UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,

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 curriculum vitae	2002
AVASTIN® Label (rev. Sept. 2011)	2003
Declaration of David M. Brown, M.D., Mylan Pharms. Inc. v.	2004
Regeneron Pharms., Inc., IPR2021-00881, Ex. 2050 (Feb. 10, 2022)	
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, Therapeutic Monoclonal	2009
Antibodies and Derivatives: Historical Perspectives and Future	
Directions, 34 BIOTECHNOLOGY ADVANCES 1149 (2016)	
Adis R&D Profile, Aflibercept: AVE 0005, AVE 005, AVE0005, VEGF	2010
Trap – Regeneron, VEGF Trap (R1R2), VEGF Trap-Eye, 9 DRUGS	
R&D 261 (2008)	
Quan Dong Nguyen et al., A Phase I Trial of an IV-Administered	2011
Vascular Endothelial Growth Factor Trap for Treatment in Patients	
with Choroidal Neovascularization due to Age-Related Macular	
Degeneration, 113 Ophthamology 1522 (2006).	
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	2014
TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS (rev.	
2, 2003)	
PHARMACEUTICAL FORMULATION DEVELOPMENT OF PEPTIDES AND	2015
PROTEINS (Sven Frokjaer & Lars Hovgaard, eds., 2000)	
Jonas L. Fast et al., Physical Instability of a Therapeutic Fc Fusion	2016
Protein: Domain Contributions to Conformational and Colloidal	
Stability, 48 BIOCHEMISTRY 11724 (2009)	

ANTIBODY FUSION PROTEINS (Steven M. Chamow & Avi Ashkenazi, eds. 1999) Hussein Hollands et al., Short-Term Intraocular Pressure Changes After Intravitreal Injection of Bevacizumab, 42 CAN. J. OPHTHAMOLOGY 807 (2007) Domenico Sanfelice et al., Cold Denaturation Unveiled: Molecular Mechanism of the Asymmetric Unfolding of Yeast Frataxin, 16 CHEMPHYSCHEM 3599 (2015) Sven Frokjaer & Daniel E. Otzen et al., Protein Drug Stability: A Formulation Challenge, 4 NATURE REVIEWS DRUG DISCOVERY 298 (2005) Somatropin, THE UNITED STATES PHARMACOPEIA 1993 (29th rev., official from Jan. 1, 2006) 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) Third-Party Submission Under 37 CFR 1.290, U.S. Patent App. No. 16/582,486 (considered Dec. 31, 2020) U.S. Patent No. 11,066,458 to Furfine et al. Russell F. Doolittle, The Multiplicity of Domains in Proteins, 64 ANN. Rev. Biochemistry 1995 Liliana M. Sampaleanu et al., Three-Dimensional Structure of the Argininosuccinate Lyase Frequently Complementing Allele Q286R, 40 Biochemistry 15,570 (2001) Arvind K. Pandey et al., Mechanisms of VEGF (Vascular Endothelial Growth Factor) Inhibitor—Associated Hypertension and Vascular Disease, 71 Hypertension, Dec. 26, 2017 Abhibav A. Shukla & Uwe Gottschalk, Downstream Processing of Fc-Fusion Proteins, in Therapeutic Fc-Fusion Proteins (S.M.	Exhibit Description	Exhibit
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OPHTHAMOLOGY 807 (2007) Domenico Sanfelice et al., Cold Denaturation Unveiled: Molecular Mechanism of the Asymmetric Unfolding of Yeast Frataxin, 16 CHEMPHYSCHEM 3599 (2015) Sven Frokjaer & Daniel E. Otzen et al., Protein Drug Stability: A Formulation Challenge, 4 NATURE REVIEWS DRUG DISCOVERY 298 (2005) Somatropin, THE UNITED STATES PHARMACOPEIA 1993 (29th rev., official from Jan. 1, 2006) International Patent Publication No. 2006/104852 to Dix et al. U.S. Patent Publication No. 2006/0217311 to Dix et al. 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) Third-Party Submission Under 37 CFR 1.290, U.S. Patent App. No. 16/582,486 (considered Dec. 31, 2020) U.S. Patent No. 11,066,458 to Furfine et al. Russell F. Doolittle, The Multiplicity of Domains in Proteins, 64 Ann. Rev. Biochemistry 1995 Liliana M. Sampaleanu et al., Three-Dimensional Structure of the Argininosuccinate Lyase Frequently Complementing Allele Q286R, 40 BIOCHEMISTRY 15,570 (2001) Arvind K. Pandey et al., Mechanisms of VEGF (Vascular Endothelial Growth Factor) Inhibitor—Associated Hypertension and Vascular Disease, 71 Hypertension, Dec. 26, 2017 Abhibav A. Shukla & Uwe Gottschalk, Downstream Processing of Fc-Fusion Proteins, in Therapeutic Fc-Fusion Proteins (S.M.		2018
Domenico Sanfelice et al., Cold Denaturation Unveiled: Molecular Mechanism of the Asymmetric Unfolding of Yeast Frataxin, 16 CHEMPHYSCHEM 3599 (2015) Sven Frokjaer & Daniel E. Otzen et al., Protein Drug Stability: A Formulation Challenge, 4 NATURE REVIEWS DRUG DISCOVERY 298 (2005) Somatropin, THE UNITED STATES PHARMACOPEIA 1993 (29th rev., official from Jan. 1, 2006) International Patent Publication No. 2006/104852 to Dix et al. U.S. Patent Publication No. 2006/0217311 to Dix et al. 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) Third-Party Submission Under 37 CFR 1.290, U.S. Patent App. No. 16/582,486 (considered Dec. 31, 2020) U.S. Patent No. 11,066,458 to Furfine et al. Russell F. Doolittle, The Multiplicity of Domains in Proteins, 64 Ann. REV. BIOCHEMISTRY 1995 Liliana M. Sampaleanu et al., Three-Dimensional Structure of the Argininosuccinate Lyase Frequently Complementing Allele Q286R, 40 BIOCHEMISTRY 15,570 (2001) Arvind K. Pandey et al., Mechanisms of VEGF (Vascular Endothelial Growth Factor) Inhibitor—Associated Hypertension and Vascular Disease, 71 Hypertension, Dec. 26, 2017 Abhibav A. Shukla & Uwe Gottschalk, Downstream Processing of Fc-Fusion Proteins, in Therapeutic Fc-Fusion Proteins (S.M.		
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Sven Frokjaer & Daniel E. Otzen et al., Protein Drug Stability: A Formulation Challenge, 4 NATURE REVIEWS DRUG DISCOVERY 298 (2005) Somatropin, THE UNITED STATES PHARMACOPEIA 1993 (29th rev., official from Jan. 1, 2006) International Patent Publication No. 2006/104852 to Dix et al. U.S. Patent Publication No. 2006/0217311 to Dix et al. 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) Third-Party Submission Under 37 CFR 1.290, U.S. Patent App. No. 16/582,486 (considered Dec. 31, 2020) U.S. Patent No. 11,066,458 to Furfine et al. Russell F. Doolittle, The Multiplicity of Domains in Proteins, 64 ANN. Rev. Biochemistry 1995 Liliana M. Sampaleanu et al., Three-Dimensional Structure of the Argininosuccinate Lyase Frequently Complementing Allele Q286R, 40 Biochemistry 15,570 (2001) Arvind K. Pandey et al., Mechanisms of VEGF (Vascular Endothelial Growth Factor) Inhibitor—Associated Hypertension and Vascular Disease, 71 Hypertension, Dec. 26, 2017 Abhibav A. Shukla & Uwe Gottschalk, Downstream Processing of Fc-Fusion Proteins, in Therapeutic Fc-Fusion Proteins (S.M.		
Count Challenge A Nature Reviews Drug Discovery 298 (2005) Comatropin, The United States Pharmacopeia 1993 (29th rev., official from Jan. 1, 2006) Count C	` '	
Countropin The United States Pharmacopeia 1993 (29th rev., official from Jan. 1, 2006)	Sven Frokjaer & Daniel E. Otzen et al., <i>Protein Drug Stability: A</i>	2020
Somatropin, The United States Pharmacopeia 1993 (29th rev., official from Jan. 1, 2006) International Patent Publication No. 2006/104852 to Dix et al. U.S. Patent Publication No. 2006/0217311 to Dix et al. 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) Third-Party Submission Under 37 CFR 1.290, U.S. Patent App. No. 16/582,486 (considered Dec. 31, 2020) U.S. Patent No. 11,066,458 to Furfine et al. Russell F. Doolittle, The Multiplicity of Domains in Proteins, 64 Ann. Rev. Biochemistry 1995 Liliana M. Sampaleanu et al., Three-Dimensional Structure of the Argininosuccinate Lyase Frequently Complementing Allele Q286R, 40 Biochemistry 15,570 (2001) Arvind K. Pandey et al., Mechanisms of VEGF (Vascular Endothelial Growth Factor) Inhibitor—Associated Hypertension and Vascular Disease, 71 Hypertension, Dec. 26, 2017 Abhibav A. Shukla & Uwe Gottschalk, Downstream Processing of Fc-Fusion Proteins, in Therapeutic Fc-Fusion Proteins (S.M.	Formulation Challenge, 4 NATURE REVIEWS DRUG DISCOVERY 298	
International Patent Publication No. 2006/104852 to Dix et al. 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) Third-Party Submission Under 37 CFR 1.290, U.S. Patent App. No. 16/582,486 (considered Dec. 31, 2020) U.S. Patent No. 11,066,458 to Furfine et al. Russell F. Doolittle, The Multiplicity of Domains in Proteins, 64 ANN. REV. BIOCHEMISTRY 1995 Liliana M. Sampaleanu et al., Three-Dimensional Structure of the Argininosuccinate Lyase Frequently Complementing Allele Q286R, 40 BIOCHEMISTRY 15,570 (2001) Arvind K. Pandey et al., Mechanisms of VEGF (Vascular Endothelial Growth Factor) Inhibitor—Associated Hypertension and Vascular Disease, 71 Hypertension, Dec. 26, 2017 Abhibav A. Shukla & Uwe Gottschalk, Downstream Processing of Fc-Fusion Proteins, in Therapeutic Fc-Fusion Proteins (S.M.	(2005)	
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Argininosuccinate Lyase Frequently Complementing Allele Q286R, 40 BIOCHEMISTRY 15,570 (2001) Arvind K. Pandey et al., Mechanisms of VEGF (Vascular Endothelial Growth Factor) Inhibitor—Associated Hypertension and Vascular Disease, 71 Hypertension, Dec. 26, 2017 Abhibav A. Shukla & Uwe Gottschalk, Downstream Processing of Fc-Fusion Proteins, in Therapeutic Fc-Fusion Proteins (S.M.	REV. BIOCHEMISTRY 1995	
BIOCHEMISTRY 15,570 (2001) Arvind K. Pandey et al., Mechanisms of VEGF (Vascular Endothelial Growth Factor) Inhibitor—Associated Hypertension and Vascular Disease, 71 Hypertension, Dec. 26, 2017 Abhibav A. Shukla & Uwe Gottschalk, Downstream Processing of Fc- Fusion Proteins, in Therapeutic Fc-Fusion Proteins (S.M.	Liliana M. Sampaleanu et al., Three-Dimensional Structure of the	2028
Arvind K. Pandey et al., Mechanisms of VEGF (Vascular Endothelial Growth Factor) Inhibitor—Associated Hypertension and Vascular Disease, 71 Hypertension, Dec. 26, 2017 Abhibav A. Shukla & Uwe Gottschalk, Downstream Processing of Fc- Fusion Proteins, in Therapeutic Fc-Fusion Proteins (S.M.	Argininosuccinate Lyase Frequently Complementing Allele Q286R, 40	
Growth Factor) Inhibitor—Associated Hypertension and Vascular Disease, 71 Hypertension, Dec. 26, 2017 Abhibav A. Shukla & Uwe Gottschalk, <i>Downstream Processing of Fc-</i> Fusion Proteins, in Therapeutic Fc-Fusion Proteins (S.M.	BIOCHEMISTRY 15,570 (2001)	
Growth Factor) Inhibitor—Associated Hypertension and Vascular Disease, 71 Hypertension, Dec. 26, 2017 Abhibav A. Shukla & Uwe Gottschalk, <i>Downstream Processing of Fc-</i> Fusion Proteins, in Therapeutic Fc-Fusion Proteins (S.M.	Arvind K. Pandey et al., Mechanisms of VEGF (Vascular Endothelial	2029
Abhibav A. Shukla & Uwe Gottschalk, <i>Downstream Processing of Fc- Fusion Proteins</i> , in Therapeutic Fc-Fusion Proteins (S.M.	· · · · · · · · · · · · · · · · · · ·	
Abhibav A. Shukla & Uwe Gottschalk, <i>Downstream Processing of Fc- Fusion Proteins</i> , in Therapeutic Fc-Fusion Proteins (S.M.	, ·	
Fusion Proteins, in Therapeutic Fc-Fusion Proteins (S.M.		2030
·		
- I - I - I - I - I - I - I - I - I - I	Chamow et al., eds. 2014)	

Exhibit Description	Exhibit #
	"
Terri Davis-Smyth et al., The Second Immunoglobulin-Like Domain of	2031
the VEGF Tyrosine Kinase Receptor Flt-1 Determines Ligand Binding	
and May Initiate a Signal Transduction Cascade, 15 EMBO J. 4919	
(1996).	
P17948 VGFR1_Human, available at	2032
https://www.uniprot.org/uniprotkb/P17948/entry	
P17948 VGFR1_Human, Entry Version 140 (txt) (Jan. 11, 2011),	2033
available at	
https://rest.uniprot.org/unisave/P17948?format=txt&versions=140	
Dan Lu et al., Identification of the Residues in the Extracellular	2034
Region of KDR Important for Interaction with Vascular Endothelial	
Growth Factor and Neutralizing Anti-KDR Antibodies. 275 J.	
BIOLOGICAL CHEMISTRY 14321 (2000)	
Matthew C. Franklin et al., The Structural Basis for the Function of	2035
Two Anti-VEGF Receptor 2 Antibodies, 19 Structure 1097 (2011)	
P35968 VGFR2_Human, available at	2036
https://www.uniprot.org/uniprotkb/P35968/entry	
P35968 VGFR2_Human, Entry Version 127 (txt) (Jan. 11, 2011),	2037
available at	
https://rest.uniprot.org/unisave/P35968?format=txt&versions=127	
Clifford R. Robinson & Robert T. Sauer, Optimizing the Stability of	2038
Single-chain Proteins by Linker Length and Composition Mutagenesis,	
95 Proc. Natl. Acad. Sci. USA, 5929 (1998)	
Bei Tong et al., Interdomain Linker Effect on the Mechanical Stability	2039
of Ig Domains in Titin, 23 Int'l J. Molecular Sci. 9836 (2022)	
Xiaoying Chen et al., Fusion Protein Linkers: Property, Design and	2040
Functionality. 65 Advanced Drug Delivery Rev. 1357 (2013)	
Jose I. Casal et al., Subunit Interface of Triosephosphate Isomerase:	2041
Site-Directed Mutagenesis and Characterization of the Altered	
Enzyme, 26 Biochemistry 1258 (1987)	

Exhibit Description	Exhibit #
Tzu-Jing Yang et al., D614G Mutation in the SARS-CoV-2 Spike	2042
Protein Enhances Viral Fitness by Desensitizing It to	2012
Temperature-Dependent Denaturation, 197 J. BIOL.	
CHEM. 101, 238 (2021)	
BIOCHEMISTRY (Jeremy M. Berg et al., eds., 5th ed. 2002)	2043
Declaration of Daralyn J. Durie in Support of this Motion for	2044
Admission Pro Hac Vice ("Durie Decl.")	
Declaration of Kira A. Davis in Support of this Motion for Admission	2045
Pro Hac Vice ("Davis Decl.")	
Default Protective Order	2046
Expert Declaration of Dr. Alexander M. Klibanov (Nov. 2, 2023)	2047
Vila-Perelló, M. & Muir, T. W., Biological Applications of Protein	2048
Splicing, 143(2) CELL 191 (2010).	
Kirikoshi, R. et al., Phosphate-Catalyzed Succinimide Formation	2049
From Asp Residues: A Computational Study of the Mechanism, 19(2)	
Int'l J. Molecular Scis. 637 (2018).	
Trial Transcript (unsealed portions), Regeneron Pharms., Inc. v.	2050
Mylan Pharms. Inc., No. 1:22-cv-00061-TSK-JPM (N.D.W. Va., June	
12–23, 2023).	
U.S. Patent Publication No. 2003/0180287 to Gombotz et al.	2051
Jørgensen, J. T. et al., Pain Assessment of Subcutaneous Injections,	2052
30(7-8) Annals of Pharmacotherapy 729 (1996)	
Wang, W., Protein Aggregation and Its Inhibition in	2053
Biopharmaceutics, 289(1-2) Int'l J. of Pharms. 1 (2005)	
Transcript of Oral Deposition of Dr. Ralph Tarantino (October 13,	2054
2023)	
LUCENTIS® FDA Approval Letter (June 30, 2006)	2055
Vial, Dorland's Illustrated Medical Dictionary (30th ed., 2003)	2056
Vial, TABER'S CYCLOPEDIC MEDICAL DICTIONARY (20th ed. 2001)	2057
Vial, Mosby's Medical, Nursing & Allied Health Dictionary	2058
(6th ed. 2002)	
Vial, Dictionary of Pharmacy (1st ed. 2004)	2059

Exhibit Description	Exhibit #
Arakawa, T., et al., Factors Affecting Short-Term and Long-Term	2060
Stabilities of Proteins, 46(1-3) ADVANCED DRUG DELIVERY REVS. 307	2000
(2001)	
Tang, X., & Pikal, M. J., Design of Freeze-Drying Processes For	2061
Pharmaceuticals: Practical Advice, 21(2) PHARM. RSCH. 191 (2004).	2001
Cao, E. et al., Effect of Freezing and Thawing Rates on Denaturation	2062
of Proteins in Aqueous Solutions, 82(6) BIOTECH. & BIOENGINEERING	2002
684 (2003).	
Brange, J., et al., <i>Toward Understanding Insulin Fibrillation</i> , 86(5) J.	2063
PHARM. SCIS. 517 (1997)	
Robinson, N. E., & Robinson, A. B., MOLECULAR CLOCKS:	2064
DEAMIDATION OF ASPARAGINYL AND GLUTAMINYL RESIDUES IN	
PEPTIDES AND PROTEINS (2004)	
Robinson, N. E., et al., Structure-Dependent Nonenzymatic	2065
Deamidation of Glutaminyl and Asparaginyl Pentapeptides, 63(5) J.	
PEPTIDE RSCH. 426 (2004)	
Solá, R. J. & Griebenow, K., Effects of Glycosylation on the Stability	2066
of Protein Pharmaceuticals, 98(4) J. Pharm. Scis. 1223 (2009)	
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., Six-Month Stability of Bevacizumab (Avastin)	2072
Binding to Vascular Endothelial Growth Factor After Withdrawal into	
a Syringe and Refrigeration or Freezing, 26(5) RETINA 519 (2006)	
U.S. Food and Drug Administration, Guideline for Industry: Quality of	2073
Biotechnological Products: Stability Testing of	
Biotechnological/Biological Products, 61 Fed. Reg. 36466 (1996),	
https://www.fda.gov/media/71441/download	
Bayer, Assessment of Long Term Treatment with Testosterone	2074
Undecanoate in Males with Hypogonadism, NCT00220298 (rev. Dec.	

Exhibit Description	Exhibit
30, 2014),	#
https://clinicaltrials.gov/study/NCT00220298?a=11&tab=table	
Stanford University, <i>High-dose Sequential Therapy and Single</i>	2075
Autologous Transplantation for Multiple Myeloma, NCT00349778	2073
(rev. Dec. 12, 2017),	
https://clinicaltrials.gov/study/NCT00349778?tab=table	
Lidocaine Hydrochloride and Dextrose (injection, solution) Label,	2076
	2070
Hospira, Inc (rev. June 2006) Eantanyl Citrata (injection, solution) Label Boyton Hoolthoons	2077
Fentanyl Citrate (injection, solution) Label, Baxter Healthcare	2077
Corporation (rev. Sept. 2006)	2079
ATGAM® Label (rev. Apr. 2010)	2078
ATGAM® Label (rev. Sept. 2023)	2079
McIlvaine, T. C., A Buffer Solution for Colorimetric Comparison,	2080
49(2) J. Bio. Chemistry 183 (1921)	
Zacchigna, M., et al., Improvement of warfarin biopharmaceutics by	2081
conjugation with poly (ethylene glycol), 23(4) Eur. J. Pharm. Scis.	
379 (2004)	
Yamaguchi, S., et al., Approval Success Rates of Drug Candidates	2082
Based on Target, Action, Modality, Application, and Their	
Combinations, 14(3) CLINICAL & TRANSLATIONAL SCI. 1113 (2021)	
Svendsen, O., et al., Intramuscular Injection of Hypertonic Saline: In	2083
Vitro and In Vivo Muscle Tissue Toxicity and Spinal Neurone C-Fos	
Expression, 97(1) Basic & Clin. Pharmacology & Toxicology 52	
(2005)	
Dupont, J. et al., Phase I and Pharmacokinetic Study of VEGF Trap	2084
Administered Subcutaneously (sc) to Patients (pts) with Advanced	
Solid Malignancies, 22(14) J. CLIN. ONCOLOGY 3009 (2004)	
Shannon, E. et al., Etanercept (Enbrel®) Alternative Storage at	2085
Ambient Temperature, 9 CLIN. PHARMACOLOGY: ADVANCES &	
APPLICATIONS 87 (2017)	

Exhibit Description	Exhibit
	2006
Rougeot, C. et al., Comparative Study of Biosynthetic Human Growth	2086
Hormone Immunogenicity in Growth Hormone Deficient Children,	
35(2) HORMONE RSCH. IN PAEDIATRICS 76 (1991)	• • • •
Mohan, C., Buffers: A guide for the preparation and use of buffers in biological systems (2003)	2087
Chelius, D. et al., Identification and characterization of deamidation	2088
sites in the conserved regions of human immunoglobulin gamma	
antibodies, 77(18) Analytical Chem. 6004 (2005)	
Tyler-Cross, R., & Schirch, V., Effects of Amino Acid Sequence,	2089
Buffers, and Ionic Strength on the Rate and Mechanism of	
Deamidation of Asparagine Residues in Small Peptides, 266(33) J.	
Вю. Снем. 22549 (1991)	
Nema, S. et al., Excipients and Their Use in Injectable Products, 51(4)	2090
PDA J. PHARM. Sci. & Tech. 166 (1997)	
Samuelsen, L. et al., Buffer solutions in drug formulation and	2091
processing: how pKa values depend on temperature, pressure and	
ionic strength, 560 International Journal of Pharmaceutics 357	
(2019)	
Pfefferkorn, C. M. et al., Effects of pH on Aggregation Kinetics of the	2092
Repeat Domain of a Functional Amyloid, Pmel17, 107(50) PNAS	
21447 (2010)	
Hansson, K., & Stenflo, J., Post-Translational Modifications in	2093
Proteins Involved in Blood Coagulation, 3(12) J. THROMBOSIS &	
HAEMOSTASIS 2633 (2005)	
Gellissen, G. et al., PRODUCTION OF RECOMBINANT PROTEIN: NOVEL	2094
MICROBIAL AND EUKARYOTIC EXPRESSION SYSTEMS, KEY AND	
CRITERIA TO THE SELECTION OF AN EXPRESSION PLATFORM (2005)	
Blodgett, J. K., et al. Specific Cleavage of Peptides Containing an	2095
Aspartic Acid (BetaHydroxamic Acid) Residue, 107(14) J. Am.	
Снем. Soc'y 4305 (1985)	
Declaration of Rebecca E. Weires re Ex.2055 (Nov. 21, 2023)	2096

Exhibit Description	Exhibit
Complete convert Delivery N. E. & Delivery A. D. Mourguitt	2007
Complete copy of Robinson, N. E., & Robinson, A. B., MOLECULAR	2097
CLOCKS: DEAMIDATION OF ASPARAGINYL AND GLUTAMINYL RESIDUES	
IN PEPTIDES AND PROTEINS (2004)	2000
Complete copy of Gellissen, G. et al., PRODUCTION OF RECOMBINANT	2098
PROTEIN: NOVEL MICROBIAL AND EUKARYOTIC EXPRESSION SYSTEMS,	
KEY AND CRITERIA TO THE SELECTION OF AN EXPRESSION PLATFORM	
(2005)	
Declaration of Dr. Alexander M. Klibanov re Ex.2071 (Nov. 21, 2023)	2099
U.S. Food and Drug Administration, Drugs@FDA: FDA-Approved	2100
Drugs, Neulasta,	
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=Basi	
cSearch.process (last visited Nov. 16, 2023)	
Press Release, Amgen Inc., FDA Approves Amgen's Neulasta for	2101
Serious and Frequent Chemotherapy Side Effect (Jan. 21, 2002),	
https://www.amgen.com/newsroom/press-releases/2002/02/fda-	
approves-amgens-neulasta-for-serious-and-frequent-chemotherapy-	
side-effect	
Department of Health & Human Services Letter to Amgen,	2102
Incorporated Approving Changes to NEULASTA® Label (rev. 2004)	
U.S. Food and Drug Administration, Drugs@FDA: FDA Approved	2103
Drugs, Lucentis,	
https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=Basi	
cSearch.process (last visited Nov. 17, 2023)	
Statutory Disclaimer of Claims 1-18 issued in U.S. Patent No.	2104
10,464,992, as filed on Patent Center on January 18, 2024	[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/

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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)

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