

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC. AND SAMSUNG BIOEPIS CO., LTD.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

IPR2023-00462¹

Patent 10,464,992 B2

**PATENT OWNER'S UNOPPOSED MOTION TO TERMINATE
PROCEEDING**

¹ IPR2023-01312 has been joined with this proceeding.

TABLE OF EXHIBITS

Exhibit Description	Exhibit #
Declaration of Dr. Alexander M. Klibanov	2001
Dr. Alexander M. Klibanov <i>curriculum vitae</i>	2002
AVASTIN® Label (rev. Sept. 2011)	2003
Declaration of David M. Brown, M.D., <i>Mylan Pharms. Inc. v. Regeneron Pharms., Inc.</i> , IPR2021-00881, Ex. 2050 (Feb. 10, 2022)	2004
MACUGEN® Label (rev. Jul. 2011)	2005
MACUGEN® FDA Approval Letter (Dec. 17, 2004)	2006
AVASTIN® FDA Approval Letter (Feb. 26, 2004)	2007
LUCENTIS® Label (rev. June 2010)	2008
Kyla R. Rodgers & Richard C. Chou, <i>Therapeutic Monoclonal Antibodies and Derivatives: Historical Perspectives and Future Directions</i> , 34 BIOTECHNOLOGY ADVANCES 1149 (2016)	2009
Adis R&D Profile, <i>Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF Trap – Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye</i> , 9 DRUGS R&D 261 (2008)	2010
Quan Dong Nguyen et al., <i>A Phase I Trial of an IV-Administered Vascular Endothelial Growth Factor Trap for Treatment in Patients with Choroidal Neovascularization due to Age-Related Macular Degeneration</i> , 113 OPHTHAMOLOGY 1522 (2006).	2011
EYLEA® Label (rev. d Nov. 2011)	2012
U.S. Patent Publication No. 2006/0058234 to Daly et al.	2013
FDA, GUIDANCE FOR INDUSTRY: Q1A(R2) STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS (rev. 2, 2003)	2014
PHARMACEUTICAL FORMULATION DEVELOPMENT OF PEPTIDES AND PROTEINS (Sven Frokjaer & Lars Hovgaard, eds., 2000)	2015
Jonas L. Fast et al., <i>Physical Instability of a Therapeutic Fc Fusion Protein: Domain Contributions to Conformational and Colloidal Stability</i> , 48 BIOCHEMISTRY 11724 (2009)	2016
ANTIBODY FUSION PROTEINS (Steven M. Chamow & Avi Ashkenazi, eds. 1999)	2017

Exhibit Description	Exhibit #
Hussein Hollands et al., <i>Short-Term Intraocular Pressure Changes After Intravitreal Injection of Bevacizumab</i> , 42 CAN. J. OPHTHAMOLOGY 807 (2007)	2018
Domenico Sanfelice et al., <i>Cold Denaturation Unveiled: Molecular Mechanism of the Asymmetric Unfolding of Yeast Frataxin</i> , 16 CHEMPHYSCHEM 3599 (2015)	2019
Sven Frokjaer & Daniel E. Otzen et al., <i>Protein Drug Stability: A Formulation Challenge</i> , 4 NATURE REVIEWS DRUG DISCOVERY 298 (2005)	2020
<i>Somatropin</i> , THE UNITED STATES PHARMACOPEIA 1993 (29th rev., official from Jan. 1, 2006)	2021
International Patent Publication No. 2006/104852 to Dix et al.	2022
U.S. Patent Publication No. 2006/0217311 to Dix et al.	2023
List of References cited by Applicant and Considered by Examiner, U.S. Patent App. No. 16/582,486 (received Mar. 2, 2021 and considered Apr. 12, 2021)	2024
Third-Party Submission Under 37 CFR 1.290, U.S. Patent App. No. 16/582,486 (considered Dec. 31, 2020)	2025
U.S. Patent No. 11,066,458 to Furfine et al.	2026
Russell F. Doolittle, <i>The Multiplicity of Domains in Proteins</i> , 64 ANN. REV. BIOCHEMISTRY 1995	2027
Liliana M. Sampaleanu et al., <i>Three-Dimensional Structure of the Argininosuccinate Lyase Frequently Complementing Allele Q286R</i> , 40 BIOCHEMISTRY 15,570 (2001)	2028
Arvind K. Pandey et al., <i>Mechanisms of VEGF (Vascular Endothelial Growth Factor) Inhibitor–Associated Hypertension and Vascular Disease</i> , 71 Hypertension, Dec. 26, 2017	2029
Abhibav A. Shukla & Uwe Gottschalk, <i>Downstream Processing of Fc-Fusion Proteins</i> , in THERAPEUTIC FC-FUSION PROTEINS (S.M. Chamow et al., eds. 2014)	2030
Terri Davis-Smyth et al., <i>The Second Immunoglobulin-Like Domain of the VEGF Tyrosine Kinase Receptor Flt-1 Determines Ligand Binding</i>	2031

Exhibit Description	Exhibit #
<i>and May Initiate a Signal Transduction Cascade</i> , 15 EMBO J. 4919 (1996).	
P17948 VGFR1_Human, available at https://www.uniprot.org/uniprotkb/P17948/entry	2032
P17948 VGFR1_Human, Entry Version 140 (txt) (Jan. 11, 2011), available at https://rest.uniprot.org/unisave/P17948?format=txt&versions=140	2033
Dan Lu et al., <i>Identification of the Residues in the Extracellular Region of KDR Important for Interaction with Vascular Endothelial Growth Factor and Neutralizing Anti-KDR Antibodies</i> . 275 J. BIOLOGICAL CHEMISTRY 14321 (2000)	2034
Matthew C. Franklin et al., <i>The Structural Basis for the Function of Two Anti-VEGF Receptor 2 Antibodies</i> , 19 STRUCTURE 1097 (2011)	2035
P35968 VGFR2_Human, available at https://www.uniprot.org/uniprotkb/P35968/entry	2036
P35968 VGFR2_Human, Entry Version 127 (txt) (Jan. 11, 2011), available at https://rest.uniprot.org/unisave/P35968?format=txt&versions=127	2037
Clifford R. Robinson & Robert T. Sauer, <i>Optimizing the Stability of Single-chain Proteins by Linker Length and Composition Mutagenesis</i> , 95 PROC. NATL. ACAD. SCI. USA, 5929 (1998)	2038
Bei Tong et al., <i>Interdomain Linker Effect on the Mechanical Stability of Ig Domains in Titin</i> , 23 INT'L J. MOLECULAR SCI. 9836 (2022)	2039
Xiaoying Chen et al., <i>Fusion Protein Linkers: Property, Design and Functionality</i> . 65 ADVANCED DRUG DELIVERY REV. 1357 (2013)	2040
Jose I. Casal et al., <i>Subunit Interface of Triosephosphate Isomerase: Site-Directed Mutagenesis and Characterization of the Altered Enzyme</i> , 26 BIOCHEMISTRY 1258 (1987)	2041
Tzu-Jing Yang et al., <i>D614G Mutation in the SARS-CoV-2 Spike Protein Enhances Viral Fitness by Desensitizing It to Temperature-Dependent Denaturation</i> , 197 J. BIOL. CHEM. 101, 238 (2021)	2042
BIOCHEMISTRY (Jeremy M. Berg et al., eds., 5th ed. 2002)	2043

Exhibit Description	Exhibit #
Declaration of Daralyn J. Durie in Support of this Motion for Admission <i>Pro Hac Vice</i> (“Durie Decl.”)	2044
Declaration of Kira A. Davis in Support of this Motion for Admission <i>Pro Hac Vice</i> (“Davis Decl.”)	2045
Default Protective Order	2046
Expert Declaration of Dr. Alexander M. Klibanov (Nov. 2, 2023)	2047
Vila-Perelló, M. & Muir, T. W., <i>Biological Applications of Protein Splicing</i> , 143(2) CELL 191 (2010).	2048
Kirikoshi, R. et al., <i>Phosphate-Catalyzed Succinimide Formation From Asp Residues: A Computational Study of the Mechanism</i> , 19(2) INT’L J. MOLECULAR SCIS. 637 (2018).	2049
Trial Transcript (unsealed portions), <i>Regeneron Pharms., Inc. v. Mylan Pharms. Inc.</i> , No. 1:22-cv-00061-TSK-JPM (N.D.W. Va., June 12–23, 2023).	2050
U.S. Patent Publication No. 2003/0180287 to Gombotz et al.	2051
Jørgensen, J. T. et al., <i>Pain Assessment of Subcutaneous Injections</i> , 30(7-8) ANNALS OF PHARMACOTHERAPY 729 (1996)	2052
Wang, W., <i>Protein Aggregation and Its Inhibition in Biopharmaceutics</i> , 289(1-2) INT’L J. OF PHARMS. 1 (2005)	2053
Transcript of Oral Deposition of Dr. Ralph Tarantino (October 13, 2023)	2054
LUCENTIS® FDA Approval Letter (June 30, 2006)	2055
<i>Vial</i> , DORLAND’S ILLUSTRATED MEDICAL DICTIONARY (30th ed., 2003)	2056
<i>Vial</i> , TABER’S CYCLOPEDIA MEDICAL DICTIONARY (20th ed. 2001)	2057
<i>Vial</i> , MOSBY’S MEDICAL, NURSING & ALLIED HEALTH DICTIONARY (6th ed. 2002)	2058
<i>Vial</i> , DICTIONARY OF PHARMACY (1st ed. 2004)	2059
Arakawa, T., et al., <i>Factors Affecting Short-Term and Long-Term Stabilities of Proteins</i> , 46(1-3) ADVANCED DRUG DELIVERY REVS. 307 (2001)	2060
Tang, X., & Pikal, M. J., <i>Design of Freeze-Drying Processes For Pharmaceuticals: Practical Advice</i> , 21(2) PHARM. RSCH. 191 (2004).	2061

Exhibit Description	Exhibit #
Cao, E. et al., <i>Effect of Freezing and Thawing Rates on Denaturation of Proteins in Aqueous Solutions</i> , 82(6) BIOTECH. & BIOENGINEERING 684 (2003).	2062
Brange, J., et al., <i>Toward Understanding Insulin Fibrillation</i> , 86(5) J. PHARM. SCIS. 517 (1997)	2063
Robinson, N. E., & Robinson, A. B., MOLECULAR CLOCKS: DEAMIDATION OF ASPARAGINYL AND GLUTAMINYL RESIDUES IN PEPTIDES AND PROTEINS (2004)	2064
Robinson, N. E., et al., <i>Structure-Dependent Nonenzymatic Deamidation of Glutaminyl and Asparaginyl Pentapeptides</i> , 63(5) J. PEPTIDE RSCH. 426 (2004)	2065
Solá, R. J. & Griebenow, K., <i>Effects of Glycosylation on the Stability of Protein Pharmaceuticals</i> , 98(4) J. PHARM. SCIS. 1223 (2009)	2066
International Patent Publication No. WO/2006/047325 to Shams	2067
U.S. Patent Publication No. 2004/0014667 to Daly et al.	2068
ENBREL® Label (rev. Sept. 27, 2004)	2069
HUMIRA® Label (rev. July 30, 2004)	2070
NEULASTA® Label (rev. Jan. 31, 2002)	2071
Bakri, S. J. et al., <i>Six-Month Stability of Bevacizumab (Avastin) Binding to Vascular Endothelial Growth Factor After Withdrawal into a Syringe and Refrigeration or Freezing</i> , 26(5) RETINA 519 (2006)	2072
U.S. Food and Drug Administration, <i>Guideline for Industry: Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products</i> , 61 Fed. Reg. 36466 (1996), https://www.fda.gov/media/71441/download	2073
Bayer, <i>Assessment of Long Term Treatment with Testosterone Undecanoate in Males with Hypogonadism</i> , NCT00220298 (rev. Dec. 30, 2014), https://clinicaltrials.gov/study/NCT00220298?a=11&tab=table	2074
Stanford University, <i>High-dose Sequential Therapy and Single Autologous Transplantation for Multiple Myeloma</i> , NCT00349778 (rev. Dec. 12, 2017), https://clinicaltrials.gov/study/NCT00349778?tab=table	2075

Exhibit Description	Exhibit #
Lidocaine Hydrochloride and Dextrose (injection, solution) Label, Hospira, Inc (rev. June 2006)	2076
Fentanyl Citrate (injection, solution) Label, Baxter Healthcare Corporation (rev. Sept. 2006)	2077
ATGAM® Label (rev. Apr. 2010)	2078
ATGAM® Label (rev. Sept. 2023)	2079
McIlvaine, T. C., <i>A Buffer Solution for Colorimetric Comparison</i> , 49(2) J. BIO. CHEMISTRY 183 (1921)	2080
Zacchigna, M., et al., <i>Improvement of warfarin biopharmaceutics by conjugation with poly (ethylene glycol)</i> , 23(4) EUR. J. PHARM. SCIS. 379 (2004)	2081
Yamaguchi, S., et al., <i>Approval Success Rates of Drug Candidates Based on Target, Action, Modality, Application, and Their Combinations</i> , 14(3) CLINICAL & TRANSLATIONAL SCI. 1113 (2021)	2082
Svendsen, O., et al., <i>Intramuscular Injection of Hypertonic Saline: In Vitro and In Vivo Muscle Tissue Toxicity and Spinal Neurone C-Fos Expression</i> , 97(1) BASIC & CLIN. PHARMACOLOGY & TOXICOLOGY 52 (2005)	2083
Dupont, J. et al., <i>Phase I and Pharmacokinetic Study of VEGF Trap Administered Subcutaneously (sc) to Patients (pts) with Advanced Solid Malignancies</i> , 22(14) J. CLIN. ONCOLOGY 3009 (2004)	2084
Shannon, E. et al., <i>Etanercept (Enbrel®) Alternative Storage at Ambient Temperature</i> , 9 CLIN. PHARMACOLOGY: ADVANCES & APPLICATIONS 87 (2017)	2085
Rougeot, C. et al., <i>Comparative Study of Biosynthetic Human Growth Hormone Immunogenicity in Growth Hormone Deficient Children</i> , 35(2) HORMONE RSCH. IN PAEDIATRICS 76 (1991)	2086
Mohan, C., <i>Buffers: A guide for the preparation and use of buffers in biological systems</i> (2003)	2087
Chelius, D. et al., <i>Identification and characterization of deamidation sites in the conserved regions of human immunoglobulin gamma antibodies</i> , 77(18) ANALYTICAL CHEM. 6004 (2005)	2088

Exhibit Description	Exhibit #
Tyler-Cross, R., & Schirch, V., <i>Effects of Amino Acid Sequence, Buffers, and Ionic Strength on the Rate and Mechanism of Deamidation of Asparagine Residues in Small Peptides</i> , 266(33) J. BIO. CHEM. 22549 (1991)	2089
Nema, S. et al., <i>Excipients and Their Use in Injectable Products</i> , 51(4) PDA J. PHARM. SCI. & TECH. 166 (1997)	2090
Samuelsen, L. et al., <i>Buffer solutions in drug formulation and processing: how pKa values depend on temperature, pressure and ionic strength</i> , 560 INTERNATIONAL JOURNAL OF PHARMACEUTICS 357 (2019)	2091
Pfefferkorn, C. M. et al., <i>Effects of pH on Aggregation Kinetics of the Repeat Domain of a Functional Amyloid, Pmel17</i> , 107(50) PNAS 21447 (2010)	2092
Hansson, K., & Stenflo, J., <i>Post-Translational Modifications in Proteins Involved in Blood Coagulation</i> , 3(12) J. THROMBOSIS & HAEMOSTASIS 2633 (2005)	2093
Gellissen, G. et al., PRODUCTION OF RECOMBINANT PROTEIN: NOVEL MICROBIAL AND EUKARYOTIC EXPRESSION SYSTEMS, KEY AND CRITERIA TO THE SELECTION OF AN EXPRESSION PLATFORM (2005)	2094
Blodgett, J. K., et al. <i>Specific Cleavage of Peptides Containing an Aspartic Acid (Beta.-Hydroxamic Acid) Residue</i> , 107(14) J. AM. CHEM. SOC'Y 4305 (1985)	2095
Declaration of Rebecca E. Weires re Ex.2055 (Nov. 21, 2023)	2096
Complete copy of Robinson, N. E., & Robinson, A. B., MOLECULAR CLOCKS: DEAMIDATION OF ASPARAGINYL AND GLUTAMINYL RESIDUES IN PEPTIDES AND PROTEINS (2004)	2097
Complete copy of Gellissen, G. et al., PRODUCTION OF RECOMBINANT PROTEIN: NOVEL MICROBIAL AND EUKARYOTIC EXPRESSION SYSTEMS, KEY AND CRITERIA TO THE SELECTION OF AN EXPRESSION PLATFORM (2005)	2098
Declaration of Dr. Alexander M. Klivanov re Ex.2071 (Nov. 21, 2023)	2099

Exhibit Description	Exhibit #
U.S. Food and Drug Administration, <i>Drugs@FDA: FDA-Approved Drugs, Neulasta</i> , https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process (last visited Nov. 16, 2023)	2100
Press Release, Amgen Inc., <i>FDA Approves Amgen’s Neulasta for Serious and Frequent Chemotherapy Side Effect</i> (Jan. 21, 2002), https://www.amgen.com/newsroom/press-releases/2002/02/fda-approves-amgens-neulasta-for-serious-and-frequent-chemotherapy-side-effect	2101
Department of Health & Human Services Letter to Amgen, Incorporated Approving Changes to NEULASTA® Label (rev. 2004)	2102
U.S. Food and Drug Administration, <i>Drugs@FDA: FDA Approved Drugs, Lucentis</i> , https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process (last visited Nov. 17, 2023)	2103
Statutory Disclaimer of Claims 1-18 issued in U.S. Patent No. 10,464,992, as filed on Patent Center on January 18, 2024	2104 [NEW]

IPR2023-00462

Patent Owner, Regeneron Pharmaceuticals, Inc., moves for termination of IPR2023-00462 under 37 CFR § 42.107(e) in view of the statutory disclaimer filed January 17, 2024, submitted herewith as Exhibit 2104. As a result of that disclaimer, no challenged claims remain. This Motion was authorized by the Board pursuant to its email dated January 18, 2024.

Counsel for Patent Owner has conferred with Counsel for Petitioner before filing this Motion. Counsel for Petitioner indicated that Petitioner does not oppose this Motion to Terminate Proceeding, but seeks to have the Board treat it as a request for adverse judgment under 37 CFR 42.73(b).

Dated: January 22, 2024

By: /Adam R. Brausa/
Adam R. Brausa, Reg. No. 60,287
MORRISON & FOERSTER LLP
425 Market Street
San Francisco, California 94105
Tel: (415) 268-6053
Email: ABrausa@mof.com

Counsel for Patent Owner

Certificate of Service (37 C.F.R. § 42.6(e)(4))

I hereby certify that the attached PATENT OWNER'S UNOPPOSED MOTION TO TERMINATE PROCEEDING was served as of the below date by electronic mail, on the Petitioner at the following correspondence address:

Lora M. Green (USPTO Reg. No. 43,541)
Yahn Lin Chu (USPTO Reg. No. 75,946)
Robert Cerwinski (*pro hac vice*, pending)
Aviv Zalcenstein (*pro hac vice*, pending)
Brigid Morris (*pro hac vice*, pending)
David Kim (USPTO Reg. No. 69,503)
GEMINI LAW LLP
40 W 24th Street, Suite 6N
New York, NY 10010
Tel.: 917-915-8832
Email: lgreen@geminilaw.com
Email: fchu@geminilaw.com
Email: rcerwinski@geminilaw.com
Email: azalcenstein@geminilaw.com
Email: bmorris@geminilaw.com
Email: dkim@geminilaw.com

Raymond N. Nimrod (Reg. No. 31,987)
Matthew A. Traupman (Reg. No. 50,832)
Landon Andrew Smith (Reg. No. 79,248)
QUINN EMANUEL URQUHART
& SULLIVAN, LLP
51 Madison Ave., 22nd Floor
New York, NY 10010
Tel.: (212) 849-7000
Email: raynimrod@quinnemanuel.com
Email: matthewtraupman@quinnemanuel.com
Email: landonsmith@quinnemanuel.com
Email: qe-samsungbioepis@quinnemanuel.com

Dated: January 22, 2024

/Adam R. Brausa/
Adam R. Brausa, Reg. No. 60,287