to increase the amount of PEG 3350 for the 40 mg per mL formulation?

A. I guess I don't understand why you're asking me that question.

Q. Well, we can get to that, but can you answer whether or not you increased the PEG 3350 in the 40 mg per mL solution?

A. Okay. So, you know, I described the formulations when I initially went through the document, and you read the formulations back to me.

You know, one is a 10 mg per mL formulation that contains 10 millimolar phosphate buffer, 135 millimolar sodium chloride, and 0.1 percent PEG 3350.

The other formulation is 40 mg per mL VEGF Trap in a formulation that contains 10 millimolar sodium phosphate buffer, 135 millimolar sodium chloride, and 0.1 percent PEG 3350.

If I'm describing the formulations as having the same composition, why are you asking me if I increased the level of one of the excipients?

Q. I'm just asking if you -- in order to maintain a stable formulation, did you have to increase the amount of any of the excipients with the increase -- to accommodate the increase in the amount of drug substance?

MR. FLETCHER: Objection.

THE WITNESS: Okay. I'm sorry. You're going to have to ask it again with the objection.

BY MR. SALMEN:

Q. Sure.

Let me ask it this way: If you were to have these two formulations side by side, 10 milligram per mL VGEF Trap and 40 milligrams per mL VEGF Trap using the IVT formulation described in this document, would there be any differences in the composition other than the amount of drug, VEGF Trap?

A. There should not be.

Q. Okay. And did you experience any solubility problems with the 40 milligram per mL solution that you did not experience with the 10 milligrams per mL solution?

A. Repeat that to me one more time.

Q. Sure.

Let me give you some context. If you look at the second-to-last paragraph on the first page, you describe there that the samples were incubated over four hours at 25 degrees Celsius.

Do you see that?

A. I do.

Q. And you concluded "No changes were observed in the visual appearance, turbidity, pH, total VEGF Trap recovered, and the percentage native VEGF Trap recovered."

Do you see that?

A. I do.

Q. So my question is in a side-by-side comparison, were there any solubility problems with the 40 milligram per mL sample that you did not experience with the 10 milligram per mL sample?

A. Okay. In this side-by-side comparison, there were no differences.

Q. You testified this morning about the litigation that you were deposed in between Regeneron and Novartis. Do you recall that?

A. I said that I was deposed for litigation with Novartis.

Q. And I believe you mentioned that Regeneron -- that the syringe at issue was available previously from Vetter. Am I stating that correctly?

A. Yes.

Q. So in this particular study, were you using one of the Vetter syringes?

A. No.

Q. Do you know what type of syringe you were using in this study?

A. Let me take a look.

Okay. So if you look at the second paragraph of the document.

Q. Yep.

A. And the second sentence says "After the contents of the drug product vial were loaded into a 1 mL BD syringe." So it was a 1 mL BD syringe.

Q. What's "BD syringe" mean?

A. So I think syringe is self-explanatory.

BD is a manufacturer known as Becton Dickinson.

Q. Okay. During your development, and along with this syringe compatibility study, were you concerned about the components of the formulation interacting with any of the components of the syringe?

A. So you're asking if I was concerned whether or not the formulation components would interact with the syringe?

Q. Yes.

A. Okay. So the reason why this specific study is conducted is to demonstrate that there is no interaction between the formulation components

and the syringe. There is always a possibility that a formulation or a drug, when it comes in contact with a new or previously untested material, could interact in some unexpected or nonexplainable way. You know, the product was in a vial, which is a very different environment than the BD syringe.

Q. Is the BD syringe a plastic vial -- I'm sorry. Strike that.

Was the BD syringe a plastic material?

A. So we're describing a 1 mL BD syringe. It was possibly one of two materials. I'd have to go pull the study to know exactly which one of the two materials it was. BD makes 1 mL syringes using polypropylene, and they also make 1 mL syringes using -- or syringes using polycarbonate.

Q. Looking at the tables of this stability study that you conducted, Dr. Graham.

A. Yes.

Q. In the last column, you reported percent native VEGF Trap recovered?

A. Yes.

Q. And would you -- did you conclude that this was an acceptable amount of recovery to demonstrate the stability of the formulation?

MR. FLETCHER: Objection.

THE WITNESS: Okay. So this is not a -- this is a condition of use study, and the metric used in this study is did I change from what I started with. It's not an assessment of stability. It's an assessment of change. So our metric is if you start with 98.8 or 98.7, you should end with 98.8 or 98.7 within the error of your assay, and this study demonstrates precisely that.

BY MR. SALMEN:

Q. Is that because the control vial demonstrated 98.7 percent native VEGF Trap recovered as compared to any of the syringes?

A. So as I said, no change within the error of the assay, and, you know, all these numbers are the same within the limitations of the assay.

Q. Okay. So do these numbers reflect that the syringe -- let me restate that.

Do these numbers reflect that the formulations being tested had good compatibility with the syringe?

A. So this demonstrates that the formulations were compatible with the syringe under the conditions tested, yes.

Q. Okay. Did this stability or syringe compatibility study -- let me strike that and

restate it.

After conducting this syringe compatibility study, did you make any recommendations to the formulation group to change the intravitreal formulation that's listed here?

A. So the purpose of this study was not for development. The purpose of this study was to demonstrate suitable in use or compatibility characteristics.

Q. At this time was the -- is it IVT or ITV as it -- how did you refer to it? I see both.

A. So I believe we were going with IVT 1 and IVT 2.

Q. So this is just a typo here on Exhibit 723?

A. Well, so we hadn't nailed down, I think, a consistent abbreviation at this point. You know, I do have some level of dyslexia. So I may be mixing it up right now. I'd have to go back to my list of acronyms that I keep so I keep myself honest, but I think for the purposes of discussion, if we say ITV versus IVT, we can call those the same at this point.

Q. Okay. No, that's fine. I just wanted to make sure I was representing it correctly.

A. Yeah, I know, I mean I looked at it, and I'm like no, yeah, it's --

Q. So at this point, in March -- as of March 10, 2006, when you made this report, was the ITV 1 formulation that included the 0.1 percent PEG, was this the lead candidate formulation for the intravitreal formulation?

A. What do you mean by "lead candidate"?

Q. Well, I think Dr. Furfine testified that this was the first one that was taken to the clinic. Is that your understanding?

A. Okay. If your question is was this the first formulation taken to the clinic, then the answer is yes.

Q. Okay. I'll describe it that way, then.

What other formulations were taken into the clinic after the ITV 1 formulation?

A. The ITV 2 formulation was taken into the clinic.

Q. Do you recall the components of that one?

A. Yes, I do.

Q. What are they?

A. So the formulation components were 10 millimolars sodium phosphate, 40 millimolars sodium chloride, 5 percent sucrose, and

0.03 percent polysorbate 20.

Q. Keep the 723 exhibit open. I want you to also look at your patent, please, the '865 patent, which I believe we marked or was previously marked as Exhibit 703.

The ITV 1 formulation that's described in this document, 723, is this an embodiment of your claim 1 of the '865 patent which appears on column 19?

MR. FLETCHER: Objection.

BY MR. SALMEN:

Q. Can you answer the question, Dr. Graham?

A. Sorry. What was the question again?

Q. So looking at your ITV 1 formulation that's described on Exhibit 723 --

A. Yep.

Q. -- can you tell me if that is an embodiment of the vial formulation that you claimed in your '865 patent, claim 1?

A. So by "embodiment," do you mean that the claims of the '865 patent cover this formulation that's in Exhibit 723?

Q. Yes.

A. Well, I mean, if we look at claim 1, you have VEGF Trap or antivascular epithelial growth

antagonist, you've got an organic cosolvent, you've got a buffer, and you've got a stabilizing agent.

The material that's described in 723 has a VEGF Trap antagonist, it has a buffer, it has an organic cosolvent, and a tonicifying agent. It does not have a stabilizing agent. So, no, it's not covered under the patent.

Q. Okay. So the sodium chloride tonicity agent would not qualify as a stabilizing agent under claim 1?

A. No.

Q. Why not?

A. Well, in the case of what defines a stabilizing agent, it is something that improves certain aspects of or provides a resistance to certain pathways of degradation that a molecule may experience.

Q. Would the polyethylene glycol qualify as a stabilizing agent given that definition?

A. No, the polyethylene glycol is really an organic cosolvent in this case.

Q. Can you provide a basis for that conclusion?

A. What do you mean by a "basis"?

Q. Why are you concluding that it is a

cosolvent and not a stabilizing agent?

A. To provide a detailed answer to that, I would have to go back and review the experimentation that was done.

Q. Let's me ask you, is the polyethylene glycol stabilizing the formulation from aggregation?

MR. FLETCHER: Objection.

THE WITNESS: I'm sorry. I can't answer that because I would have to review specific data looking at that, and I don't have a recollection of data looking at the effect of polyethylene glycol on aggregation.

BY MR. SALMEN:

Q. Okay. Why don't you tell me, then, what the poly -- what role the polyethylene glycol is performing in the formulation that leads you to conclude that it is acting as a cosolvent?

A. So -- and this is to the best of my recollection -- I believe that polyethylene glycol was shown to improve stability to agitation stress.

Q. Did the polyethylene -- was the polyethylene glycol used to bring the VEGF Trap into solution to dissolve it?

A. It was not a solubilizing agent, no.

Q. Dr. Graham, this solution that's described here, this ITV formulation, was this made from using a drug substance formulation being added to a -- other components to form the intravitreal formulation?

Let me ask it this way: Was there a separate drug substance formulation for VEGF Trap-Eye -- VEGF Trap?

A. Okay. You've kind of asked me four questions here, most of which, in my mind, are not equivalent questions.

When you're saying "was this," what are you referring to? Let's start there.

Q. Let me -- give me a second. I'll find you an example.

Do you have Exhibit 708 in your binder?

A. Not in front of me at this point. Hang on. I will warn you, I am running out of table space here.

Q. Okay.

A. Grab those back. I may want them.

Okay. You said Exhibit 708?

Q. Yes.

A. Okay.

Q. And do you see this is an email from

December 2003 that was forwarded to you? Do you see that?

A. Yes.

Q. The subject line -- sorry -- the subject line of this email is "Drug Substance Buffer." Do you see that?

A. Uh-huh.

Q. Okay. So when I was referring to a drug substance formulation, I was referring to this. Is it your understanding that this is how the drug substance formulation was comprised?

A. Okay. Can I have a minute to read through this?

Q. Sure.

A. Let's try this again. So what is your question?

Q. Well, first, do you have a recollection of this being the drug substance solution as opposed to the drug product solution?

A. So the drug substance solution for what?

Q. VEGF Trap.

A. For Eylea?

Q. Yes.

A. So this was not the drug substance solution for Eylea.

Q. What was this the drug substance solution for?

A. This was the drug substance solution for Zaltrap.

Q. Can you explain to me how you were able to identify that?

A. The primary and most significant difference is the presence of citrate.

Q. So in the drug substance formulation that was used for the Eylea intravitreal formulation, citrate was not included?

A. That's correct. There was no citrate in that drug substance formulation.

Q. Was there a reason why citrate was not included in that formulation?

A. Well, so we had determined that the presence of citrate in a formulation when it was given subcutaneously could cause stinging, kind of like a wasp sting, if you can imagine that, and we kind of conceptually felt that, you know, stinging in your arm is one thing, stinging in the eye is something totally different. So we believed it was best to remove the sodium citrate because we thought it would cause stinging in the eye.

Q. So you never developed an intravitreal

formulation that included a citrate buffer for VEGF Trap?

A. During what time frame?

Q. From 2005 when you were -- when you moved to the formulation development group to any time through filing of your patent application in June 16, 2006.

A. I don't recall manufacturing or developing a citrate-containing intravitreal formulation for human use.

Q. Is that because you concluded it would not have been suitable as an intravitreal formulation?

MR. FLETCHER: Objection.

THE WITNESS: What is your definition of "suitable"?

BY MR. SALMEN:

Q. I am using the words from your '865 patent, claim 1, "a vial comprising an ophthalmic formulation suitable for intravitreal administration."

A. Okay. So if I answer that based on my knowledge at the time, I would not have been able to deem a citrate-containing formulation as either suitable or not suitable because we would have had to have performed some level of testing in animals

to demonstrate whether or not it was well tolerated, and I do not believe that we ever injected a citrate-containing formulation into an animal at that time -- well, at least not into a nonhuman primate at that time.

Q. Okay. So I just want to see if we can come to an understanding of what the drug substance buffer was for the intravitreal formulation. So I'm back at Exhibit 708.

A. Sure.

Q. And you said the intravitreal drug substance formulation did not include 5 millimolar citrate; is that correct?

A. I did say that, yes.

Q. What was the phosphate buffer concentration of the intravitreal drug substance buffer?

A. It was 10 millimolar phosphate.

Q. Did the intravitreal drug substance buffer have a concentration of 100 millimolar sodium chloride?

A. No.

Q. What was that concentration?

A. I don't believe there was any added sodium chloride. There was none.

Q. Okay. Did the drug substance buffer for the intravitreal formulation have any polysorbate 20 in it?

A. There was no added polysorbate 20 to the drug substance.

Q. Were there any other excipients in the drug substance formulation for the intravitreal product?

A. No.

Q. So it was just 10 millimolar phosphate?

A. Yes.

Q. Okay.

MR. FLETCHER: If we are moving on, we've been going for over an hour. Let's take a break.

MR. SALMEN: Sure.

THE VIDEOGRAPHER: We are going off the record. The time is 2:46 p.m. This is the end of Media Unit No. 4.

(A short break was taken.)

THE VIDEOGRAPHER: We are going back on the video record. The time is 2:58 p.m., and this is Media Unit 5.

BY MR. SALMEN:

Q. Dr. Graham, I'd like to pick up where we left off. I'm going to direct you to a new

exhibit. This will be a new one. So they may have to print this one up for you. The first page is Bates No. 580791.

MR. SALMEN: And this is Tab 13, Mike.

That doesn't look like the right document. Hang on.

Sorry. 580791 instead of 570. It's Tab 16, please. We can show this on the screen.

BY MR. SALMEN:

Q. I'll just ask you some foundational questions, Dr. Graham, until you get a printed copy of it.

(Whereupon, Exhibit 736 was marked for identification.)

THE WITNESS: Am I done with these others?

BY MR. SALMEN:

Q. You can set them aside for now, but you may want to keep your patent handy.

THE TECHNICIAN: I believe that will be Exhibit 736.

MR. SALMEN: Yes. Can we mark this Exhibit 736, please?

BY MR. SALMEN:

Q. Dr. Graham, do you see the cover email here is dated Friday, April 21, 2006?

A. Yes.
Q. This is an email from you; is that correct?
A. Yes.
Q. And you provide one statement in the body of the email that reads, quote, "Attached are the 40 mg per mL and placebo recipe for the 0.03 percent polysorbate containing ITV formulation."
Do you see that?
A. Correct.
Q. And then there's an attachment?
A. I'll take your word for it.
Q. Do you see the attachment line there?
A. I'm taking your word for it.
Q. Well, let's turn the page.
Have you gotten your own paper copy now?
A. Yeah, I just got it.
MR. FLETCHER: The witness now has a paper copy.
MR. SALMEN: Mike, we can take this down now.
THE WITNESS: Okay.
BY MR. SALMEN:
Q. At the top of the page 1 of the attachment, you see it says "page 1 of 1"?

A. Yes.
Q. And is that your name and signature there?
A. It certainly is.
Q. Okay. Can you describe what this document is referring to, page 1 of 1?
Let me ask a better question.
What is the "Placebo for ITV VEGF Trap in a Polysorbate Containing Formulation" referring to?
A. So in our world at Regeneron, a placebo is a matched solution to a drug product formulation or a, more appropriately, drug formulation that lacks the active ingredient.
Q. Okay. So this placebo formulation does not include the active ingredient VEGF Trap; is that correct?
A. That is correct.
Q. Okay. If we look at the next page, there is another part of this attachment that has two pages to it, and is that your name and signature at the top?
A. Of page 1, yes; page 2, yes.
Q. Okay. And the header for this page, which is Bates-numbered 580792 is, quote, "Revised pH for 40 mg per mL VEGF Trap for ITV in a 0.03 percent polysorbate-containing formulation."

Do you see that?
A. I do.
Q. Here -- is this the ITV 2 formulation that you were referring to earlier?
A. No, it is not.
Q. What's the difference between this to the ITV 2 formulation?
A. So there are several differences.
Q. Okay. Let's go down the list.
A. So the ITV 2 formulation that I described earlier has a lower level of sodium chloride, and it contains sucrose.
Q. And the ITV 2 formulation is the one that you said was carried through to the clinic; is that correct?
A. That is correct.
Q. Okay.
A. Well, that one is the one that was carried through commercially. I don't know if we ever dosed this, but I don't recall.
Q. So I want to compare this formulation to the ITV 1 formulation with the polyethylene glycol. So if you need that formulation in front of you, that was Exhibit 723.
A. Okay.

Q. Both of these formulations, the ITV 1 formulation on Exhibit 723 and the formulation on exhibit -- sorry --

MR. SALMEN: Mike, what number did we mark this?

THE TECHNICIAN: The last one was --

MR. SALMEN: 736?

THE TECHNICIAN: Correct.

BY MR. SALMEN:

Q. Let me ask the question again, Dr. Graham.

Both of these formulations use 10 millimolar phosphate buffers; is that correct?

A. They do.

Q. Both of these formulations use 135 millimolar NaCl; is that correct?

A. Yes.

Q. And the 40 milligram per mL sample in Exhibit 723 would include the same 40 milligrams per mL of VEGF Trap that appears in the 736 exhibit; correct?

A. Yes.

Q. And they both have the same pH, pH of 6.3; correct?

A. Yes.

Q. So would you agree with me that the only

difference in these two formulations is that ITV 1 used polyethylene glycol 3350 and the Exhibit 736 formulation used 0.03 percent polysorbate 20?

A. With respect to basic composition, yes, that is correct.

Q. And did you draft Exhibit 736, this report that's titled "Revised pH for 40 mg per mL VEGF Trap for ITV in a 0.03 percent Polysorbate Containing Formulation"?

A. Well, I certainly signed off on it. I'm not sure if I drafted the entirety of the document.

Q. And before you signed off on it, you would have reviewed it to make sure it was accurate?

A. I would have, yes.

Q. Okay. In this table it shows the different materials used in the formulation that's described directly above the table; correct?

A. It does.

Q. And for water for injection, the function is solvent; correct?

A. Uh-huh.

Q. And for phosphate, the function is reported as buffer; correct?

A. Correct.

Q. And then there's another entry for

phosphate dibasic 7-hydrate, and the function is buffer; is that correct?

Sorry. Was that a yes?

A. That was a yes.

Q. Next in Row 4 there's sodium chloride, and the reported function there is salt. Do you see that?

A. Correct.

And there is a note on that.

Q. "See Note 1 below."

What is that referring to? Is that on page 2?

A. That is on page 2, which is interesting.

Q. Okay. Let's finish the table, and then we'll get to that note, if that's okay.

And then the next material that's listed in Row 5 is 10 percent polysorbate 20, and the function of that is reported as stabilizer; correct?

A. That's what the table says, yes.

Q. Okay. Now, in the ITV 1 formulation that differs only by the use of polyethylene glycol instead of polysorbate 20, would you describe the function of the polyethylene glycol in the ITV 1 formulation as functioning as a stabilizer?

A. No, I would describe it as a cosolvent.

And, you know, as I'm looking at the recipes on the other document, that really should be described as a cosolvent as well. I am rather surprised I put stabilizer. I suspect what happened is we grabbed the recipe that was set up to include sucrose in it and just substituted a couple materials in and didn't go through and get the functions, but --

Q. Okay. Well, sucrose hadn't been -- sucrose hadn't been included in the formulation at this point; right?

A. Well, this was in 2006. So by 2006 we were testing sucrose-containing formulations. In fact, the first time we made the sucrose-containing ITV formulation was September 29 of 2005 and don't ask me why I know that but I know that.

Q. I am going to ask you why do you know that?

A. Because I looked it up because I was asked, you know, was it on or before a date, and I think it was November or thereabouts, and I thought we had actually done it before. So I went and looked and, sure enough, we had done it before.

Q. I'm going direct your attention to Exhibit 725.
A. 725?
Q. Yeah. It should be in your binder.
A. All right. Can I ask a question? Can I get rid of 708?
Q. What is 708?
A. That's the drug one you were asking questions about drug substance.
Q. Yes. But don't get rid of 736. We're going to come back to that one.
A. You said 725?
Q. Yes.
A. Okay.
Q. Now, in 725, this is an email from you dated May 8, 2006. Do you see that?
A. I do.
Q. You're addressing this to Ellen. Do you see that?
A. To Ellen-Marie Koehler-Stec, yes, I see that.
Q. And here you provide compositions for two formulations; is that correct?
A. Correct.
Q. And what you identify as the backup

formulation, that comprises 10 millimolar phosphate, 135 millimolar sodium chloride, 0.03 percent polysorbate 20, 5 to 10 milligrams per mL of VEGF Trap, and pH 6.3. Do you see that?

A. I do.

Q. And the subject line of this email is "VEGF Trap Formulations for ITV"?

A. Correct.

Q. And "ITV" is a reference to intravitreal; right?

A. Correct.

Q. So this was the backup formulation for intravitreal VEGF Trap?

A. It was a backup formulation we had considered, yes.

Q. Here you describe it as "the backup formulation," correct?

A. I do describe it as "the."

Q. And can you confirm this formulation is the same formulation we were just describing in Exhibit 736?

A. In terms of the 40 mg per mL variance, yes, I believe it is the same.

Q. Okay. Now, I think you previously

testified that, in your opinion, the reference to polysorbate 20, 10 percent, functioning as a stabilizer in 736 was an error. Is that your testimony?

A. Yeah. It should really be a cosolvent.

Q. Okay. And you see on the previous page in the placebo formulation, Row 5, 10 percent polysorbate 20 is -- the reported function is also stabilizer. Do you see that?

A. Yep, I do.

MR. SALMEN: Okay. And can we pull up another exhibit? It's going to be a new one. Tab 36, please. And, Mike, we'll mark this as the next exhibit number. Actually, it's Tab 37.

(Whereupon, Exhibit 737 was marked for identification.)

MR. SALMEN: Sorry.

THE TECHNICIAN: Okay. And that will be exhibit DX 737.

MR. SALMEN: So Tab 37 we're marking as DX 737.

I'll state for the record that DX 737 bears Bates number RGN-EYLEA-MYLAN 00571130 through 571132.

Are we getting Dr. Graham a hard copy of that, Tom, or should we put it on the screen?

MR. FLETCHER: Just give us one minute. It's printing.

MR. SALMEN: Mike, can you pull it up on the screen?

BY MR. SALMEN:

Q. And, Dr. Graham, I'll just ask you foundational questions until you have a hard copy.

Do you see the cover email here is dated Thursday, April 6, 2006?

A. Okay.

Q. Do you see that?

A. Yep.

Q. And this is an email from -- can you identify who this email address is?

A. I believe it was a scanner.

Q. Okay. And it went directly to you?

A. If that's, in fact, what it was, a scanner, yes, that would have gone directly to me.

Q. And the one line in this email reads "This is data from the scanner"; is that correct?

A. Yes.

Q. And does this indicate to you that you, yourself, would have scanned this document to your email?

A. I mean, anybody that has access to the

scanner could have scanned it to my email.

Q. But this would have shown up in your email box; correct?

A. It could have come into my inbox, yes.

Q. And let me know when you have a hard copy of this document.

A. They just handed it to me.

Q. Okay.

MR. SALMEN: Mike, we can take that down now, please.

BY MR. SALMEN:

Q. You'll see here the attachment that was scanned in. So I'm starting on the second page of the exhibit. At the top it reads "page 1 of 2." Do you see that?

A. I do.

Q. And your name and signature are above that. Do you see that?

A. I do.

Q. And as similar to what I asked you with regard to Exhibit 736, would you have reviewed this for accuracy before you signed it?

A. Yes.

Q. And you see the -- there's a formulation that's described here on page 1?

A. Yes.
Q. And the title of this is "40 mg per mL VEGF Trap for ITV in a sucrose and polysorbate-containing formulation SPEC C710."
Do you see that?
A. Yes.
Q. Is this the ITV 2 formulation?
A. It appears to be, yes.
Q. Okay. And here you again list the -- in the table below the formulation, you list the materials; is that correct?
A. I do.
Q. And then in the last column of that table, you provide the function of those materials. Do you see that?
A. I do.
Q. And here for sucrose -- sucrose was not in the 736 formulation; correct? Exhibit 736 formulation?
A. Which one is 736?
Q. It's the one we just looked at that has a similar table to this one.
A. Yeah. No, it was not.
Q. Here sucrose is listed in Row 5, and the reported function is stabilizer. Do you see that?

A. I do.

Q. Do you have any disagreement with that reported function?

A. With sucrose, no.

Q. And here in Exhibit 737, page 1 of 2 that bears your signature, which you would have reviewed for accuracy before you signed it, in Row 6, it says 10 percent polysorbate 20, and the reported function is stabilizer. Do you see that?

A. I do.

Q. Do you disagree with the reported function that you listed here?

A. I do. I'm at least consistent when I make a mistake. It should be cosolvent. So it's interesting when you see the errors you made -- what? -- 16 years ago, give or take.

Q. Let me ask you, Dr. Graham, what would polysorbate be stabilizing the formulation from in this solution?

MR. FLETCHER: Objection.

THE WITNESS: Well, so polysorbate 20 functions as a cosolvent, which imparts resistance or stability, if you want to call it, to specific types of stresses. These include interfacial stability under conditions like filtration, contact

with certain surfaces. It also provides resistance to agitation stress and shear stress, among other types of stress.

BY MR. SALMEN:

Q. Are you familiar with the term "surfactant"?

A. I am.

Q. What role does a surfactant serve in a formulation?

A. Well, a surfactant is typically used as an organic cosolvent. It is a specific class of molecules which can be used as cosolvents in much the way PEGs or polyethylene glycols can be used as cosolvents.

Q. So would the role of a surfactant in the formulation be identical to the answer you just described as of the role that polysorbate served in stabilizing the ITV 2 formulation?

A. Could you repeat the question, please?

Q. I first asked you what the role of a surfactant was in a pharmaceutical formulation.

Do you recall providing an answer to that?

A. I do.

Q. So my question is, is that role identical to the roles you described for the polysorbate 20

which you reported as functioning as a stabilizer in the ITV 2 formulation of Exhibit 737?

MR. FLETCHER: Objection.

THE WITNESS: All right. There's a lot of words in there. I got an objection. I'm sorry. You have to repeat yourself again.

MR. SALMEN: I'll ask the court reporter to repeat that question.

(Whereupon, the record was read.)

THE WITNESS: Okay. So the polysorbate 20, which is present in the ITV formulation as a cosolvent, provides demonstrated resistance to agitation stress and presumably provides resistance to other types of stress as well.

BY MR. SALMEN:

Q. Does the polysorbate 20 in the ITV 2 formulation described on Exhibit 737 act as a surface active agent?

A. Can you define what you mean by "surface active agent"?

Q. A surfactant.

A. I'm sorry. I don't understand what you mean by a "surface active agent."

Q. What's your understanding of a surfactant?

Does it have a definition for you?

A. So a surfactant is an amphiphilic molecule that has the ability to work as a bridge between hydrophobic and hydrophilic areas.

Q. Is that the same definition that you gave for a cosolvent in the formulation, ITV 2, as described in Exhibit 737?

A. This is the definition I would give to a cosolvent, yes.

Q. Is the polysorbate 20 in the ITV 2 formulation that's described in Exhibit 737 a surfactant?

A. So polysorbate 20 is a surfactant which is a particular subset of organic cosolvents that are used during development or to impart desired characteristics to protein formulations.

Q. Are you aware of any textbook or handbook that refers to polysorbate 20 as a cosolvent?

A. I mean, quite frankly, I haven't relied on textbooks or handbooks in my development work. So it's not something that I referred to because there really is no handbook for protein formulation development. Every protein is different. Every protein has different requirements. So it's kind of a challenging field, and you've got to determine

everything empirically.

Q. So, Dr. Graham, you testified that polysorbate 20 functions in the ITV 2 formulation on Exhibit 737 as a cosolvent which imparts resistance or stability. Do you recall --

A. I do.

Q. -- providing that testimony?

Explain to me why with that description it's inaccurate, in your opinion, for Exhibit 737 to report the function of polysorbate 20 as a stabilizer.

A. Well, if, for example, I was to make a formulation that contained polysorbate and maybe buffer and a protein, that formulation would actually become less stable than a comparable formulation without the presence of polysorbate for certain types of stress. An example would be thermal stress. Addition of polysorbate to formulations is destabilizing when you subject materials to thermal stress.

Q. Okay. So looking at Exhibit 737, the table that you provide there, Row 6, 10 percent polysorbate 20, if the function column stated imparts resistance or stability to specific types of stresses, would that be accurate?

A. If it stated that it was a cosolvent that imparts stability to agitation stress or interfacial stress, that would be accurate, yes.

Q. Can I ask when you came to the conclusion that the table in 737 for ITV formulation 2 was inaccurate in its report of -- as stabilizer for polysorbate 20? When did you first come to that conclusion?

A. When I saw it today, I looked at it, and I said, "Shoot, I made a mistake."

Q. Let me direct your attention to page 2 of 2 of Exhibit 737.

Are you there, Dr. Graham?

A. Which page? 2 of 2?

Q. Sorry. So I'm at Exhibit 737, which is the cover of the exhibit is the email that says "Data from Scanner."

A. Oh, sorry. Okay.

Q. So I want to talk about the drug substance formulation that's referenced on page 2 of 2.

A. Okay.

Q. Okay. The first paragraph states, quote, "This recipe is based on drug substance at a VEGF Trap concentration ranging from 65 to 45 milligrams per mL in 10 millimolar phosphate

with no NaCl."

Do you see that?

A. I do.

Q. Is this the drug substance formulation that you were describing earlier in our discussion that was used for the intravitreal formulations?

A. I was describing a drug substance that contained 10 millimolar phosphate only, yes.

Q. And this drug substance formulation did not include any polysorbate; correct?

A. There was no added polysorbate.

Q. And there was no added polyethylene glycol in this drug substance formulation; correct?

A. There was no added polyethylene glycol.

Q. How was this drug substance formulation stored?

A. At the time we stored it frozen at minus 80 degrees C.

Q. So then it would have to be thawed before it was used to make the drug product formulation; is that correct?

A. If it had been frozen, it would need to be thawed to be used, but the drug substance can be taken directly from manufacturing and, you know, converted to formulated drug substance.

Q. Okay. So can you describe how the drug product formulation was created here starting with the drug substance formulation?

A. You want me to walk step by step through what we would do?

Q. Well, I'm just referring to the document where it provides recipe notes.

A. Okay.

Q. And within the context of this document, can you tell me, yes, step by step, how the drug product formulation was prepared?

A. So, typically, what we would do is determine how much of the drug substance we wanted to formulate. Is it 1 liter? 2 liters? 10 liters? 300 liters? Whatever that is.

And you would look at what, in this case, the concentration of the drug substance is, and based on that concentration, you would know you needed to achieve a final dilution of the drug substance to hit your target 40 mg per mL protein concentration.

From that piece of information, you would understand the volume of concentrated excipient buffer that would have to be added to the drug substance to achieve the FDS at the desired

concentration.

Once you knew that, you would also know what the total volume of formulated drug substance is that you would make. So when you have the total volume of formulated drug substance, you would go back and calculate the amount of excipients added such that you would achieve the final concentration that is described in the table.

After you've calculated that -- you know, keep in mind that you have to account for anything that's already in the drug substance which, in this case, is the phosphate -- you would weigh out the appropriate amount of each one of the items on the list, with the exception of the polysorbate, and as a solid, add them to your volume of liquid that would be -- or partial volume of liquid that would be added to the DS to achieve the formulation and mix them until the solvent solids dissolved.

Once the solids dissolved, because you were going to leave yourself a little bit of volume, you would add the polysorbate to that concentrated buffer mix as a liquid because it's a 10 percent solution. You would mix that until it was uniform, but you would take care not to cause bubbling.

And at that point you would have a concentrate that when added to your mass or volume, however you want to measure it, of drug substance produces an amount of formulated drug substance which contains the correct composition of all the components.

Q. So if I understand correctly, and I think this is reflected in Recipe Note 2, all of the excipients, so everything with the exception of the drug substance, are combined first and mixed into solution before they're added to the drug substance; is that correct?

A. That is correct.

Q. And is that what you were referring to as the concentrated -- the concentrated solution?

A. The concentrated excipient buffer, yes.

Q. Okay. I'll refer to it as the concentrated excipient buffer.

Would that concentrated excipient buffer comprise the 10 millimolar phosphate?

A. Okay. So that concentrated excipient buffer would contain 10 millimolar phosphate, yes.

Q. And referring to page 1 of 2 of this exhibit, would it contain all of the excipients listed in the formulation with the exception of the

VEGF Trap?

A. The excipient buffer would contain all of the excipients listed, and it would not contain the VEGF Trap.

Q. Okay. In that concentrated excipient buffer solution, what is the function of the sucrose?

A. In the concentrated excipient buffer solution?

Q. Yes.

A. Well, the sucrose is there such that it can be added to the protein. There is no function in the concentrated excipient solution.

Q. What is the function of the polysorbate in the concentrated excipient buffer solution?

A. It has no function at that point.

Q. So if I understand you correctly, the sucrose doesn't have a function until the drug substance VEGF Trap is present in the solution?

A. That's when it has a function, yes.

Q. And with respect to the polysorbate, it does not have a function in the solution until the VEGF Trap is present?

A. That is correct.

Q. In the drug substance solution, the drug

substance formulation, what's the role of the 10 millimolar phosphate?

A. So to be clear, you're asking for the role of the 10 millimolar phosphate in the drug substance, not the --

Q. Yes. Correct.

A. It's a buffer.

Q. Okay. And is water part of that solution?

A. Is --

Q. Is water part of the drug substance formulation?

A. So water is contained in the drug substance, yes.

Q. What is the role of the water in the drug substance formulation?

A. It works as a solvent.

Q. How does it work as a solvent?

A. How does it work as a solvent?

Q. Yes.

A. Wow. I mean, basically, it holds the protein in solution.

Q. That's in the drug substance formulation, the water acts as a solvent to hold the drug substance in solution?

A. That's correct, yes.

Q. In the ITV 2 formulation that's described here on Exhibit 737, this formulation also includes water; correct?

A. It does.

Q. What is the role or function of water in that formulation?

A. It's a solvent.

Q. How does it function as -- how does the water function as a solvent in the ITV 2 formulation?

A. In the same manner as it functions as a solvent in the drug substance.

Q. Does the water impart resistance from specific types of stresses on the drug substance?

A. Not to my knowledge, no.

Q. Okay. So I told you I would get back to a comment you made earlier, and I want to stay true to my promise. But you had pointed to the "See Note 1 Below," and I think we were actually referring to the previous document that has a similar table to this. But you said that looked interesting to you.

Can you explain why the Note 1 looked interesting to you?

And, actually, let me -- let me turn you

to Exhibit 736 because I don't think these two are -- say the same thing in this regard.

A. 736.

Q. Yes.

A. 737. This is 736. That's 736.

Q. Are you there?

A. I am here. I am looking at the note.

Q. So in seeing this reference in the table to "See Note 1 Below," I believe it was with respect to the sodium chloride. You said that looked interesting. So I wanted you to explain why that looked interesting to you.

A. So Note 1 in reference to sodium chloride, that was something that was carried forward. So I recognized kind of another error in there. Because if you read Note 1, it says "The amount of phosphate buffer must be reduced to account for the buffer entering the formulation from the drug substance. For example, if 45 percent of the final volume results from the addition of the drug substance, the amount of phosphate, monobasic and phosphate dibasic dihydrate listed in the table below" -- or table above in this case -- "would be reduced by 45 percent."

And I kind of looked at that, and I'm,

like, saying, "Shoot, there's another mistake," when it was on the salt. I did correct it in the subsequent one, I think, but...

Q. Okay.

A. I mean, I'm human. I make mistakes. Sorry about that. But it is what it is.

Q. I was going to shift gears. So maybe now is a good time for a quick break.

THE VIDEOGRAPHER: Going off the record. The time is 3:52 p.m. This is the end of Media Unit No. 5.

(A short break was taken.)

THE VIDEOGRAPHER: We are going back on the video record. Time is 4:06 p.m. This is Media Unit 6.

BY MR. SALMEN:

Q. Dr. Graham, I want to pick up where we left off, discussing Exhibits 736 and 737, and you've testified that the reference in these -- in the tables for the exhibits for the function of polysorbate as a stabilizer was a mistake on your part; is that correct?

A. I have, yes.

Q. And in 737, that was the ITV 2 formulation that went to clinic; is that correct?

A. Give me a minute.

Yes, that did go to clinic, I believe.

Q. You can keep that Exhibit 737 out.

MR. SALMEN: I ask, Mike, can we pull up Tab 43, please, and mark this as Exhibit 738?

(Whereupon, Exhibit 738 was marked for identification.)

BY MR. SALMEN:

Q. It's just a one-page document here, Dr. Graham.

MR. SALMEN: And, Tom, do you want to provide him a paper copy of this one?

MR. FLETCHER: We are working on it.

MR. SALMEN: Okay. Thank you.

Mike, if we pull this up on the screen, I'll ask Dr. Graham some foundational questions while he's waiting for the paper copy.

MR. FLETCHER: It's not in Exhibit Share yet.

MR. SALMEN: What we are marking as Exhibit 738 bears Bates number RGN-EYLEA-MYLAN 00338970, and if we blow up the top few lines of this, Mike.

BY MR. SALMEN:

Q. Dr. Graham, do you see the top of this document refers to BLA 125387? Do you recognize that as the BLA for Eylea?

A. I do.

Q. And this is Section 3.2.P.1, "Description and Composition of Drug Product." Do you see that?

A. I do.

Q. And go ahead and read the first paragraph --

A. I need to wait for the paper copy.

Q. I'll read it into the record then for you. The first sentence of the first paragraph here reads "VEGF Trap-Eye drug product (DP), 40 mg per mL is a sterile solution for intravitreal (IVT) injection. The DP is produced by formulating afilbercept drug substance in an aqueous buffered solution at pH 6.2, containing 10 millimolar sodium phosphate, 40 millimolar sodium chloride, 0.03 percent weight per volume polysorbate 20, and 5 percent weight per volume sucrose (see Table 1)."

Do you see that?

A. Uh-huh.

Q. Is it your understanding that this document was submitted as part of the BLA to FDA?

A. Yes.

Q. And this was submitted for the purpose of gaining FDA approval to market the VEGF Trap-Eye drug product in the United States?

A. Yes, it was.
Q. And is this the same formulation as the ITV 2 formulation that we were discussing with respect to Exhibit 737?
A. It's similar, yes.
Q. It uses the same concentration and buffer; correct?
A. It does.
Q. And it uses the same percentage of polysorbate 20; correct?
A. That is true.
Q. And then I believe it uses the same percent of sucrose; is that correct?
A. That is also correct, yes.
Q. And it also uses the same concentration of sodium chloride; is that correct?
A. Yes.
Q. The pH in the BLA document is reported as 6.2; is that correct?
A. That is correct.
Q. And the pH on Exhibit 737 is reported as pH 6.25?
A. Yes.
Q. Is that the only difference in these formulations?

A. That is the difference, yes, that I can see.

MR. SALMEN: Okay. Mike, if we can blow up the table on Exhibit 738.

THE WITNESS: I have a paper copy. I can't see what's blown up on the screen. It doesn't come up clearly. So...

BY MR. SALMEN:

Q. Okay. I'll have it up here for my benefit, then, if that's okay, Dr. Graham.

A. Sure.

Q. And I'll ask you to have Exhibit 737 open as well, the table there.

And do you see both tables, the one in Exhibit 737 on page 1 of 2 and Exhibit 738, the BLA document, both refer to water for injection as components in the formulation?

A. That is correct.

Q. And the function in both tables is solvent; is that correct?

A. That is correct.

Q. And the phosphate, the phosphate monobasic monohydrate is reported as a buffer in Exhibit 737; correct?

A. It is.

Q. And it's referred to as a buffering agent in the BLA document that was submitted to FDA; is that correct?

A. Yes.

Q. Are those two terms synonymous, buffer and buffering agent?

A. They are.

Q. And referring back to Exhibit 737, the table refers to phosphate dibasic 7-hydrate as a buffer; correct?

A. It does.

Q. And that corresponds to the entry on Exhibit 738, the BLA document submitted to FDA, sodium phosphate dibasic heptahydrate as a -- functioning as a buffering agent; correct?

A. That is correct.

Q. The sodium chloride entry on Exhibit 737, the function is reported as a salt; correct?

A. It is.

Q. Is the sodium chloride in the 737 formulation, the ITV 2 formulation, a tonicity agent?

A. It is, yes.

Q. Now, with respect to the sucrose in the 737 exhibit, formulation ITV 2, sucrose is reported

as a stabilizer. Do you see that?

A. It is.

Q. And in the BLA document, Exhibit 738, which was submitted to FDA, it's reported as a stabilizing agent. Do you see that?

A. Yes.

Q. Are those two terms synonymous to you, stabilizer and stabilizing agent?

A. They are not exactly synonymous. They share some common meanings, yes.

Q. What differences?

A. Well, so a stabilizer, in my world and my experience, typically, refers to some sort of a polyol, like sucrose or mannitol, sorbitol is an example, and those are typically responsible for adding some level of thermal stability. So a stabilizer is a subclass of stabilizing agent.

Q. Okay. And now I'll direct your attention to Exhibit 737, the row referencing 10 percent polysorbate 20. The function reported in this exhibit is stabilizer. Do you see that?

A. Yep.

Q. And that's the function that you identified as being a mistake on your part?

A. Solvent, yes.

Q. In the BLA document that was submitted to FDA, Exhibit 738, the polysorbate 20 is reported as a stabilizing agent. Do you see that?

A. I do.

Q. Was that a mistake, reporting it as a stabilizing agent to FDA?

A. So as I defined for the sucrose, stabilizing agent is a large subset of different things. Polyols are a stabilizer. Organic cosolvents, while not a stabilizer per se, can be a stabilizing agent for interfacial stresses and certain type of surface interactions, agitation stress. So it's kind of a very broad descriptive term that does not really call out the actual functionality of the molecule that's added.

Q. So if I understand your testimony correctly, polysorbate is a stabilizing agent but not a stabilizer?

A. That would be correct, yes.

Q. Would a polyethylene glycol be a stabilizing agent and not a stabilizer?

A. When it's used as an organic cosolvent, yes, it would be a stabilizing agent but not a stabilizer, yes. It can have other functions as well.

Q. So the polyethylene glycol in the ITV 1 formulation can serve two purposes, a stabilizing agent and a cosolvent?

A. Well, in the ITV formulation, the polyethylene glycol is an organic cosolvent. Now, I was thinking broadly. You know, you're giving me documents that would be going to the FDA. So I started thinking about other uses of polyethylene glycol that I have experienced with different types of formulations.

Q. Okay. Well, if we -- when I asked you about the claims of the '865 patent with respect to the polyethylene glycol formulation, the ITV 1, you testified that the polyethylene glycol was not a stabilizing agent in that formulation.

A. No. I said it was not a stabilizer.

Q. Well, look at the -- look at the claims of the '865 patent, column 19.

A. Okay.

Q. Column 19, claim 1, the formulation comprises, among other things, a stabilizing agent, not a stabilizer. Do you see that?

A. I do see a stabilizing agent, yes.

Q. So when I asked you about claim 1 with respect to the polyethylene glycol formulation, you

testified that the polyethylene glycol was not a stabilizing agent in that formulation; is that correct?

MR. FLETCHER: Objection.

THE WITNESS: Okay. So ask your question again.

BY MR. SALMEN:

Q. In the ITV 1 formulation, is polyethylene glycol a stabilizing agent?

A. So in that formulation its function is an organic cosolvent. Okay?

Q. In the ITV 2 formulation, with respect to claim 1 of the '865 patent, what is the function of the polysorbate 20?

A. The polysorbate 20 is an organic cosolvent.

Q. Is that its function?

A. That is its function.

Q. So I guess I'm not understanding why Regeneron listed here, in its BLA document, Exhibit 738, that the function of polysorbate 20 is stabilizing agent and not solvent, like water for injection. Can you explain that?

A. Well, polysorbate 20 has never been considered to be a solvent.

Q. Okay. Let me try another document. Let me shift gears for a second, Dr. Graham.

MR. SALMEN: Mike, can we pull up exhibit -- what we marked at the beginning of the day -- 733?

BY MR. SALMEN:

Q. Dr. Graham, sorry, just quick question on this.

MR. SALMEN: Can we pull up the middle of this document, Mike?

BY MR. SALMEN:

Q. Have you seen this before, Dr. Graham, Notice of Deposition of Ken Graham?

A. I mean, quite honestly, I'm not sure.

Can I -- can you get me a print doc version of this so I can look at it?

Q. These are just administrative points that I wanted to make here, Dr. Graham.

A. Well, the challenge is your lovely picture is covering about -- I don't know -- 25 percent of the screen with the relevant text. My eyes are, like, in between where I can see with and without glasses. So I put the glasses on; it's kind of blurry and sort of can read it. I take the glasses off; it's kind of blurry and sort of can read it. I can make out "Please take notice," but that's

about it.

Q. Okay. I'll wait for you to get a paper copy of this.

A. Thank you. I mean, I'm not trying to be difficult here. I just can't see the bloody document. Okay.

Q. No problem.

Do you have a paper copy of it now?

A. I do.

Q. Do you recognize this?

A. I don't know if I actually have seen this, but it's saying that I will be deposed. So do I know about it? Yes. Have I laid my hands on the document before? I'm not sure.

Q. Okay. Again, just an administrative-type question, Dr. Graham. You understand that you're present here today being deposed at Mylan's request in the litigation that Regeneron filed against Mylan?

A. I believe that is correct, yes.

Q. Okay. You can put that down.

I also asked you at the beginning of the day if you've been deposed before. Do you recall that?

A. I do.

Q. You mentioned three to four times; is that correct?

A. No. I said this is the fourth time.

Q. Oh, this is the fourth time.

The most recent previous deposition was in the Regeneron-Novartis litigation; correct?

A. Yes.

Q. Do you recall the deposition you gave prior to that one?

A. That one also involved the Regeneron-Novartis litigation.

Q. Okay. In either of those depositions, Dr. Graham, did you provide factual testimony regarding the development of the Eylea formulation?

A. My recollection is it was focused on the prefilled syringe.

Q. And the prefilled syringe does comprise a formulation of VEGF Trap-Eye; right?

A. The prefilled syringe is filled with a formulation of VEGF Trap-Eye.

Q. Okay. And is it the identical formulation that's used in the vial for Eylea?

A. It has the same composition, yes.

Q. So during your two prior depositions, did you provide any factual testimony regarding your

development of the formulation or composition that's used in the prefilled syringe?

A. I mean, I don't recall being asked about that. I'd have to go back and review what was discussed. The memory that I have etched in my brain is discussing characteristics of the syringe, specifically, the levels of silicone oil in the syringe. That's what I remember predominantly from that.

Q. Was compatibility of the Eylea formulation with the syringe one of the issues that you provided testimony about?

A. Honestly, I don't recall.

Q. So you recall today we looked at a study that you conducted regarding syringe compatibility of the ITV formulation that you were developing for Eylea; right?

A. That would be the compatibility with the BD syringe? Is that what you're referring to?

Q. Yes.

A. Yes, we did discuss that.

Q. So my question is during your deposition in the Regeneron-Novartis matter, did you provide any testimony regarding compatibility studies that were conducted for the Eylea formulation with the

syringe at issue in that case?

A. As I previously stated, the only thing I really have etched in my memory is lengthy discussions about the amount of silicone oil that was contained in the Ompi syringe. I know I discussed that at length and -- I'm sorry -- but I honestly -- you know, we're dealing with over the span of two years here at least.

Q. So that was the last two depositions, Dr. Graham, both in the Regeneron-Novartis matter.

What was the first time you were deposed?

A. Okay. My recollection of that was it was for an International Trade Commission case, again, having to do with the Vetter prefilled syringe and also involving Novartis and Regeneron.

Q. Was that the same subject matter that was at issue in the district court case that you were deposed in?

A. Within my understanding of the legal intricacies, I believe the answer would be yes.

Q. Was the same patent at issue, Novartis patent at issue, as in the district court case you were referring to?

A. Yes.

Q. I'm going to direct your attention to

exhibit -- Defendant's Exhibit 726 in your binder.

A. Okay.

Q. Okay. Do you recognize Exhibit 726?

A. Can I look through it?

Q. Sure. I just ask from the cover page, can you recognize the exhibit?

A. From the cover page, no, I don't recognize the exhibit.

Q. Okay. Do you see on the right-hand column of the cover page, there's a reference to WO 2006/047325? Do you see that?

A. I see that.

Q. And on the left-hand side, along that same line, there is an international publication date. Do you see that?

A. Are you referring to May of 2006?

Q. Correct. May 4, 2006, international publication date. Do you see that?

A. I do.

Q. And the applicant, further down on the left-hand column, is Genentech. Do you see that?

A. I do.

Q. And the inventor is Shams. Do you see that?

A. I do.

Q. And the title, just below the line across the middle of the page is, "Method for treating intraocular neovascular diseases"?

A. Yes.

Q. And you'll see in the figure below -- I'm sorry -- below the figure, there is an abstract that reads: "A method is provided for administering to a mammal suffering from, or at risk for, an intraocular neovascular disorder with regular dosing of a therapeutically effective amount of VEGF antagonist, followed by less frequent dosing of a therapeutically effective amount of VEGF antagonist."

Do you see that?

A. I do.

Q. Do you have any recollection now of what the subject matter of this publication is?

A. Do I have a recollection of what the subject matter is, or can I tell you what the subject matter is based on the title?

Q. Can you tell me what the subject matter is based on the title?

A. It looks like it is a clinical trial design that might have been used by Genentech.

Q. Okay. I'm going to direct you to page 31

of this document. I'm reading the numbers on the bottom middle of each page 31.

A. Okay.

Q. And you see at the bottom of this page, the last paragraph, there's a description there of the ranibizumab injection?

A. Where are you looking?

Q. The last paragraph on page 31, there's an italicized header that says "Ranibizumab Injection"?

A. Okay. I see that.

Q. And it says "For intravitreal administration, the study drug, ranibizumab, is supplied in a liquid-filled vial of ranibizumab. Each vial contains 0.7 milliliters of either 6 mg per mL (0.3 milligram dose level) or 10 mg per mL (0.5 milligram dose level) of ranibizumab aqueous solution (pH 5.5) with 10 millimolar of histidine, 100 mg per mL of trehalose, and 0.01 percent polysorbate 20."

Do you see that?

A. I see that, and it continues on, "All study drug is stored frozen."

Q. Yep.

A. Or excuse me -- "...stored at 2 to 8 and

should not be frozen. Drug vials must be protected from direct sunlight." Is that the paragraph?

Q. Yes, that's the paragraph.

A. Okay.

Q. Dr. Graham, would you agree that the 10 millimolar histidine here is present in the role of buffer in this formulation?

A. That's likely the purpose of having it in the formulation, yes, I would agree with that.

Q. And the 100 milligrams per mL of trehalose is present as a stabilizing agent as we've previously discussed that term; correct?

A. Yeah. It would be a thermal stabilizer, yes.

Q. And what would be the role of the 0.01 percent of polysorbate 20 in this formulation?

A. Well, my ability to answer that would be dependent on understanding how it impacts the formulation. If I'm answering it based solely on my experience, I would be using it as a cosolvent which provides some sort of interfacial stabilization or, you know, resistance to agitation stress. What the exact role in this I can't say. Ranibizumab is an FAB fragment which is a radically different molecule than any of the molecules that

I have developed formulations for.

Q. What are the other potential roles that a 0.01 percent polysorbate 20 could be serving in this formulation?

A. I would have to think about that and get back to you. I honestly don't know at this point in time. I would need to think about it and look -- I mean, ideally look at data for how the molecule behaves.

Q. So the role of the polysorbate in this formulation would be dependent on its interaction with the molecule?

MR. FLETCHER: Objection.

THE WITNESS: So you asked me -- you'll have to ask your question again. I mean, I'm not, I guess, following you.

BY MR. SALMEN:

Q. I was just trying to clarify your answer.

Is the role of the 0.01 percent polysorbate 20 in this ranibizumab injection formulation dependent on the polysorbate's interaction with the ranibizumab protein in that formulation?

MR. FLETCHER: Objection.

THE WITNESS: Okay. You asked me what would be

other roles for the polysorbate outside of the ones that were in my experience. Those other roles I would have to think about, study the molecule. I don't know that the polysorbate interacts with the molecule. I don't know how this behaves. It's something that I have not thought about and I've not done research on. As I said, this is a very different molecule, and as I understand it, has very different behavioral characteristics than either an antibody or a fusion protein.

BY MR. SALMEN:

Q. Would the concentration -- would different concentrations of the ranibizumab in the formulation affect -- have an effect on the role of the 0.01 percent polysorbate in that formulation?

MR. FLETCHER: Objection.

THE WITNESS: I've not studied ranibizumab.

BY MR. SALMEN:

Q. Okay. What if I -- I'll ask you the same question with respect to ITV 2, the formulation used for Eylea. Would different concentrations of the VEGF Trap protein in that formulation affect the role of the polysorbate?

A. So you're asking if the role of the polysorbate in the Eylea formulation is dependent

on the concentration of afilbercept in the Eylea formulation?

Q. Yes.

A. We added polysorbate to the formulation based on needs that we established during our development work. The polysorbate is present to provide the same role regardless of the protein concentration or fulfill the same role.

Q. And that role is to stabilize the formulation from various stresses?

A. Well, I think I stated that it works in that formulation and has been demonstrated to provide stabilization against agitation stress.

Q. Does the polysorbate in that formulation work in conjunction with the water, the solvent, to keep the VEGF Trap active ingredient in solution?

A. So what do you mean by "works in conjunction with"?

Q. That's -- I really can't use any different terms than that, Dr. Graham. Those are the terms I want to use in my question.

Does the polysorbate, 0.03 percent polysorbate 20, in the ITV 2 formulation work in conjunction with the water for injection to keep the VEGF Trap in solution?

A. I think what I had described to you previously is that the polysorbate in its role is a bridge between portions of the molecule and the water around it, and it functions in a bridging manner as a cosolvent. That's what it does.

Q. The water acts -- is the only excipient in the formulation acting as a solvent of the VEGF Trap; correct?

A. The water in the formulation is a solvent.

Q. That wasn't my question, Dr. Graham.

The water for injection in the ITV 2 formulation described on Exhibit 737 is the only component in the formulation that is there in the function of solvent; correct?

A. The water in the formulation is a solvent.

Q. Is it the only solvent in the formulation?

A. It is a solvent in the formulation, yes.

Q. You're not answering my question, Dr. Graham. My question is very specific.

Is the water for injection in the ITV 2 formulation described on Exhibit 737 the only solvent in the formulation?

A. It is the solvent for the formulation.

MR. SALMEN: Why don't we take a break? Let me gather my notes. How much time are we on the

record?

THE VIDEOGRAPHER: Let's just go off, and I'll let you know, if that's okay.

MR. SALMEN: Okay.

THE VIDEOGRAPHER: We are going off the record. The time is 4:49 p.m.

(A short break was taken.)

THE VIDEOGRAPHER: We are going back on the video record. The time is 5:00 p.m. This is Media Unit 7.

BY MR. SALMEN:

Q. Dr. Graham, referring back to the ITV 2 formulation, which I believe that we've been referencing Exhibit 737 for that exact formulation.

A. Okay.

Q. So, again, for context, the water for injection, the function there is reported as solvent?

A. Yes.

Q. And your testimony earlier is that Row 6, which describes the 10 percent polysorbate 20, the function there which states stabilizer was a mistake and should read cosolvent; is that correct?

A. Yes.

Q. So my question, Dr. Graham, is the

0.03 percent polysorbate 20 in this formulation, does that operate in conjunction with the water to dissolve the VEGF Trap active ingredient?

A. So the polysorbate in the formulation solution functions as a bridge between the protein and the solution that provides interfacial or stability to agitation stress.

Q. Does the 0.03 percent polysorbate 20 in the ITV 2 formulation described in Exhibit 737 reduce surface or interfacial tension in that formulation?

A. I've not measured that. So I don't know.

Q. Is polysorbate 20 at 0.03 percent in the ITV 2 formulation described in Exhibit 737 used to dissolve the VEGF Trap protein?

A. What do you mean by "used to dissolve"?

Q. Those are the words that I want to use, Dr. Graham. Can you answer that question as stated?

A. Well, I don't understand your question as stated with those words.

Q. Is the polysorbate 20 at 0.03 percent a solvent of VEGF Trap protein?

A. So it's an organic cosolvent that plays a specific role and provides stability to agitation

stress that we've demonstrated.

Q. Can you answer my question, though, Dr. Graham? Is it a solvent of the VEGF Trap protein?

A. So rephrase your question for me.

Q. I can't rephrase it. That's exactly how I want it asked.

Is the 0.3 -- strike that.

Is the 0.03 percent polysorbate 20 in the ITV 2 formulation described on Exhibit 737 a solvent of VEGF Trap protein in that formulation?

A. So, again, it's an organic cosolvent that plays a specific role in the formulation.

Q. So is the answer to my question, no, it is not a solvent in the ITV 2 formulation?

A. The answer to your question is it is an organic cosolvent that provides stability when subjected to agitation stress.

Q. The 0.03 percent polysorbate 20 in the ITV 2 formulation described in Exhibit 737 is not used in conjunction with water to dissolve the VEGF Trap; correct?

Do you need the question read back to you, Dr. Graham?

A. Go ahead. Have the question read back to

me.

MR. SALMEN: Court reporter, would you please read the question back?

(Whereupon, the record was read.)

THE WITNESS: The 0.3 percent polysorbate 20 that's contained in the formulation functions as an organic cosolvent and is a bridge between the afilbercept and the formulation. I -- when we formulate the molecule, we start off with a liquid drug substance or a drug substance in a liquid form, and we add the excipients, which includes the polysorbate in a liquid form. We combine them, and we get a formulation that has the desired properties.

BY MR. SALMEN:

Q. And in that process where you stated that you start with a liquid drug substance, the drug substance in a liquid form, that formulation only comprises the 10 millimolar phosphate buffer and water; correct?

A. The drug substance for afilbercept contains 10 millimolar phosphate, afilbercept, and water for injection.

Q. And the water for injection in that drug

substance formulation is the solvent; correct?

A. It is the solvent in that case, correct.

Q. And in the drug substance formulation, the water for injection is used to dissolve the VEGF Trap protein; correct?

A. Well, I've never taken VEGF Trap protein and dissolved it in water for injection.

Q. What does it mean -- sorry.

A. I always worked with it as a solution. You know, it seems like you're hung up on some sort of a small molecule where you start off with a solid and you bring your solid into a solution or into a formulation. This is a very complex biological molecule that we maintain in a liquid state throughout the processing up and to including the point where we add the final excipients that create the stable solution or formulation that is known as Eylea.

Q. Can you explain to me why, in Exhibit 737, you identified the function of water for injection as solvent? How is it acting in the formulation to demonstrate that function?

A. Well, we have sodium phosphate monobasic monohydrate. Is that a solid or a liquid?

Q. You can answer that.

A. I asked you. Is it a solid or a liquid?
Q. Is the phosphate monobasic monohydrate in that formulation a solid or a liquid?
A. Is that a solid or is that a liquid?
Q. I don't want to be argumentative here, Dr. Graham. I asked the question to you.
A. All right. So I described to you the process how we formulate the molecule. Did I not?
Q. Yes.
A. Okay. And in that process we combine sodium phosphate monobasic monohydrate, which is a salt and a solid, with sodium phosphate dibasic dihydrate, sodium chloride, which is also a salt and sucrose, all of which are solids, and those are combined with the water for injection to form a solution. To that we then add the 10 percent polysorbate 20 solution, and we make a concentrated excipient mix. That is combined with the liquid VEGF Trap drug substance to produce the desired formulation.
Q. And in the liquid VEGF Trap drug substance formulation, the water for injection is the solvent; correct?
A. It is the solvent, yes.
Q. And you testified earlier that in the

concentrated excipient solution, the sucrose, the polysorbate, have no function in that concentrated excipient solution; correct?

A. Well, for them to have a function, they need to be interacting -- well, actually I've not assessed their function in a concentrated excipient mix, quite frankly.

Q. Well, your testimony earlier was they served no function in the concentrated excipient solution; correct?

A. Yes, that is what I said.

Q. So what changes with respect to the function of the polysorbate when the drug substance is added?

A. So the polysorbate and the other excipients that are present when you have the drug substance there as well provides specific or plays a specific role in the formulation. With it the formulation is very robust, and you can subject it to agitation stress, and it remains intact. Without it, when you subject the formulation to agitation stress, the formulation does not remain intact.

Q. So is the drug substance formulation, which does not have the polysorbate and the

sucrose, is that an unstable formulation that does not remain intact?

A. It is not as resistant to stresses as the drug product formulation.

Q. It's at least resistant to freezing; right?

A. You can freeze it, yes.

Q. And it's resistant to thawing; correct?

A. Well, depends on what's your definition of resistant to freezing and thawing is.

Q. How would you define "resistant to thawing"?

A. So for the drug substance, yeah, you can freeze it. You really don't want to do it more than once or twice. You know, the formulated drug substance, by comparison, can be frozen and thawed multiple times.

Q. Dr. Graham, are you familiar with the Remington textbook?

A. The Remington textbook?

Q. Yeah.

A. I'm not sure what you're talking about.

Q. Are you familiar with Martin's Physical Pharmacy and Pharmaceutical Sciences handbook?

A. I've never studied the text, no.

Q. Let me ask you about your patents before we conclude here, Dr. Graham.

Looking at the '865 patent -- and you understand what I am referring to when I say the "specification of the '865 patent"?

A. Would you please define that for me?

Q. Sure.

So I'm going to refer to the specification of the patent as essentially the entirety of the patent with the exception of the claims at the very end, which I'll refer to as the claims. Is that okay?

A. I don't know that I have a choice in the matter. So the answer is yes.

Q. I just want to make sure -- so, now, when we started today, Dr. Graham, I asked you what your contribution was to the formulation that's claimed here in the '865 patent. Can you tell me what that was?

A. What I said this morning?

I talked about helping solve some of the problems with particulates.

Q. And that was essentially your first task when you joined the formulation development group in 2005; correct?

A. Well, I wouldn't say it was my first task. I would say it was something that I was involved with relative to this. I had other tasks.

Q. So at the time when you joined the formulation development group in 2005, you stated that the ITV 1 formulation at the time was experiencing a precipitation problem; correct?

A. Shortly after I joined the group, yes, that is my recollection.

Q. And how did you and the formulation development group resolve that precipitation problem?

A. We changed the formulation.

Q. How did you change the formulation?

A. So we did a series of studies. We examined the impact of stabilizers like sucrose and mannitol, polyols. We examined other organic cosolvents than the PEG that was being used. I believe we actually also looked at pH assay function and changed the composition of the formulation such that it included sucrose, reduced the amount of sodium chloride that was in the formulation, removed the PEG 3350, and added polysorbate 20.

Q. Did the buffer stay the same?

A. The 10 millimolar phosphate buffer was the same.

Q. Why didn't you change the buffer to address the precipitation formulation?

I'm sorry. Strike that.

Why didn't you change the buffer to address the precipitation problem you were experiencing in the ITV 1 formulation?

A. Well, as I recall, we were not seeing challenges with the drug substance --

(Simultaneous speaking.)

BY MR. SALMEN:

Q. Okay.

A. -- that we stored it.

Q. And was phosphate buffer the preferred buffer in the formulation development group?

I think you described it as a buffer that was native to the body.

A. It was a buffer -- phosphate is a native buffer in the body. I wouldn't go so far as to say it was a preferred buffer in formulation development. That's something that's determined on a molecule-by-molecule basis.

Q. Well, let me ask you, for VEGF Trap, for intravitreal administration, was phosphate buffer

the preferred buffer?

A. So we ultimately settled on -- or "settled" is the wrong word. We continued to use the phosphate buffer that our drug substance was in.

Q. And you did not use a citrate buffer for the intravitreal administration formulation; correct?

A. I don't ever recall utilizing a citrate buffer for intravitreal administration.

Q. And you also don't recall, prior to filing this patent application in 2006, using a histidine buffer for your developed intravitreal formulation of VEGF Trap; correct?

A. I cannot think of an example of a histidine-based formulation for intravitreal injection.

Q. Okay. Why don't we go off the record for just a couple minutes?

Dr. Graham, I think I'm very close to done. So, hopefully, we can wrap this up very soon.

THE VIDEOGRAPHER: Going off the record. The time is 5:25.

(A short break was taken.)

THE VIDEOGRAPHER: We are going back on the video record. The time is 5:33 p.m.

BY MR. SALMEN:

Q. Dr. Graham, what did you do to prepare for today's deposition?

A. I reviewed some documents, was asked some questions by my attorneys, and that was about it.

Q. Okay. When did you meet with your attorneys?

A. The last time I met with them was yesterday.

Q. And how long did you meet?

A. Oh, a few hours, six hours, give or take.

Q. Did you review Dr. Furfine's deposition transcript?

A. I did not see Dr. Furfine's deposition transcript.

Q. Did you review the exhibits, the previously marked exhibits, that I had provided for you in the binder?

I'm not suggesting that you had the binder in advance. Just asking whether or not you reviewed those premarked exhibits that have the exhibit stickers on them.

A. Well, what I reviewed did not have --

I don't think had stickers on them. I mean, they had numbers -- what do you refer to those numbers at the bottom as?

Q. Exhibit numbers. Oh, the Bates numbers.

A. Thank you. Bates numbers.

So I think what I saw had Bates numbers on it. I don't -- I mean, I could be wrong, but I don't recall, like, the exhibit numbers. Like you have Exhibit Furfine 723, I don't know that I saw that.

Q. Did you review the entirety of your '865 patent, Exhibit 703?

A. Read through parts of it.

Q. What parts of it did you focus on?

A. I looked at the claims and some of the examples.

Q. Which examples did you review?

A. I guess pretty much all of them.

Q. Dr. Graham, are you being compensated for your time yesterday and today at the deposition?

A. What do you mean by "being compensated"?

Q. Is Regeneron paying you for the hours you've spent preparing and sitting for today's deposition?

A. Okay. I'm not receiving additional

compensation from Regeneron for going to a deposition. I am an employee, a salaried employee. So I draw a salary from them.

Q. Okay. That answers my question.

Do you have any financial interest in the sales of Eylea in the United States?

A. You mean like getting a rebate or anything like that?

Q. Stock.

A. I own stock in Regeneron, yes.

Q. And if the sales of Regeneron, if those impact the value of the stock, does that affect the compensation that you receive from owning those stocks?

A. So could you repeat what you just said?

I don't know that it came through correctly.

Q. That's okay. I am going to strike the question.

Regeneron Protected Material

Q. And if the value of that Regeneron stock goes down, would the overall amount to you go down as well?

A. Well, see, this is where you're kind of confusing me. I mean, it's stock that I own. So if the price of stock goes up, you have more value. If the price of stock goes down, you have less value. But, you know, the amount that I own in my, you know, compensation from Regeneron, my salary, remains the same.

Q. So if the price of the Regeneron stock goes down, it would be of less value to you than it is now; correct?

A. That's true, yes.

Q. If a biosimilar of the Eylea product hit the market, would you anticipate the value of Regeneron stock to go down?

A. Quite frankly, I don't know what would happen.

Q. Are you concerned that the value of the Regeneron stock would go down if an Eylea biosimilar hit the market?

A. Well, it's certainly a possibility. You know, it would really depend on the nature of the biosimilar product. You know, is it truly a

biosimilar or is it not as good for some reason? I don't know. We've had competitor molecules come online, and some have very negatively impact -- or haven't very negatively impacted us.

You know, I would expect if I listen to some of the stock advisors that you could see a huge drop in the stock price, but I -- honestly, I don't know. I haven't studied it, and it's not something that I focus in on on a daily basis.

Q. Okay. I have no further questions, Dr. Graham. Thank you for your time today.

MR. FLETCHER: Why don't we go off the record?

THE VIDEOGRAPHER: Going off the record. The time is 5:40 p.m.

(A short break was taken.)

THE VIDEOGRAPHER: We are going back on the video record. The time is 5:48 p.m.

EXAMINATION

BY MR. FLETCHER:

Q. Dr. Graham, I have a few questions for you.

Earlier today you discussed the concept of a stabilizing feature. Do you recall that?

A. I do.

Q. I'd like you to turn to column 2 of your

patent, Exhibit 703, the '865 patent.

A. Okay.

Q. Are you there?

A. I am.

Q. Can I please direct your attention to lines 39 to 48 of your patent? Let me know when you have had a chance to review that section.

MR. SALMEN: Can you give the column and line number again, please?

MR. FLETCHER: Certainly, Counsel. Column 2, lines 39 to 48.

THE WITNESS: Okay.

BY MR. FLETCHER:

Q. Dr. Graham, did Mylan's counsel direct your attention to this passage at any point in today's questioning?

A. I don't recall that he did, no.

Q. In the context of this disclosure, in particular, column 2, lines 39 to 48, what molecules are identified as stabilizing agents?

A. Okay. So the stabilizing agent may be sucrose, sorbitol, glycerol, trehalose, or mannitol.

Q. What molecules are identified as organic cosolvents?

MR. SALMEN: Objection. Form. Foundation. Leading.

THE WITNESS: So the patent says, and I quote, "In one or more specific embodiments, the organic cosolvent may be polysorbate, for example, polysorbate 20 or polysorbate 80, polyethylene glycol (PEG), for example, PEG 3350, or polyethylene glycol, or a combination thereof."

BY MR. FLETCHER:

Q. In the context of the disclosure of the '865 patent, how is polysorbate 20 categorized?

A. It's categorized as an organic cosolvent.

Q. Dr. Graham, earlier today you also discussed some sayings that your colleague Dan Dix had. Do you recall that?

A. I do.

Q. How did you receive Dan's sayings?

A. Well, Dan's sayings were "you will never have," and in my experience with formulation development or science, the statement "never" is really not something that you can go with. So I really didn't believe what Dan said.

Q. Dr. Graham, have you personally ever made an intravitreal formulation of afilbercept that contains histidine?

A. I have.

Q. Despite what your colleague Dan Dix said?

A. I have. Former colleague.

MR. FLETCHER: Dr. Graham, I have no further questions at this time.

FURTHER EXAMINATION

BY MR. SALMEN:

Regeneron Protected Material

Q. Turn you back to the paragraph that your counsel referred you to on column 2, lines 39 to 48. He asked you some questions about that paragraph; correct?

A. Yes.

Q. I want to direct you to the example, Example 1. Example 1 describes a formulation. This is on column 8, beginning at line around 37. "An ophthalmic liquid formulation containing 50 milligram per mL VEGF Trap (SEQ ID NO:4), 10 millimolar phosphate, 50 millimolar sodium chloride, 0.1 percent polysorbate 20, 5 percent sucrose, and pH 6.25..."

Do you see that?

A. I do.

Q. The word "cosolvent" is not used anywhere in this paragraph; correct?

A. No, it is not.

Q. Example 2 below that, line 60, is another formulation described. "A liquid formulation containing 50 milligrams per mL VEGF Trap

(SEQ ID NO:4), 10 millimolar phosphate, 50 millimolar sodium chloride, 3 percent polyethylene glycol 3350, 5 percent sucrose, and pH 6.25..."

Do you see that?

A. I do.

Q. The word "cosolvent" doesn't appear anywhere in the description of this liquid formulation; correct?

A. No, it does not.

MR. SALMEN: I have no further questions.

MR. FLETCHER: I don't have any further questions.

Thank you, Dr. Graham.

THE VIDEOGRAPHER: We are going --

MR. SALMEN: Thank you, Dr. Graham.

THE VIDEOGRAPHER: We are going off the record. The time is 5:56 p.m. This concludes today's testimony given by Kenneth Graham. The total number of media units used was seven, and they will be retained by Veritext Legal Solutions. Thank you.

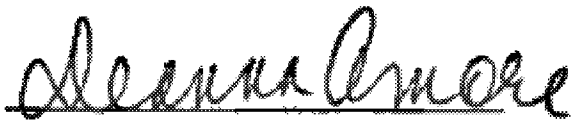
C E R T I F I C A T E

I, DEANNA AMORE, a Shorthand Reporter and notary public, within and for the State of Illinois, County of DuPage, do hereby certify:

That KENNETH S. GRAHAM, Ph.D., the witness whose examination is hereinbefore set forth, was first duly sworn by me and that this transcript of said testimony is a true record of the testimony given by said witness.

I further certify that I am not related to any of the parties to this action by blood or marriage, and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 20th day of January 2023.



Deanna M. Amore, CRR, RPR, CSR

Veritext Legal Solutions
1100 Superior Ave
Suite 1820
Cleveland, Ohio 44114
Phone: 216-523-1313

January 22, 2023

To: Thomas Fletcher, Esq.

Case Name: Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals, Inc.
Veritext Reference Number: 5642329
Witness: Kenneth S. Graham, Ph.D. Deposition Date: 1/19/2023

Dear Sir/Madam:

Enclosed please find a deposition transcript. Please have the witness review the transcript and note any changes or corrections on the included errata sheet, indicating the page, line number, change, and the reason for the change. Have the witness' signature notarized and forward the completed page(s) back to us at the Production address shown

above, or email to production-midwest@veritext.com.

If the errata is not returned within thirty days of your receipt of this letter, the reading and signing will be deemed waived.

Sincerely,

Production Department

NO NOTARY REQUIRED IN CA

DEPOSITION REVIEW
CERTIFICATION OF WITNESS

ASSIGNMENT REFERENCE NO: 5642329
CASE NAME: Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals, Inc.
DATE OF DEPOSITION: 1/19/2023
WITNESS' NAME: Kenneth S. Graham, Ph.D.

In accordance with the Rules of Civil Procedure, I have read the entire transcript of my testimony or it has been read to me.

I have made no changes to the testimony as transcribed by the court reporter.

_____ _____
Date Kenneth S. Graham, Ph.D.

Sworn to and subscribed before me, a Notary Public in and for the State and County, the referenced witness did personally appear and acknowledge that:

They have read the transcript;
They signed the foregoing Sworn Statement; and
Their execution of this Statement is of their free act and deed.

I have affixed my name and official seal

this _____ day of_____, 20____.

_____
Notary Public

_____
Commission Expiration Date

DEPOSITION REVIEW
CERTIFICATION OF WITNESS

ASSIGNMENT REFERENCE NO: 5642329
CASE NAME: Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals, Inc.
DATE OF DEPOSITION: 1/19/2023
WITNESS' NAME: Kenneth S. Graham, Ph.D.
In accordance with the Rules of Civil Procedure, I have read the entire transcript of my testimony or it has been read to me.
I have listed my changes on the attached Errata Sheet, listing page and line numbers as well as the reason(s) for the change(s).
I request that these changes be entered as part of the record of my testimony.

I have executed the Errata Sheet, as well as this Certificate, and request and authorize that both be appended to the transcript of my testimony and be incorporated therein.

_____ _____
Date Kenneth S. Graham, Ph.D.

Sworn to and subscribed before me, a Notary Public in and for the State and County, the referenced witness did personally appear and acknowledge that:
They have read the transcript;
They have listed all of their corrections in the appended Errata Sheet;
They signed the foregoing Sworn Statement; and
Their execution of this Statement is of their free act and deed.
I have affixed my name and official seal this _____ day of_____, 20____.

_____
Notary Public

_____
Commission Expiration Date

ERRATA SHEET

VERITEXT LEGAL SOLUTIONS MIDWEST

ASSIGNMENT NO: 5642329

PAGE/LINE(S) / CHANGE /REASON

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Date Kenneth S. Graham, Ph.D.

SUBSCRIBED AND SWORN TO BEFORE ME THIS _____

DAY OF _____, 20_____ .

_____

Notary Public

_____

Commission Expiration Date

Exhibit Y

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

REGENERON PHARMACEUTICALS, INC., Plaintiff, v. MYLAN PHARMACEUTICALS INC., Defendant.	Case No. 1:22-cv-00061-TSK **OUTSIDE COUNSEL'S EYES ONLY – SUBJECT TO PROTECTIVE ORDER**

MYLAN PHARMACEUTICALS INC.'S ANSWERS AND OBJECTIONS TO REGENERON'S FOURTH SET OF INTERROGATORIES (NOS. 6-14)

Pursuant to Federal Rules of Civil Procedure 26 and 33, Mylan Pharmaceuticals Inc. ("Mylan" or "Defendant") hereby submits its Answers and Objections to Plaintiff Regeneron Pharmaceuticals, Inc.'s ("Regeneron" or "Plaintiff") Fourth Set of Interrogatories (Nos. 6-14).

PRELIMINARY STATEMENT

These Answers and Objections are based on information and documents presently available as a result of a search and review process that is ongoing. Mylan's Answers to the Interrogatories are without prejudice to, and do not constitute a waiver of, Mylan's rights to rely on other documents or information at trial. Mylan expressly reserves the right to supplement and/or amend its Answers as necessary, as provided for in FED. R. CIV. P. 26(e), particularly in light of ongoing discovery in this case.

An Answer to any Interrogatory should not be deemed or construed as a representation that there is, in fact, information responsive to the Interrogatory, that Mylan performed any of the acts described in the Interrogatory, or that Mylan acquiesces in the characterization of the conduct or activities described in the Interrogatory.

Nothing in Mylan's Answers should be construed as Mylan's waiver of any rights or Objections that otherwise might be available to Mylan, nor should any of Mylan's Answers be deemed as an admission of relevancy, materiality or admissibility into evidence of the Interrogatories or the Answers thereto.

OBJECTIONS APPLICABLE TO THE INTERROGATORIES

Each of these Objections is applicable to each of Plaintiff's Interrogatories (the "General Objections") and is incorporated into each and every one of Mylan's Answers as though fully set forth therein and is in addition to any specific Objections stated for a particular Interrogatory.

1. Mylan herein incorporates by reference, to the extent applicable, each of its Objections Applicable to All Requests as set forth in its Responses and Objections to Plaintiff's First Set of Requests for Production of Documents (Nos. 1-6), dated September 30, 2022.

2. Mylan objects to the extent the Interrogatories as set forth by Plaintiff constitute separate individual Interrogatories under Federal Rule of Civil Procedure 33 in excess of the maximum number of Interrogatories permitted by same. *See* FED. R. CIV. P. 33(a)(1); Local Rule 26.01(c)(4); *High Point Sarl v. Sprint Nextel Corp.*, No. 09-2269-CM-DJW, 2011 WL 4036424, at *3 (D. Kan. Sept. 12, 2011) ("Parties cannot evade this presumptive limitation through the device of joining as 'subparts' questions that seek information about discrete separate subjects.") (citation omitted); *Ritchie Risk-Linked Strategies Trading (Ireland), Ltd. v. Coventry First LLC*, 273 F.R.D. 367, 369 (S.D.N.Y. 2010) (interrogatories with subparts "amount essentially to discrete questions in and of themselves"); *Cramer v. Fedco Auto. Components Co.*, No. 01-CV-0757E(SR), 2004 WL 1574691, at *4 (W.D.N.Y. May 26, 2004) ("Parties cannot evade this presumptive limitation through the device of joining as 'subparts' questions that seek information about discrete separate subjects.").

3. Mylan objects to Plaintiff's Interrogatories, Definitions, and Instructions to the extent they seek to impose obligations on Mylan beyond or different than those required by the Federal Rules of Civil Procedure and any applicable local rules and orders of the Court.

4. Mylan objects to Plaintiff's Interrogatories to the extent that they seek discovery relating to or concerning products other than the product described in Mylan's BLA No. 761274.

Subject to these General Objections, and subject to additional Objections made to each Interrogatory below, Mylan responds as follows:

ANSWERS TO INTERROGATORIES

INTERROGATORY NO. 6

If Mylan contends that the manufacture, use, sale, offer for sale, or importation of Mylan's aflibercept, including use of Mylan's aflibercept in accordance with the proposed labeling (including the prescribing information and patient package insert) for such products, would not infringe one or more claims of the Initial Patents, then to the extent not already identified in a detailed statement under 42 U.S.C. § 262(l)(3)(B)(ii)(I), identify the claims that Mylan contends would not be infringed, all bases on which Mylan contends any such claim would not be infringed (either literally or under the doctrine of equivalents), all facts on which Mylan relies for such contention, and all documents and circumstances relating to those facts and all individuals with knowledge of those facts.

RESPONSE: In addition to its General Objections, Mylan objects to this Interrogatory as vague, ambiguous, overly broad, not relevant to any party's claim or defense and not proportional to the needs of the case, particularly to the extent it seeks information regarding "*all* bases on which Mylan contends any such claim would not be infringed (either literally or under the doctrine of equivalents), *all* facts on which Mylan relies for such contention, and *all* documents and circumstances relating to those facts and *all* individuals with knowledge of those facts." Mylan further objects to this Interrogatory to the extent it seeks discovery protected by the attorney client privilege, work product doctrine and/or any other applicable privilege or immunity. In addition,

Mylan objects to this Interrogatory to the extent it seeks information subject to confidentiality with a third party.

Mylan further objects to this Request to the extent that it seeks to improperly shift the burden of proving non-infringement to Mylan, and because it is premature, including because fact discovery, claim construction, and expert discovery are ongoing. This Court has found interrogatory requests seeking non-infringement contentions to be inappropriate and premature because "[p]laintiff[s] bear[] the burden to prove infringement and cannot use interrogatories to determine [d]efendant[s'] 'crystallized non-infringement arguments.'" *Automated Merch. Sys. Inc. v. Crane Co.*, 2011 WL 2648887, at *4 (N.D.W. Va. 2011) (quoting *Cummings–Allison v. SBM Co., Ltd.*, 2009 WL 806753, at *1-2 (E.D. Tex. 2009)). "Prior to knowing how the Court will construe the claims at issue, [the request] would be premature because it would be difficult to determine how the [technology] allegedly infringe[s]." *Id.*

Mylan further objects to this Request as premature and highlights that courts in the Fourth Circuit have found interrogatories premature when seeking information related to non-infringement contentions prior to the delineation of claim assertion and the close of discovery. *CertusView Techs., LLC v. S & N Locating Servs., LLC*, C.A. No. 2:13-cv-346 (E.D. Va. 2014) (Dkt. No. 116, 4). The Eastern District of Virginia specifically noted that the defendant's obligation to respond was triggered "once the scope of the interrogatories [was] clarified." *Id.* Delineation of asserted claims, along with an associated meet-and-confer, "clarified the information sought in great detail." *Id.* Mylan states that, unlike the interrogatories in *CertusView*, Regeneron has not sufficiently "clarified" which claims it seeks to assert and, thus, which claims Mylan must craft non-infringement arguments for. Since or around service of this set of interrogatories, Regeneron has narrowed its asserted claims twice: once in a December 16, 2022

letter from Thomas Fletcher and a second time upon service of Regeneron's infringement contentions on January 12, 2023. Additionally, unlike the plaintiff in *CertusView*, Regeneron is required to further delineate its asserted claims by a specific date. Pursuant to the Scheduling Order (Dkt. No. 87), Regeneron must, again, narrow its claims, potentially by seven (7) days after the close of fact discovery on January 18, 2023. As Mylan will not know with certainty which claims Regeneron intends to assert until Regeneron narrows them again, Mylan notes that this Request is premature *at least* until January 25, 2023.

Without waiving its Objections, and subject to them, and to the extent Mylan understands this Interrogatory, Mylan responds as follows:

Mylan states that it has already produced detailed statements under 42 U.S.C. § 262(l)(3)(B)(ii)(I), giving notice to Regeneron as to Mylan's preliminary non-infringement defenses. Mylan further states that discovery is ongoing, and Mylan has yet to see Regeneron's opening expert reports on infringement, or all information purportedly being obtained under subpoena from third parties which may impact the non-infringement analysis.

Accordingly, Mylan expressly reserves the right to supplement and/or amend its response to this Interrogatory, as necessary and appropriate, including as expert discovery and claim construction proceeds and/or as otherwise provided under the Local Rules or any other applicable Rule or order of the Court should circumstances related to this litigation change.

INTERROGATORY NO. 7

If Mylan contends that the manufacture, sale, offer for sale, or importation of Mylan's aflibercept would not induce the infringement of one or more claims of the Initial Patents, then to the extent not already identified in a detailed statement under 42 U.S.C. § 262(l)(3)(B)(ii)(I), identify the claims as to which Mylan contends that infringement would not be induced, all bases for that contention, all facts on which Mylan relies for that contention, and all documents and circumstances relating to those facts and all individuals with knowledge of those facts.

RESPONSE: In addition to its General Objections, Mylan objects to this Interrogatory as vague, ambiguous, overly broad, not relevant to any party's claim or defense and not proportional to the needs of the case, particularly to the extent it seeks information regarding "*all* bases for that contention, *all* facts on which Mylan relies for that contention, and *all* documents and circumstances relating to those facts and *all* individuals with knowledge of those facts." Mylan further objects to this Interrogatory to the extent it seeks discovery protected by the attorney client privilege, work product doctrine and/or any other applicable privilege or immunity. Mylan also objects to this Interrogatory as not relevant to any party's claim or defense as it seeks information related to confidential information outside the scope of this litigation. In addition, Mylan objects to this Interrogatory to the extent it seeks information subject to confidentiality with a third party.

Mylan further objects to this Request to the extent that it seeks to improperly shift the burden of proving non-infringement to Mylan, and because it is premature, including because fact discovery, claim construction, and expert discovery are ongoing. This Court has found interrogatory requests seeking non-infringement contentions to be inappropriate and premature because "[p]laintiff[s] bear[] the burden to prove infringement and cannot use interrogatories to determine [d]efendant[s'] 'crystallized non-infringement arguments.'" *Automated Merch. Sys. Inc. v. Crane Co.*, 2011 WL 2648887, at *4 (N.D.W. Va. 2011) (quoting *Cummings–Allison v. SBM Co., Ltd.*, 2009 WL 806753, at *1-2 (E.D. Tex. 2009)). "Prior to knowing how the Court will construe the claims at issue, [the request] would be premature because it would be difficult to determine how the [technology] allegedly infringe[s]." *Id.*

Mylan further objects to this Request as premature and highlights that courts in the Fourth Circuit have found interrogatories premature when seeking information related to non-infringement contentions prior to the delineation of claim assertion and the close of discovery.

CertusView Techs., LLC v. S & N Locating Servs., LLC, C.A. No. 2:13-cv-346 (E.D. Va. 2014) (Dkt. No. 116, 4). The Eastern District of Virginia specifically noted that the defendant's obligation to respond was triggered "once the scope of the interrogatories [was] clarified." *Id.* Delineation of asserted claims, along with an associated meet-and-confer, "clarified the information sought in great detail." *Id.* Mylan states that, unlike the interrogatories in *CertusView*, Regeneron has not sufficiently "clarified" which claims it seeks to assert and, thus, which claims Mylan must craft non-infringement arguments for. Since or around service of this set of interrogatories, Regeneron has narrowed its asserted claims twice: once in a December 16, 2022 letter from Thomas Fletcher and a second time upon service of Regeneron's infringement contentions on January 12, 2023. Additionally, unlike the plaintiff in *CertusView*, Regeneron is required to further delineate its asserted claims by a specific date. Pursuant to the Scheduling Order (Dkt. No. 87), Regeneron must, again, narrow its claims, potentially by seven (7) days after the close of fact discovery on January 18, 2023. As Mylan will not know with certainty which claims Regeneron intends to assert until Regeneron narrows them again, Mylan notes that this Request is premature *at least* until January 25, 2023.

Without waiving its Objections, and subject to them, and to the extent Mylan understands this Interrogatory, Mylan responds as follows:

Mylan states that it has already produced detailed statements under 42 U.S.C. § 262(l)(3)(B)(ii)(I), giving notice to Regeneron as to Mylan's preliminary non-infringement defenses. Mylan further states that discovery is ongoing, and Mylan has yet to see Regeneron's opening expert reports on infringement, or all information purportedly being obtained under subpoena from third parties which may impact the non-infringement analysis.

Accordingly, Mylan expressly reserves the right to supplement and/or amend its response to this Interrogatory, as necessary and appropriate, including as expert discovery and claim construction proceeds and/or as otherwise provided under the Local Rules or any other applicable Rule or order of the Court should circumstances related to this litigation change.

INTERROGATORY NO. 8

If Mylan contends that any claims of the Initial Patents are invalid or unenforceable, then to the extent not already identified in a detailed statement under 42 U.S.C. § 262(l)(3)(B)(ii)(I), identify for each challenged claim all facts, documents, and circumstances on which Mylan relies for its contention, all bases for Mylan's contention, all statutes or legal doctrines Mylan relies upon for such contention, and all prior art or other references or information Mylan relies on for such contention.

RESPONSE: In addition to its General Objections, Mylan objects to this Interrogatory as vague, ambiguous, overly broad, not relevant to any party's claim or defense and not proportional to the needs of the case, particularly to the extent it seeks "*all* facts, documents, and circumstances on which Mylan relies for its contention, *all* bases for Mylan's contention, *all* statutes or legal doctrines Mylan relies upon for such contention, and *all* prior art or other references or information Mylan relies on for such contention." Mylan further objects to this Interrogatory to the extent it seeks discovery protected by the attorney client privilege, work product doctrine and/or any other applicable privilege or immunity. Mylan also objects to this Interrogatory as not relevant to any party's claim or defense as it seeks information related to confidential information outside the scope of this litigation. In addition, Mylan objects to this Interrogatory to the extent it seeks information subject to confidentiality with a third party. Mylan further objects to the extent it seeks information outside of Mylan's possession, custody, or control.

Mylan further objects to this Request to the extent that it is premature, including because fact discovery, claim construction, and expert discovery are ongoing. This Court has noted that "[p]rior to knowing how the Court will construe the claims at issue, [the request] would be

premature because it would be difficult to determine" legal conclusions reliant on the same. *Automated Merch. Sys. Inc. v. Crane Co.*, 2011 WL 2648887, at *4 (N.D.W. Va. 2011)

Mylan further objects to this Request as premature and highlights that courts in the Fourth Circuit have found interrogatories premature when seeking information related to contentions prior to the delineation of claim assertion and the close of discovery. *CertusView Techs., LLC v. S & N Locating Servs., LLC*, C.A. No. 2:13-cv-346 (E.D. Va. 2014) (Dkt. No. 116, 4). The Eastern District of Virginia specifically noted that the defendant's obligation to respond was triggered "once the scope of the interrogatories [was] clarified." *Id.* Delineation of asserted claims, along with an associated meet-and-confer, "clarified the information sought in great detail." *Id.* Mylan states that, unlike the interrogatories in *CertusView*, Regeneron has not sufficiently "clarified" which claims it seeks to assert and, thus, which claims Mylan must craft invalidity arguments for. Since or around service of this set of interrogatories, Regeneron has narrowed its asserted claims twice: once in a December 16, 2022 letter from Thomas Fletcher and a second time upon service of Regeneron's infringement contentions on January 12, 2023. Additionally, unlike the plaintiff in *CertusView*, Regeneron is required to further delineate its asserted claims by a specific date. Pursuant to the Scheduling Order (Dkt. No. 87), Regeneron must, again, narrow its claims, potentially by seven (7) days after the close of fact discovery on January 18, 2023. As Mylan will not know with certainty which claims Regeneron intends to assert until Regeneron narrows them again, Mylan notes that this Request is premature *at least* until January 25, 2023.

Without waiving its Objections, and subject to them, and to the extent Mylan understands this Interrogatory, Mylan responds as follows:

Information responsive to this Interrogatory already has been provided to Regeneron through service of Defendant Mylan Pharmaceuticals Inc.'s Invalidity Contentions Regarding U.S.

Patent Nos. 10,888,601, 11,084,865, 11,104,715, and 11,253,572 on January 12, 2023. Mylan expressly reserves the right to supplement and/or amend its response to this Interrogatory, as necessary and appropriate, including as discovery proceeds and/or as otherwise provided under the Local Rules or any other applicable Rule or order of the Court should circumstances related to this litigation change.

INTERROGATORY NO. 9

To the extent not already identified in a detailed statement under 42 U.S.C. § 262(l)(3)(B)(ii)(I), identify any other bases (other than as set forth in your responses to Interrogatory Nos. 6–8) on which Mylan contends that the Court should not find that the manufacture, use, offer for sale, sale, or importation of Mylan's aflibercept would infringe at least one valid and enforceable claim of the Initial Patents or that Mylan is not liable for inducing the infringement of one or more claims of the Initial Patents, including an identification of all facts, documents, and circumstances on which Mylan relies for any such contention.

RESPONSE: In addition to its General Objections, Mylan objects to this Interrogatory as vague, ambiguous, overly broad, not relevant to any party's claim or defense and not proportional to the needs of the case, particularly to the extent it seeks information regarding "*any* other bases (other than as set forth in your responses to Interrogatory Nos. 6–8) on which Mylan contends that the Court should not find that the manufacture, use, offer for sale, sale, or importation of Mylan's aflibercept would infringe at least one valid and enforceable claim of the Initial Patents or that Mylan is not liable for inducing the infringement of one or more claims of the Initial Patents, including an identification of *all* facts, documents, and circumstances on which Mylan relies for any such contention." Mylan further objects to this Interrogatory to the extent it seeks discovery protected by the attorney client privilege, work product doctrine and/or any other applicable privilege or immunity. Mylan also objects to this Interrogatory as not relevant to any party's claim or defense as it seeks information related to confidential information outside the scope of this

litigation. In addition, Mylan objects to this Interrogatory to the extent it seeks information subject to confidentiality with a third party.

Mylan further objects to this Request to the extent that it seeks to improperly shift the burden of proving non-infringement to Mylan, and because it is premature, including because fact discovery, claim construction, and expert discovery are ongoing. This Court has found interrogatory requests seeking non-infringement contentions to be inappropriate and premature because "[p]laintiff[s] bear[] the burden to prove infringement and cannot use interrogatories to determine [d]efendant[s'] 'crystallized non-infringement arguments.'" *Automated Merch. Sys. Inc. v. Crane Co.*, 2011 WL 2648887, at *4 (N.D.W. Va. 2011) (quoting *Cummings–Allison v. SBM Co., Ltd.*, 2009 WL 806753, at *1-2 (E.D. Tex. 2009)). "Prior to knowing how the Court will construe the claims at issue, [the request] would be premature because it would be difficult to determine how the [technology] allegedly infringe[s]." *Id.*

Mylan further objects to this Request as premature and highlights that courts in the Fourth Circuit have found interrogatories premature when seeking information related to non-infringement contentions prior to the delineation of claim assertion and the close of discovery. *CertusView Techs., LLC v. S & N Locating Servs., LLC*, C.A. No. 2:13-cv-346 (E.D. Va. 2014) (Dkt. No. 116, 4). The Eastern District of Virginia specifically noted that the defendant's obligation to respond was triggered "once the scope of the interrogatories [was] clarified." *Id.* Delineation of asserted claims, along with an associated meet-and-confer, "clarified the information sought in great detail." *Id.* Mylan states that, unlike the interrogatories in *CertusView*, Regeneron has not sufficiently "clarified" which claims it seeks to assert and, thus, which claims Mylan must craft non-infringement arguments for. Since or around service of this set of interrogatories, Regeneron has narrowed its asserted claims twice: once in a December 16, 2022

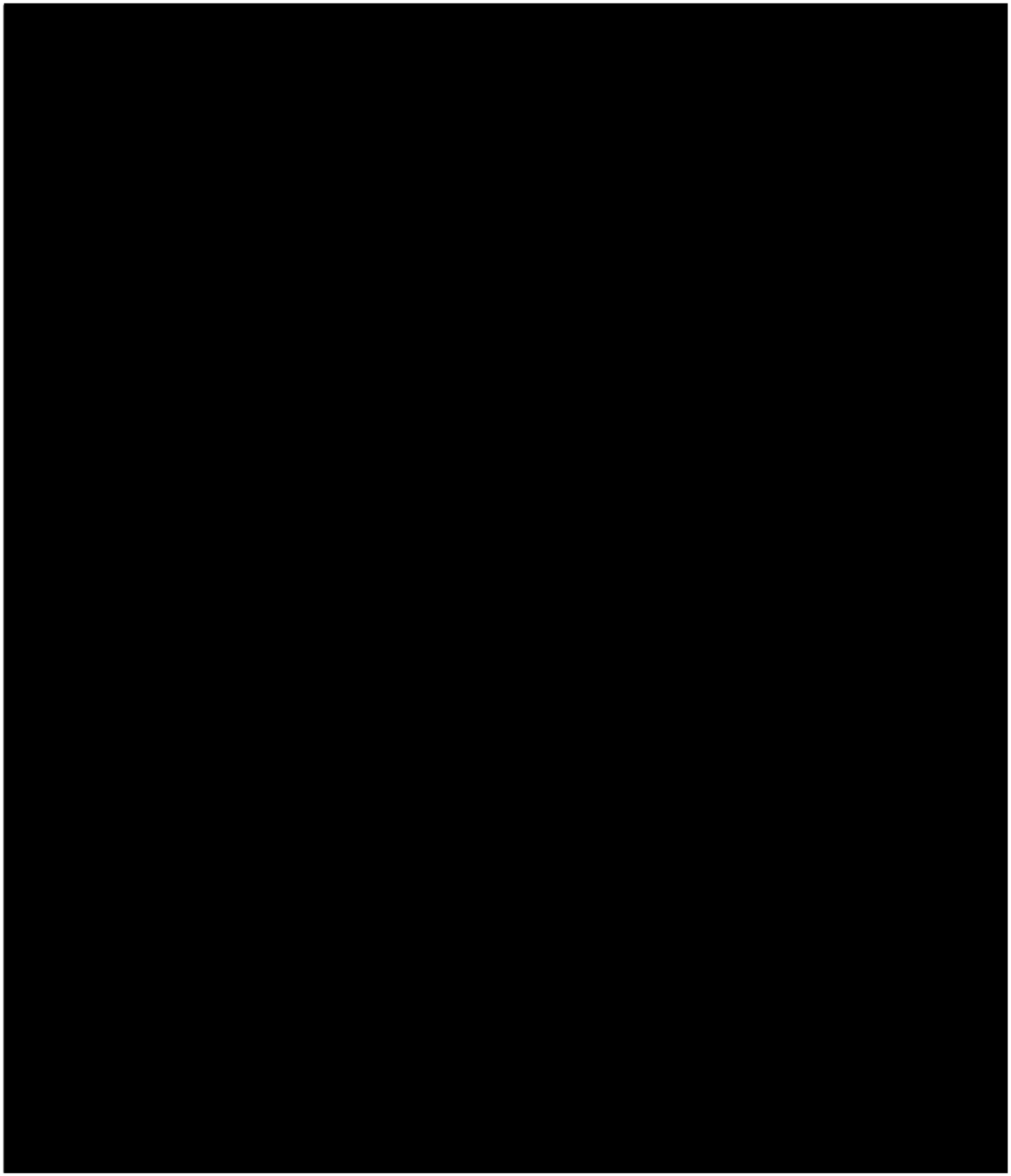
letter from Thomas Fletcher and a second time upon service of Regeneron's infringement contentions on January 12, 2023. Additionally, unlike the plaintiff in *CertusView*, Regeneron is required to further delineate its asserted claims by a specific date. Pursuant to the Scheduling Order (Dkt. No. 87), Regeneron must, again, narrow its claims, potentially by seven (7) days after the close of fact discovery on January 18, 2023. As Mylan will not know with certainty which claims Regeneron intends to assert until Regeneron narrows them again, Mylan notes that this Request is premature *at least* until January 25, 2023.

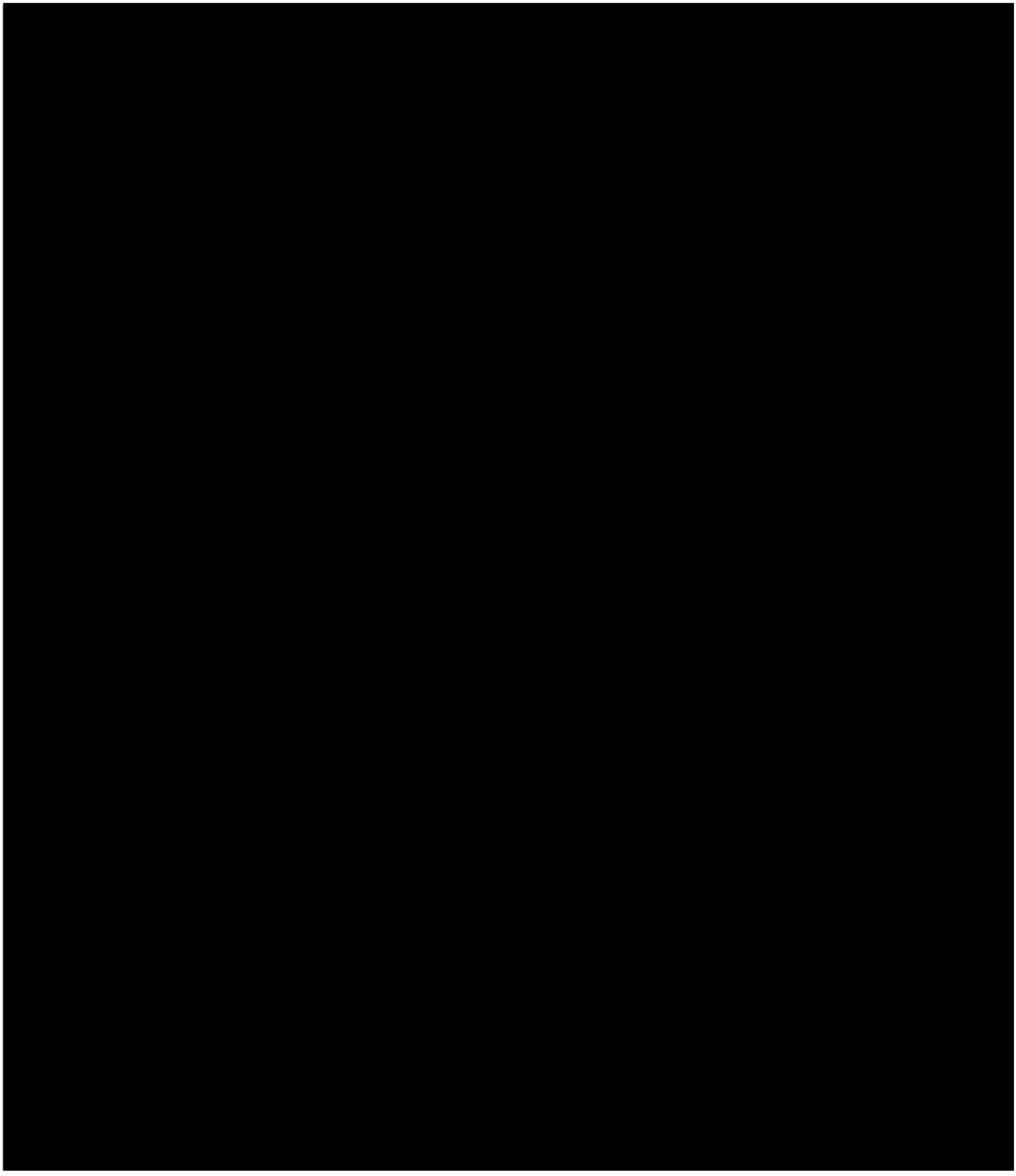
Without waiving its Objections, and subject to them, and to the extent Mylan understands this Interrogatory, Mylan responds as follows:

Mylan states that it has already produced detailed statements under 42 U.S.C. § 262(l)(3)(B)(ii)(I), giving notice to Regeneron as to Mylan's preliminary non-infringement defenses. Mylan further states that discovery is ongoing, and Mylan has yet to see Regeneron's opening expert reports on infringement, or all information purportedly being obtained under subpoena from third parties which may impact the non-infringement analysis.

Accordingly, Mylan expressly reserves the right to supplement and/or amend its response to this Interrogatory, as necessary and appropriate, including as expert discovery and claim construction proceeds and/or as otherwise provided under the Local Rules or any other applicable Rule or order of the Court should circumstances related to this litigation change.

[redacted]





[redacted]

INTERROGATORY NO. 13

Identify what, if any, differences exist between (1) how Mylan intends physicians to use its proposed aflibercept product; and (2) how physicians use Eylea.

RESPONSE: In addition to its General Objections, Mylan objects to this Interrogatory as vague, ambiguous, overly broad, not relevant to any party's claim or defense and not proportional to the needs of the case, particularly to the extent it seeks information regarding "what, *if any*, differences exist" between the two mentioned products. Mylan further objects to this Interrogatory to the extent it seeks discovery protected by the attorney client privilege, work product doctrine and/or any other applicable privilege or immunity. Mylan also objects to this Interrogatory as not relevant to any party's claim or defense as it seeks information related to confidential information outside the scope of this litigation. In addition, Mylan objects to this Interrogatory to the extent it seeks information subject to confidentiality with a third party. Mylan further objects to the extent it seeks information outside of Mylan's possession, custody, or control.

Without waiving its Objections, and subject to them, and to the extent Mylan understands this Interrogatory, Mylan responds as follows:

Mylan has no knowledge of how physicians will use its proposed aflibercept product and, thus, cannot "identify… differences" that exist between how physicians will use Mylan's proposed aflibercept product and how physicians use Eylea®. Mylan states that in submitting its BLA, it "seek[s] approval for an interchangeable biological product" following guidelines set forth by the Food and Drug Administration (FDA). (Niesner Tr. 132:12-14). Following the FDA's guidelines, Mylan notes that this interchangeable product under the name YESAFILI "is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with[] Neovascular (Wet) Age-Related Macular Degeneration (AMD)[,] Macular Edema Following Retinal Vein Occlusion (RVO)[,] Diabetic Macular Edema (DME)[,] [and] Diabetic Retinopathy (DR)." MYL-AFL-BLA1079688. The recommended dosage and administration schema, as well as contraindications, can be found in the labeling for YESAFILI drafted in accordance with FDA guidelines. MYL-AFL-BLA1079689-MYL-AFL-BLA1079695.

Mylan expressly reserves the right to supplement and/or amend its response to this Interrogatory, as necessary and appropriate, including as discovery proceeds and/or as otherwise provided under the Local Rules or any other applicable Rule or order of the Court should circumstances related to this litigation change.

INTERROGATORY NO. 14

Identify by Bates number the version of Mylan's draft labeling for its aflibercept biosimilar as to which Mylan is seeking FDA approval.

RESPONSE: In addition to its General Objections, Mylan objects to this Interrogatory as vague, ambiguous, overly broad, not relevant to any party's claim or defense and not proportional to the needs of the case. Mylan further objects to this Interrogatory to the extent it seeks discovery protected by the attorney client privilege, work product doctrine and/or any other applicable privilege or immunity. Mylan also objects to this Interrogatory as not relevant to any party's claim

or defense as it seeks information related to confidential information outside the scope of this litigation.

Without waiving its Objections, and subject to them, and to the extent Mylan understands this Interrogatory, Mylan responds as follows:

[redacted]

Mylan expressly reserves the right to supplement and/or amend its response to this Interrogatory, as necessary and appropriate, including as discovery proceeds and/or as otherwise provided under the Local Rules or any other applicable Rule or order of the Court should circumstances related to this litigation change.

Date: January 18, 2023

/s/ Gordon H. Copland

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