IN THE UNITED STATES DISTRICT COURT
FOR THE SOUTHERN DISTRICT OF NEW YORK
WHITE PLAINS DIVISION

NOVARTIS VACCINES AND DIAGNOSTICS, INC., NOVARTIS PHARMA AG, and GRIFOLS WORLDWIDE OPERATIONS LIMITED, Plaintiffs, v. REGENERON PHARMACEUTICALS, INC., Defendant.	Civil Action No. 7:18-cv-2434 **COMPLAINT FOR PATENT INFRINGEMENT** **DEMAND FOR JURY TRIAL**

COMPLAINT

Plaintiffs Novartis Vaccines and Diagnostics, Inc., Novartis Pharma AG, and Grifols Worldwide Operations Limited (collectively, "Plaintiffs"), by and through their undersigned counsel, hereby allege claims for patent infringement against Defendant Regeneron Pharmaceuticals, Inc. as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code.

THE PARTIES

2. Plaintiff Novartis Vaccines and Diagnostics, Inc. ("NVD") is a corporation organized and existing under the laws of the state of Delaware, having its place of business located at One Health Plaza, East Hanover, New Jersey 07936.

3. Plaintiff Novartis Pharma AG is a corporation organized and existing under the laws of Switzerland, having an office and place of business located at Lichtstrasse 35, CH-4056

Basel, Switzerland. NVD and Novartis Pharma AG are collectively referred to herein as "Novartis."

4. Plaintiff Grifols Worldwide Operations Limited ("Grifols") is a corporation organized and existing under the laws of Ireland, having an office and place of business located at Grange Castle Business Park, Grange Castle, Clondalkin, Dublin 22, Ireland.

5. On information and belief, Defendant Regeneron Pharmaceuticals, Inc. ("Regeneron") is a corporation organized and existing under the laws of the State of New York, with its principal place of business located at 777 Old Saw Mill River Road, Tarrytown, New York 10591.

6. On information and belief, Regeneron has two primary locations, both of which are in the State of New York. Regeneron's research and administrative offices are located in Tarrytown, New York. Regeneron has a manufacturing facility in Rensselaer, New York.

7. On information and belief, Regeneron is engaged in the research, development, manufacture, and sale of, among other things, pharmaceutical products.

JURISDICTION AND VENUE

8. This is an action for patent infringement under the Patent Act, 35 U.S.C. § 100 *et seq.*, including § 271.

9. This Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

10. This Court has personal jurisdiction over Regeneron because, *inter alia*, Regeneron is a corporation organized and existing under the laws of the state of New York and / or has established minimum contacts with the forum such that the exercise of jurisdiction over the Defendant will not offend traditional notions of fair play and substantial justice.

11. On information and belief, Regeneron maintains research and development facilities in New York; owns property in New York; maintains numerous employees in New York; solicits and conducts business in New York; is registered to do business in New York; has appointed agents for service of process in New York; and has regularly used the New York courts for litigation, including patent enforcement actions.

12. Venue is proper in this judicial District pursuant to 28 U.S.C. §§ 1391(b) and (c) and 1400(b).

THE PATENT-IN-SUIT

13. On November 18, 1997, United States Patent No. 5,688,688 ("the '688 patent"), entitled "Vector for Expression of a Polypeptide in a Mammalian Cell," was duly and legally issued to inventors Paul A. Luciw, Dino Dina, Steven Rosenberg, Barbara S. Chapman, Richard M. Thayer, and Nancy L. Haigwood. A true and correct copy of the '688 patent is attached hereto as Exhibit A.

14. Upon issuance, the '688 patent was assigned to Chiron Corporation ("Chiron"), a biotechnology company that was formerly based in Emeryville, California.

15. On April 20, 2006, Chiron was acquired by merger and became an indirect, wholly owned subsidiary of non-party Novartis AG.

16. The '688 patent was assigned to NVD and the assignment recorded with the United States Patent and Trademark Office ("PTO") on or about January 27, 2011. On or about January 9, 2014, Grifols acquired certain assets belonging to NVD. As part of this acquisition, the '688 patent was assigned in part to Grifols, and Grifols became a co-owner of the '688 patent with NVD.

17. Grifols is a named Plaintiff solely because Grifols is a co-owner of the ’688 patent. Grifols is not seeking damages or any other monetary relief resulting from the filing of this complaint.

18. The ’688 patent is exclusively licensed by NVD to Novartis Pharma AG in the field of eye diseases.

19. Plaintiffs hold all rights, title and interest in the ’688 patent.

20. The ’688 patent discloses and claims, among other things, gene expression constructs for the expression of polypeptides in mammalian cells.

21. Non-party Lonza Group AG (“Lonza”), through one or more of its affiliates, manufactured and sold a commercial gene expression system—the Lonza GS Expression System™—that uses the same technology claimed in the ’688 patent. A typical expression vector used in the Lonza GS Expression System™ includes each of the four primary elements of the claimed inventions: (a) an upstream SV40 origin of replication; (b) a downstream SV40 polyadenylation region; (c) a transcriptional regulatory region from the human cytomegalovirus (“hCMV”) immediate early region IE1, inclusive of the promoter, enhancer, and Intron A; and (d) a polypeptide coding sequence encoding a heterologous polypeptide. Accordingly, use of the expression vectors associated with the Lonza GS Expression System™, or use of an expression system into which such vectors are incorporated, infringes one or more claims of the ’688 patent.

INFRINGEMENT BY DEFENDANT

22. Plaintiffs reallege and incorporate by reference paragraphs 1-21 above as though fully stated herein.

23. Eylea® is a vascular endothelial growth factor (VEGF) inhibitor approved for the treatment of Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema

Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) in Patients with DME. (Eylea® Prescribing Information at § 1 (Exhibit B)).

24. Upon information and belief, Eylea® was first approved by the United States Food and Drug Administration ("FDA") on or about November 18, 2011.

25. The active ingredient of Eylea® is aflibercept, "a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1." (Eylea® Prescribing Information (Exhibit B) at § 11). It acts as "a soluble decoy receptor that binds VEGF-A and PlGF," thereby inhibiting angiogenesis by preventing activation of VEGFR-1 and VEGFR-2. (*Id*. at § 12.1).

26. Upon information and belief, Defendant has manufactured, marketed and sold Eylea® in the United States since its first FDA approval on or about November 18, 2011. (*See, e.g.*, Regeneron 2016 Form 10-K (Exhibit D) at 40-41 (reporting Regeneron manufacture of, *inter alia*, EYLEA and ZALTRAP in Rensselaer, NY)).

27. Lucentis® is a humanized therapeutic antibody fragment designed for intraocular use which binds to and inhibits the biologic activity of human VEGF-A. (Lucentis® Prescribing Information (Exhibit E) at § 11).

28. Lucentis® was first approved by FDA on or about June 30, 2006. The license granted approval for the manufacture of the drug substance (ranibizumab) at Genentech, Inc., South San Francisco, California; for the fill of the final formulated product at Novartis Pharma Stein AG, Stein, Switzerland (which includes product intended for global supply); and for the labeling and packaging of the filled vials at Genentech, Inc., South San Francisco, California. (Lucentis® FDA Approval Letter (Exhibit F) at 1).

29. Lucentis® also received marketing authorization by the European Medicines Agency (EMA) on January 22, 2007. (Lucentis® EMA Summary of Product Characteristics (Exhibit G) at 26). According to that authorization, the manufacturers of the active drug substance are Genentech, Inc., 1 DNA Way, South San Francisco, CA 94080 and Roche Singapore Technical Operations Pte. Ltd., 10 Tuas Bay Link, Singapore 637394, and the manufacturer responsible for batch release is Novartis Pharma GmbH, Roonstrasse 25, 90429 Nuremberg, Germany. (*Id.* at 55).

30. Like Eylea®, Lucentis® is indicated for the treatment of Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), and Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR). (Lucentis® Prescribing Information (Exhibit E) at § 1; *see also* Lucentis® EMA Summary of Product Characteristics (Exhibit G) at 2).

31. Lucentis® and Eylea® are competing products in the market of vitreoretinal eye disorder therapies.

32. Prior to the approval of Eylea® in 2011, Lucentis® was the only approved protein-based therapy indicated for the treatment of AMD and the other vitreoretinal disorders for which Lucentis® is indicated. As such, a demand for Lucentis® existed in the market.

33. Zaltrap®, "in combination with 5-fluorouracil, leucovorin, irinotecan-(FOLFIRI), is indicated for patients with metastatic colorectal cancer (mCRC) that is resistant to or has progressed following an oxaliplatin-containing regimen." (Zaltrap® Prescribing Information (Exhibit C) at § 1). Zaltrap® is administered via intravenous infusion. (*Id*. at § 2.1)

34. Upon information and belief, Zaltrap® was first approved by FDA on or about August 3, 2012.

35. The active ingredient of Zaltrap® is ziv-aflibercept, "a recombinant fusion protein consisting of Vascular Endothelial Growth Factor (VEGF)-binding portions from the extracellular domains of human VEGF Receptors 1 and 2 fused to the Fc portion of the human IgG1." (Zaltrap® Prescribing Information (Exhibit C) at § 11). It "acts as a soluble receptor that binds to human VEGF-A . . . to human VEGF-B . . . and to human PlGF[,]" thereby "inhibit[ing] the binding and activation of their cognate receptors[,]" which "can result in decreased neovascularization and decreased vascular permeability." (*Id*. at § 12.1).

36. Upon information and belief, Defendant has manufactured, marketed and sold Zaltrap® in the United States since its first FDA approval on or about August 3, 2012. (*See, e.g.*, Zaltrap® EMA Summary of Product Characteristics (Exhibit H) at 27 (disclosing Regeneron as "the manufacturer of the biological active substance" in Zaltrap®); Regeneron 2017 Form 10-K (Exhibit I) at F-20 (reporting revenue "primarily related to a percentage of net sales of ZALTRAP and manufacturing ZALTRAP commercial supplies for Sanofi."); *id*. at 46 (reporting Regeneron manufacture of, *inter alia*, EYLEA and ZALTRAP in Rensselaer, NY); Regeneron 2016 Form 10-K (Exhibit D) at 40-41 (same); Regeneron-959 (Zaltrap®) PTE (Exhibit J) at 121 (FDA approval for Regeneron to manufacture ZALTRAP drug substance in Rensselaer, NY)).

37. Upon information and belief, the recombinant fusion protein active ingredient used in Zaltrap® is identical to the recombinant fusion protein active ingredient used in Eylea®. (*See, e.g.*, João Rafael de Oliveira Dias et al., *Fusion Proteins for Treatment of Retinal Diseases: Aflibercept, Ziv-Aflibercept, and Conbercept*, 2 INT'L J. RETINA & VITREOUS 1, 2 (2016) (Exhibit K)).

38. Upon information and belief, Regeneron's manufacture of aflibercept—the recombinant fusion protein active ingredient used in both Eylea® and Zaltrap®—utilizes Plaintiffs' patented technology as claimed under the '688 patent.

39. Upon information and belief, Regeneron manufactures Eylea® and Zaltrap® utilizing a "non-human mammalian host cell expression system" and/or "method for producing a non-human mammalian cell" that is covered by one or more claims of the '688 patent.

40. Claim 1, the analysis of which is provided here for exemplary purposes only, and is not intended to limit the assertion of the remaining claims of the '688 patent, reads as follows:

> **1.** A non-human mammalian host cell expression system for improved expression comprising a non-human mammalian host cell with a vector for expression of a polypeptide in a mammalian cell comprising a first polynucleotide sequence that comprises:
>
> a) an upstream SV40 origin of replication;
>
> b) a downstream SV40 polyadenylation region;
>
> c) a transcription regulatory region from human cytomegalovirus immediate early region HCMV IE1, wherein the transcription regulatory region includes the first HCMV IE1 intron proximal to the 3' end of the HCMV IE1 promoter, is interposed between the SV40 origin of replication and the SV40 polyadenylation region, and is capable of directing the transcription of a polypeptide coding sequence operably linked downstream from the transcription regulatory region, and
>
> d) the polypeptide coding sequence encoding a heterologous polypeptide operably linked downstream of the transcription regulatory region.

(*Ex Parte* Reexamination Certificate, the '688 patent (Exhibit A) at col. 1, ll. 22-40).

41. For example, upon information and belief, Defendant is the sole assignee of United States Patent No. 7,070,959 ("Regeneron-959") (Exhibit L).

42. Regeneron-959, upon information and belief, purports to disclose Regeneron's production of aflibercept, the recombinant fusion protein active ingredient used in both Eylea® and Zaltrap®.

43. Regeneron-959 indicates that Regeneron uses a pEE14 expression vector that was developed at Celltech Ltd. (later acquired by Lonza) for the expression of aflibercept (herein, the "Lonza pEE14 Expression Vector"). (*See, e.g.*, Regeneron-959 (Exhibit L) at col. 16, ll. 19-20). Specifically, upon information and belief, Regeneron inserted "a heterologous polypeptide coding sequence" into the Lonza pEE14 Expression Vector in accordance with at least claims 1 and 15 of the '688 patent.

44. On or about December 21, 2011, Regeneron filed an application for patent term extension ("PTE") for the Regeneron-959 patent with respect to the regulatory review period of Eylea®. (*See* Regeneron-959 (Eylea®) PTE (Exhibit O) at 1-2). Therein, Regeneron informed the PTO that Regeneron-959 claims a method of manufacturing the active drug substance in Eylea®. (*See, e.g.*, *id.* at 4-6 (referencing claim 11)).

45. On or about October 1, 2012, Regeneron (through its purported "agent" and exclusive licensee of Regeneron-959, sanofi-aventis U.S. LLC) filed a second application for PTE for Regeneron-959 with respect to the regulatory review period of Zaltrap®. (*See* Regeneron-959 (Zaltrap®) PTE (Exhibit J) at 3-4). Therein, Regeneron informed the PTO that Regeneron-959 claims a method of manufacturing the active drug substance in Zaltrap®. (*See, e.g.*, *id.* at 6-8 (referencing claim 11)).

46. Upon information and belief, Regeneron utilizes the method disclosed in Regeneron-959, including use of the Lonza pEE14 Expression Vector, to produce aflibercept, the recombinant fusion protein active ingredient used in both Eylea® and Zaltrap®.

47. The Lonza pEE14 Expression Vector used in the Regeneron-959 method comprises the following "backbone components," in order from 5' to 3':

a) An SV40 origin of replication, provided by an SV40 late promoter;

b) A "GS minigene," comprising the coding sequence, an intron, and 2 kb of 3' flanking DNA from the glutamine synthetase gene of the Chinese Hamster;

c) The major immediate-early gene promoter-enhancer of the human cytomegalovirus, including the leader intron;

d) A polylinker; and

e) An SV40 polyadenylation signal.

(Christopher R. Bebbington, *Expression of Antibody Genes in Nonlymphoid Mammalian Cells*, 2 METHODS: COMPANION TO METHODS ENZYMOLOGY 136 (1991) (Exhibit M) at 137, 138 (Fig. 1), 139 (Fig. 4); United States Patent No. 5,827,739 (Exhibit N) at col. 6, ll. 36-43 (describing the GS minigene)).

48. Upon information and belief, Regeneron inserts "a heterologous polypeptide coding sequence" into the Lonza pEE14 Expression Vector by inserting DNA coding for aflibercept "at a multiple cloning site [polylinker] downstream of the CMV promoter." (Regeneron-959 (Exhibit L) at col. 29, ll. 12-41; *id*. at col. 16, ll. 7-21).

49. The resulting vector—which comprises a "heterologous polypeptide coding sequence" for aflibercept inserted into the Lonza pEE14 Expression Vector—is, upon information and belief, introduced into non-human mammalian host cells—specifically, Chinese Hamster Ovary (CHO) cells. (Regeneron-959 (Exhibit L) at col. 11, ll. 58-59; *see also* Eylea® Prescribing Information (Exhibit B) at § 11; Zaltrap® Prescribing Information (Exhibit C) at § 11; Regeneron-959 (Eylea®) PTE (Exhibit O) at 7; Regeneron-959 (Zaltrap®) PTE (Exhibit J) at 4-8).

50. In sum, upon information and belief, Regeneron's method of manufacturing the recombinant fusion protein active ingredient used in both Eylea® and Zaltrap® meets every element of claim 1 of the '688 patent as follows:

1. A non-human mammalian host cell expression system for improved expression comprising a non-human mammalian host cell with a vector for expression of a polypeptide in a mammalian cell comprising a first polynucleotide sequence that comprises:	*See* ¶¶ 33-41 above.
a) an upstream SV40 origin of replication;	*See* ¶ 39 above.
b) a downstream SV40 polyadenylation region;	*See* ¶ 39 above.
c) a transcription regulatory region from human cytomegalovirus immediate early region HCMV IE1, wherein the transcription regulatory region includes the first HCMV IE1 intron proximal to the 3' end of the HCMV IE1 promoter, is interposed between the SV40 origin of replication and the SV40 polyadenylation region, and is capable of directing the transcription of a polypeptide coding sequence operably linked downstream from the transcription regulatory region, and	*See* ¶ 39 above.
d) the polypeptide coding sequence encoding a heterologous polypeptide operably linked downstream of the transcription regulatory region	*See* ¶ 40 above.

51. Similarly, upon information and belief, Regeneron's method of manufacturing the active drug substance in both Eylea® and Zaltrap® meets the elements of one or more of the remaining claims of the '688 patent.

COUNT I

(Regeneron's Infringement of United States Patent No. 5,688,688)

52. Plaintiffs reallege and incorporate by reference paragraphs 1-51 above as though fully stated herein.

53. Regeneron's manufacture of Eylea® incorporates technology covered by one or more claims of the '688 patent.

54. Regeneron's manufacture of Zaltrap® incorporates technology covered by one or more claims of the '688 patent.

55. Regeneron has manufactured Eylea® in the United States using the Lonza GS Expression System™ with a heterologous polypeptide coding sequence for aflibercept inserted therein.

56. Regeneron has manufactured Zaltrap® in the United States using the Lonza GS Expression System™ with a heterologous polypeptide coding sequence for aflibercept inserted therein.

57. Regeneron has infringed one or more claims of the '688 patent in violation of 35 U.S.C. § 271, literally and/or under the doctrine of equivalents, by, among other things, making, using, offering for sale, selling, and/or importing within this judicial District and elsewhere in the United States, without license or authority from Novartis, products and technologies that fall within the scope of one or more claims of the '688 patent, either literally or under the doctrine of equivalents. The infringing products include, without limitation, Eylea® and Zaltrap®.

58. Upon information and belief, Regeneron has been aware of the existence of the '688 patent and has no reasonable basis for believing that its manufacture of Eylea® does not

infringe the ’688 patent, thus rendering the case “exceptional,” as that term is used in 35 U.S.C. § 285.

59. Upon information and belief, Regeneron has been aware of the existence of the ’688 patent and has no reasonable basis for believing that its manufacture of Zaltrap® does not infringe the ’688 patent, thus rendering the case “exceptional,” as that term is used in 35 U.S.C. § 285.

60. Regeneron’s acts of infringement set forth above have caused irreparable injury to Plaintiffs, and Plaintiffs are entitled to recover from Regeneron the damages sustained by Novartis as a result of Regeneron’s wrongful acts in an amount subject to proof at trial.

61. Upon information and belief, Regeneron’s infringement of the ’688 patent has been willful, wanton, and deliberate, justifying the assessment of treble damages pursuant to 35 U.S.C. § 284.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs respectfully request that this Court enter judgment in its favor and against Defendant Regeneron as follows:

A. For a determination that Regeneron has infringed one or more claims of the ’688 patent, either literally or under the doctrine of equivalents;

B. Awarding Novartis compensatory damages for Regeneron’s infringement, together with interest and costs pursuant to 35 U.S.C. § 284;

C. For a determination that Regeneron’s infringement of the ’688 patent has been willful, wanton, and deliberate, and that the damages against it be increased up to treble on this basis;

D. For a determination that this is an exceptional case under 35 U.S.C. § 285 and an award of attorneys' fees and costs to Novartis is warranted in this action; and

E. Granting such other and further relief as this Court deems just and proper.

JURY DEMAND

Pursuant to Federal Rule of Civil Procedure 38(b), Plaintiffs hereby demand a trial by jury on all issues triable to a jury.

Dated: March 19, 2018

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