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and Amgen Manufacturing Limited

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

AMGEN INC. and AMGEN MANUFACTURING LIMITED, Plaintiffs, v. ADELLO BIOLOGICS, LLC, Defendant.	Civil Action No. 2:18-cv-03347 (CCC-MF) *Electronically Filed*

PLAINTIFFS AMGEN INC.'S AND AMGEN MANUFACTURING LIMITED'S ANSWER TO DEFENDANT ADELLO BIOLOGICS, LLC'S COUNTERCLAIMS

Plaintiffs Amgen Inc. and Amgen Manufacturing Limited (together, "Amgen") hereby answer the Counterclaims of Defendant Adello Biologics, LLC's ("Adello"), for which every allegation not expressly admitted is denied, as follows:

PARTIES

1. Upon information and belief, Amgen admits the allegations of Paragraph 1.

2. Amgen admits that Amgen Inc. is a corporation existing under the laws of the State of Delaware. Amgen admits that Amgen Manufacturing Limited ("AML") is a corporation

existing under the laws of the Territory of Bermuda. Any remaining allegations of this paragraph are denied.

JURISDICTION AND VENUE

3. Amgen admits that Adello's Counterclaims purport to arise under the patent laws of the United States, as enacted under Title 35 of the United States Code and the provisions of the Declaratory Judgment Act, 28 U.S.C. §§ 2201-2202. Amgen admits that the Court has subject matter jurisdiction over such counterclaims pursuant to 28 U.S.C. §§ 1331-1338.

4. For the purposes of this action, Amgen admits that this Court has personal jurisdiction over Amgen. The remaining allegations of this paragraph are denied.

5. Amgen admits that its Complaint asserts that Adello committed an act of infringement with respect to U.S. Patent Nos. 6,180,391, 7,083,948, 7,118,884, 7,384,765, 7,427,659, 7,662,930, 7,735,525, 7,781,395, 8,191,566, 8,273,707, 8,940,878, 8,952,138, 9,418,416, 9,632,095, 9,643,997, 9,704,239, and 9,856,287 under 35 U.S.C. § 271(e)(2)(C)(ii) and that Adello will infringe one or more claims of each of the Patents-in-Suit under 35 U.S.C. §§ 271(a) and 271(g). Amgen admits that an actual and justiciable controversy has arisen and now exists between Adello and Amgen as to whether Adello infringes any claim of the Patents-in-Suit, but denies that an actual and justiciable controversy exists as to whether the claims of the Patents-in-Suit are valid.

6. For the purposes of this action, Amgen admits that venue is proper in this district. The remaining allegations of this paragraph are denied.

BACKGROUND

7. Amgen admits that the BPCIA created an abbreviated pathway for the approval of biosimilar versions of approved biologic drugs. 42 U.S.C. § 262(k). Amgen admits that Pub. L. No. 111–148, § 7001(b), the Biologics Price Competition and Innovation Act of 2009, states, "It

is the sense of the Senate that a biosimilars pathway balancing innovation and consumer interests should be established." Any remaining allegations of this paragraph are denied.

8. Upon information and belief, Amgen admits that Adello develops, manufactures, and seeks regulatory approval for importing, marketing, distributing, and selling biopharmaceutical products (including products intended to be sold as biosimilar versions of successful biopharmaceutical products developed by others) in the state of New Jersey and throughout the United States. Upon information and belief, Amgen admits that Adello has its principal place of business in New Jersey, with its headquarters and research and development laboratory located at 20 New England Avenue, Piscataway, New Jersey. Any remaining allegations of this paragraph are denied.

9. Amgen admits that it has been approved by FDA to market NEUPOGEN®, and that the active ingredient in NEUPOGEN® is filgrastim, a recombinantly expressed protein known as G-CSF. Amgen admits that NEUPOGEN® counteracts neutropenia, which is a deficiency in neutrophils. Amgen admits that NEUPOGEN® was first approved for therapeutic use to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anticancer drugs associated with a significant incidence of severe neutropenia with fever, and that FDA later approved several additional indications, including the treatment of patients with severe chronic neutropenia, patients with acute myeloid leukemia receiving induction or consolidation chemotherapy, patients receiving bone marrow transplant, and patients undergoing peripheral blood progenitor cell collection and therapy. Upon information and belief, Amgen admits that Adello submitted aBLA No. 761082 seeking FDA approval for a biosimilar version of Plaintiffs' NEUPOGEN® under the abbreviated licensing pathway of 42 U.S.C. § 262(k), which allows Adello to reference

and rely on the approval and licensure of Plaintiffs' NEUPOGEN® product in support of Adello's request for FDA approval.

10. Amgen admits that NEUPOGEN® first received FDA approval in 1991. The remaining allegations of this paragraph are denied.

11. Amgen admits that its NEUPOGEN® product has been on the market in the United States for more than 12 years. The remaining allegations of this paragraph are denied.

12. Amgen admits that U.S. Patent Nos. 5,582,823 and 5,580,755, which are assigned on its face to Amgen Inc., issued on December 1996 and expired in December 2013. The remaining allegations of this paragraph are denied.

13. Amgen admits that Amgen Inc.'s annual report for the fiscal year ended December 31, 2017 reported total sales of NEUPOGEN® in the United States for the year ended December 31, 2017 to be $369 million. Any remaining allegations of this paragraph are denied.

14. Upon information and belief, Amgen admits that Teva Pharmaceutical Industries Ltd. ("Teva") announced in August 2012 that FDA granted approval for tbo-filgrastim, which Teva states is a short-acting recombinant form of G-CSF, indicated to reduce the duration of severe neutropenia in patients with certain types of cancer (non-myeloid malignancies) who are receiving chemotherapy that affects the bone marrow. Amgen admits that in 2011, Amgen, Teva Pharmaceuticals USA Inc., and Teva Pharmaceutical Industries Ltd. settled litigation involving U.S. Patent Nos. 5,582,823 and 5,580,755 after the patents were held enforceable and valid. Upon information and belief, Amgen admits that Teva launched GRANIX™ (short-acting G-CSF) in the United States in November 2013.

15. Amgen admits that Amgen filed a Complaint in October 2014 against Sandoz alleging patent infringement in connection with Sandoz's aBLA seeking FDA approval to market

a biosimilar of NEUPOGEN® and that the Northern District of California granted Sandoz's motion for summary judgment of non-infringement with respect to U.S. Patent No. 8,940,878 in December 2017. The remaining allegations of this paragraph are denied.

16. Upon information and belief, Amgen admits that it received a letter from in-house counsel for Apotex Inc. in December 2014, notifying Amgen that the Apotex aBLA had been accepted for review by FDA. Amgen admits that it filed a complaint against Apotex in the United States District Court for the Southern District of Florida, alleging infringement of U.S. Patent No. 8,952,138 in August 2015 after Apotex and Amgen engaged in the statutory information exchange under 42 U.S.C. § 262(*l*). Amgen admits that Dr. Roger Hart is an inventor of the '138 patent. Amgen admits that at trial in the United States District Court for the Southern District of Florida, Dr. Hart testified as follows:

> Q. Now, did Amgen use the method of your patent in its manufacture of Neupogen?
> A. No, it did not.
> Q. Did it use the method of your patent in its manufacture of Neulasta?
> A. No, it did not.
> Q. Why not?
> A. The processes to produce human-grade Neupogen and Neulasta, or Neupogen in particular, existed, was licensed, was validated, and was providing patients with commercial-grade material at the time of this invention. And the cost and challenges associated with making process changes is always a decision of cost versus benefit. And the process, as practiced by Amgen, in a very well-controlled and reliable and licensed fashion, it was deemed that the process was well controlled and that there was no need to alter the refolding process.

Amgen admits that on September 6, 2016, the District Court for the Southern District of Florida entered a final judgment of non-infringement of the asserted claims of U.S. Patent No. 8,952,138. Amgen admits that on November 13, 2017, the Federal Circuit affirmed that

judgment. Upon information and belief, Amgen admits that Apotex's aBLA has not yet been approved.

17. Upon information and belief, Amgen admits the allegations of this paragraph.

18. Amgen admits that Adello sent a letter to Amgen dated September 11, 2017 stating that on September 8, 2017, FDA accepted for review Adello's aBLA for a proposed biosimilar to NEUPOGEN®, and that the letter purports to provide Amgen with Adello's notice of commercial marketing pursuant to 42 U.S.C. § 262(*l*)(8)(A). Any remaining allegations of this paragraph are denied.

19. Amgen admits that on March 8, 2018, Amgen filed a Complaint against Adello alleging infringement of the Patents-in-Suit. The Patents-in-Suit speak for themselves. The content of the FDA label for NEUPOGEN® speaks for itself. At this stage of the proceeding, Amgen can neither admit nor deny the remaining allegations of this paragraph, but Amgen admits that it does not practice at least some of the Patents-in-Suit in its manufacture of NEUPOGEN®.

THE PATENTS-IN-SUIT

U.S. Patent No. 6,180,391 ("the '138 Patent")

20. Admitted.

21. Amgen admits that U.S. Patent No. 6,180,391 ("the '391 Patent") issued on January 30, 2001 and expires on January 26, 2019.

22. Admitted.

23. Amgen admits that Claims 1-8 and 14-17 of the '391 Patent state:

What is claimed is:

1. A translational repression vector system for use in cloning or expressing a specific heterologous gene in bacteria, said system comprising a DNA sequence encoding a translational repressor operably linked to a constitutive promoter, and said heterologous gene operably linked to an inducible promoter and a translational repressor recognition sequence; wherein pre-induction leakage of said inducible promoter is abolished without the loss of inducibility.

2. The system of claim **1**, wherein said translational repressor is bacteriophage MS2 coat protein (MS2CP).

3. An process for cloning or expressing a heterologous gene in bacteria, said process comprising:

culturing host cells transformed with a plasmid vector, said vector comprising a DNA sequence encoding an inducible promoter, a DNA sequence encoding said heterologous gene linked to a translational repressor recognition site and to said inducible promoter, and a DNA sequence encoding a translational repressor operably linked to a constitutive promoter; wherein said translational repressor controls expression of said heterologous gene.

4. An process for cloning or expressing a heterologous gene in bacteria, said process comprising:

culturing host cells which have been co-transformed with a first plasmid vector comprising a DNA sequence encoding an inducible promoter and said heterologous gene linked to a translational repressor recognition site and to said inducible promoter, and a second plasmid vector comprising a DNA sequence encoding a translational repressor operably linked to a constitutive promoter; wherein said translational repressor controls expression of said heterologous gene.

5. An process for cloning or expressing a heterologous gene in bacteria, said process comprising:

culturing host cells harboring a DNA sequence encoding a translational repressor operably linked to a constitutive promoter, transformed with a plasmid vector, said vector comprising a DNA sequence encoding an inducible promoter, and a DNA sequence encoding said heterologous gene linked to a translational repressor recognition site and to said inducible promoter; wherein said translational repressor controls expression of said heterologous gene.

6. An process for cloning or expressing a heterologous gene in bacteria, said process comprising:

culturing host cells harboring a DNA sequence encoding an inducible promoter, a DNA sequence encoding said heterologous gene linked to a translational repressor recognition site and to said inducible promoter, and a DNA sequence encoding a translational repressor operably linked to a constitutive promoter; wherein said translational repressor controls expression of said heterologous gene.

7. A process as in one of claims **3–6**, wherein said translational repressor is bacteriophage MS2 coat protein.

8. A process as in one of claims **3–5**, wherein said vector further comprises SEQ ID NO:2.

14. An process for cloning or expressing a heterologous gene in bacteria, said process comprising:

culturing host cells which have been co-transformed with a first plasmid vector comprising a DNA sequence encoding said heterologous gene under the control of a T4 middle promoter, and a second plasmid vector comprising a DNA sequence encoding an inducible promoter, motA and asiA gene sequences each linked to a translational repressor recognition site and to said inducible promoter, and a translational repressor operably linked to a constitutive promoter; wherein said

translational repressor controls expression of said motA and asiA genes, and wherein said motA and asiA genes direct transcription from the T4 middle promoter while inhibiting transcription from said inducible promoter.

15. A process of claim **14**, wherein said second plasmid vector further comprises a DNA sequence encoding an accessory protein.

16. An process for cloning or expressing a heterologous gene, said process comprising:

culturing host cells harboring a DNA sequence encoding an inducible promoter, motA and asiA gene sequences each linked to a translational repressor recognition site and to said inducible promoter, and a translational repressor operably linked to a constitutive promoter, transformed with a plasmid vector comprising a DNA sequence encoding said heterologous gene linked under the control of a T4 middle promoter; wherein said translational repressor controls expression of said motA and asiA genes, and wherein said motA and asiA genes direct transcription from the T4 middle promoter while inhibiting transcription from said inducible promoter.

17. A process as in one of claims **14–16**, wherein said translational repressor is bacteriophage MS2 coat protein.

* * * * *

Any remaining allegations of this paragraph are denied.

24. Amgen admits that the ’391 Patent specification at 11:22-25 states: “For purposes of the present invention, a "translational repressor" is defined as protein capable of specifically binding a recognition site on a piece of RNA and inhibiting translation.” Any remaining allegations of this paragraph are denied.

25. Amgen admits that Claims 9-12 state:

> **9**. An MS2 controlled T7 gene 1 cassette, said cassette comprising a DNA sequence encoding an inducible promoter and the MS2 recognition site each linked to T7 gene 1, and the MS2 coat protein gene under the control of a weak constitutive promoter.
>
> **10**. A bacterial host cell capable of expressing a heterologous gene and harboring an MS2 controlled T7 gene 1 cassette.
>
> **11**. An process for expressing a heterologous gene in bacteria, said process comprising:
>
> culturing host cells harboring an MS2 controlled T7 gene 1 cassette and transformed with a plasmid vector containing a DNA sequence encoding said heterologous gene under the control of a T7 promoter.
>
> **12**. A process of claim **11**, wherein said heterologous gene is a T7 early gene.

Any remaining allegations of this paragraph are denied.

26. Amgen admits that Claim 13 states:

> **13**. A staged inducible promoter system for cloning or expressing a heterologous gene in bacteria, said system comprising DNA encoding motA and asiA gene sequences that direct transcription from specific promoters, while inhibiting general transcription from bacterial host promoters.

Any remaining allegations of this paragraph are denied.

27. Amgen admits that Claims 18-20 state:

> **18**. An MS2-based T4 cassette, said cassette comprising a DNA sequence encoding an inducible promoter, motA and asiA gene sequences each linked to an MS2 recognition sequence and to said inducible promoter, and the MS2 coat protein gene under the control of a constitutive promoter.
>
> **19**. A prokaryotic host cell capable of expressing a heterologous gene and harboring an MS2-based T4 cassette.
>
> **20**. An improved process for cloning or expressing a heterologous gene, said process comprising:
>
> culturing host cells harboring an MS2-based T4 cassette and transformed with an expression vector containing a DNA sequence encoding said heterologous gene under the control of a T4 promoter.

Any remaining allegations of this paragraph are denied.

28. Amgen admits that Claim 21 states: "A DNA comprising the sequence of SEQ ID NO: 1." Any remaining allegations of this paragraph are denied.

29. Amgen admits that Claim 22 states: "A DNA comprising the sequence of SEQ ID NO: 2." Any remaining allegations of this paragraph are denied.

U.S. Patent No. 7,083,948 ("the '948 Patent")

30. Admitted.

31. Admitted.

32. Admitted.

33. Amgen admits that the claims of the '948 Patent state:

What is claimed is:

1. A method for purifying a protein of interest comprising:

(a) combining an isolated recombinant, non-antibody polypeptide purification reagent with the protein of interest, wherein all or part of the polypeptide purification reagent is the product of an in vitro selection for binding to the protein of interest;

(b) adjusting conditions such that the polypeptide purification reagent can bind to the protein of interest and such that the polypeptide purification reagent, when bound to the protein of interest forms a precipitate; and

(c) recovering the polypeptide purification reagent bound to the protein of interest as a precipitate,

wherein the performance of steps (a)–(c) purifies the protein of interest.

2. The method of claim **1**, further comprising the following steps:

(d) re-suspending the precipitate under conditions such that the protein of interest does not bind to the polypeptide purification reagent and the polypeptide purification reagent does not form a precipitate; and

(e) separating the protein of interest from the polypeptide purification reagent by affinity chromatography using an affinity reagent that specifically binds to the polypeptide purification reagent.

3. The method of claim **1**, further comprising the following steps:

(d) resuspending the precipitate under conditions such that the protein of interest does not bind to the polypeptide purification reagent and the polypeptide purification reagent does not form a precipitate;

(e) adjusting the conditions such that the polypeptide purification reagent forms a precipitate and the protein of interest does not bind to the polypeptide purification reagent; and

(f) separating the precipitate from the solution.

4. The method of claim **1**, wherein the protein of interest comprises an F_C portion of an antibody.

5. The method of claim **1**, wherein the polypeptide purification reagent comprises at least two binding domains.

6. The method of claim **1**, wherein the polypeptide purification reagent comprises part or all of a C-type lectin.

7. The method of claim **1**, wherein the precipitate is a crystal.

8. The method of claim **1**, wherein the precipitate is not a crystal.

9. The method of claim **8**, wherein one molecule of the polypeptide purification reagent can bind to another molecule of the polypeptide purification reagent.

10. The method of claim **8**, wherein the polypeptide purification reagent comprises at least two binding domains.

11. The method of claim **10**, wherein at least two of the binding domains each bind to different epitopes on the protein of interest.

12. A method for purifying a protein of interest comprising:

(a) combining a recombinant, non-antibody polypeptide purification reagent with the protein of interest under conditions such that a precipitate lacking a regular, crystalline structure comprising the polypeptide purification reagent and the protein of interest is formed; and

(b) recovering the polypeptide purification reagent bound to the protein of interest as a precipitate

wherein the performance of steps (a) and (b) purifies the protein of interest.

13. The method of claim **12**, further comprising:

(c) resuspending the precipitate under conditions such that the polypeptide purification reagent does not bind to the protein of interest;

(d) separating the polypeptide purification reagent from the protein of interest; and

(e) recovering both the polypeptide purification reagent and the protein of interest.

14. The method of claim **12**, wherein the protein of interest comprises an F_C portion of an antibody.

15. The method of claim **14**, wherein the polypeptide purification reagent comprises at least two binding domains that can bind to an F_C portion of an antibody.

16. The method of claim **15**, wherein at least two of the binding domains comprise all or part of Protein A.

17. A method of purifying a protein of interest comprising:

(a) combining a recombinant, non-antibody polypeptide purification reagent with the protein of interest, wherein the polypeptide purification reagent comprises a binding domain and a distinct scaffold domain, wherein the scaffold domain comprises an amino acid sequence conferring a propensity to form a precipitate;

(b) adjusting conditions such that the polypeptide purification reagent can bind to the protein of interest and such that the polypeptide purification reagent, when bound to the protein of interest, can form a precipitate; and

(c) recovering the polypeptide purification reagent bound to the protein of interest as a precipitate

wherein the performance of steps (a)–(c) purifies the protein of interest.

18. The method of claim **17**, wherein the protein of interest comprises all or part of antibody or a substantially similar protein.

19. The method of claim **17**, wherein a binding domain in the polypeptide purification reagent has been selected in vitro to bind to the protein of interest.

20. The method of claim **17**, wherein the polypeptide purification reagent comprises at least 2 binding domains.

21. The method of claim **20**, wherein at least 2 binding domains comprise all or part of Protein A.

22. The method of claim **17**, wherein plural molecules of the polypeptide purification reagent can bind to the scaffold domains of other molecules of the polypeptide purification reagent, thereby forming a precipitable polymer.

23. The method of claim **17**, further comprising:

resuspending the precipitate under conditions such that the polypeptide purification reagent does not bind to the protein of interest and does not form a precipitate;

adjusting the conditions such that the polypeptide purification reagent does not bind to the protein of interest and does form a precipitate; and

separating the precipitate from the solution.

24. The method of claim **12**, wherein the recombinant, non-antibody polypeptide purification reagent comprises at least one scaffold domain comprising all or part of a C type lectin and at least one binding domain.

* * * * *

Any remaining allegations of this paragraph are denied.

34. Amgen admits that the ’948 Patent specification at 8:40-42 states: “Non-antibody polypeptide: A non-antibody polypeptide is one that does not comprise an immunoglobulin or immunoglobulin-like domain.” Any remaining allegations of this paragraph are denied.

35. Amgen admits that the ’948 Patent at 8:52-56 states: “A polypeptide purification reagent is a molecule, which comprises protein, that can reversibly and specifically bind to a protein of interest and can be used to purify the protein of interest by the methods of the invention.” Any remaining allegations of this paragraph are denied.

36. Amgen admits that the ’948 Patent specification at 8:66-67 states: “Precipitate: A precipitate is a solid that separates out from a solution or suspension.” Any remaining allegations of this paragraph are denied.

U.S. Patent No. 7,118,884 ("the '884 Patent")

37. Admitted.

38. Admitted.

39. Admitted.

40. Amgen admits that the claims of the '884 Patent state:

US 7,118,884 B1

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What is claimed is:

1. A method for reducing precipitation in a bacterial fermentation process for producing a recombinant protein comprising inclusion of phosphate glasses as a phosphorus source in the nutrient media during production of said protein; wherein said process is a high cell density fermentation process.

2. The method of claim 1 wherein said phosphate glasses are selected from the group consisting of sodium phosphate glasses having chain lengths ranging from about $\tilde{n}$=2 to about $\tilde{n}$=100, wherein the chain length is defined as PO_4—$(PO_3)_{\tilde{n}}$—PO_4.

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3. The method of claim 2 wherein said sodium phosphate glass has a chain length of about $\tilde{n}$=4 to about $\tilde{n}$=20.

4. The method of claim 3 wherein said sodium phosphate glass has a chain length of $\tilde{n}$=11.

5. The method of claim 1 wherein said high cell density fermentation is selected from the group consisting of a batch fermentation, a continuous fermentation, and a fed-batch fermentation.

6. A method for increasing cell density in a bacterial fermentation process for producing a recombinant protein comprising inclusion of phosphate glasses as the phosphorus source in the nutrient media during production of said protein; wherein said process is a high cell density fermentation process.

7. The method of claim 6 wherein said phosphate glasses are selected from the group consisting of sodium phosphate glasses having chain lengths ranging from about $\tilde{n}$=2 to about $\tilde{n}$=100, wherein the chain length is defined as PO_4—$(PO_3)_{\tilde{n}}$—PO_4.

8. The method of claim 7 wherein said sodium phosphate glass has a chain length of about $\tilde{n}$=4 to about $\tilde{n}$=20.

9. The method of claim 8 wherein said sodium phosphate glass has a chain length of $\tilde{n}$=11.

10. The method of claim 6 wherein said high cell density fermentation is selected from the group consisting of a batch fermentation, a continuous fermentation, and a fed-batch fermentation.

11. A method for reducing precipitation in a high cell density fermentation process for producing a recombinant protein in *E. coli*, comprising inclusion of a phosphate glass having a chain length of about $\tilde{n}$=4 to about $\tilde{n}$=20, wherein the chain length is defined as PO_4—$(PO_3)_{\tilde{n}}$—PO_4, as a phosphorus source in the nutrient media during production of said protein.

12. The method of claim 11 wherein said phosphate glass has a chain length of about $\tilde{n}$=11.

* * * * *

Any remaining allegations of this paragraph are denied.

41. Amgen admits that the '884 Patent specification at 5:33-48 states:

Contemplated for use in the practice of this invention as a phosphate source in the medias are a wide range of phosphate glasses. Phosphate glasses are linear polyphosphates having relatively specialized applications. For a general discussion of linear polyphosphates, including phosphate glasses, see Corbridge, D.E.C., *Phosphorus: An Outline of its Chemistry, Biochemistry and Technology*, Fourth Edition, Chapter 3, pages 210—302 (1990). Phosphate glasses can be prepared over a wide range of composition and consist mainly of a mixture of cations and discrete polyphosphate chains. The glasses formed with Na+ cations have been examined most thoroughly, and exist in a continuous series, stable at normal temperatures, from the composition P_2O_5 up to $5Na_2O.100P_2O_5$. Phosphate glasses are formed by condensation of orthophosphate anions, i.e. heating NaH_2PO_4 to -650° C. and quenching.

Any remaining allegations of this paragraph are denied.

U.S. Patent No. 7,384,765 ("the '765 Patent")

42. Admitted.

43. Admitted.

44. Admitted.

45. Amgen admits that the claims of the '765 Patent state:

US 7,384,765 B1

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What is claimed is:

1. A method comprising culturing a recombinantly engineered cell line in culture medium in normal osmotic conditions, wherein the cell line is recombinantly engineered to express a polypeptide of interest, the medium has an effective amount of betaine, whereby cell survival and expression of said polypeptide of interest are improved relative to cells grown without betaine, wherein the cells are grown during a proliferative phase in the absence of betaine, and in the presence of betaine in an induction phase.

2. The method of claim **1** wherein the cell line is a non-animal cell line.

3. The method of claim **1** wherein the cell line is a prokaryotic cell line.

4. The method of claim **3** wherein the prokaryotic cell line is an *E. coli* cell line.

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5. The method of claim **2** wherein the cell line is an insect cell line.

6. The method of claim **5** wherein the insect cell line is an Sf9 cell line.

7. The method of claim **2** wherein the cell line is a plant cell line.

8. The method of claim **2** wherein the cell line is a yeast cell line.

9. The method of claim **1**, wherein the betaine is selected from the group consisting of glycine betaine and betaine aldehyde.

10. The method of claim **9**, wherein the betaine is at a concentration of about 20 mM.

11. The method of claim **10**, wherein the polypeptide of interest is selected from the group consisting of a soluble TNF receptor, a soluble IL-4 receptor, a soluble IL-1 type II receptor, a soluble flt3 ligand, a soluble CD40 ligand, an erythropoietin, an antibody, an Fc-fusion protein, a calcitonin, a growth hormone, an insulin, an insulinotropin, insulin-like growth factors, a parathyroid hormone, an interferons, a nerve growth factor, a glucagons, an interleukins, a colony stimulating factor, a glucocerebrosidase, a superoxide dismutase, a tissue plasminogen activator, a Factor VIII, a Factor IX, an apolipoprotein E, an Apolipoprotein A-I, a globin, an IL-2 receptor, an IL-2 antagonist, alpha-1 antitrypsin, and an alpha-galactosidase A.

12. The method of claim **11**, wherein the cell line is cultured in a bioreactor.

13. The method of claim **11**, further comprising collecting the protein of interest.

14. The method of claim **11**, wherein the cell line is grown in suspension culture.

* * * * *

Any remaining allegations of this paragraph are denied.

U.S. Patent No. 7,427,659 ("the '659 Patent")

46. Admitted.

47. Admitted.

48. Admitted.

49. Amgen admits that the claims of the '659 Patent state:

EX PARTE REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claims **1**, **3**, **5**, **7**, **9** and **11** are determined to be patentable as amended.

Claims **2**, **4**, **6**, **8**, **10** and **12**, dependent on an amended claim, are determined to be patentable.

New claims **13-21** are added and determined to be patentable.

1. A method for separating a *recombinant* target protein from a mixture containing the *recombinant* target protein and non-target *cell culture* protein contaminants *produced by cell culture expression of the recombinant protein*, comprising:

a) contacting the mixture *containing a recombinant target protein and a non-target cell culture protein contaminant produced by cell culture expression of the recombinant protein* with a hydrophobic adsorbent comprising branched alkyl functional groups having from 4 to about 8 carbon atoms, at least one of which is a tertiary carbon atom, in an aqueous salt solution under loading conditions that permit the non-target *cell culture* protein contaminants to bind to the adsorbent and the *recombinant* target protein to pass through the hydrophobic adsorbent in a flow-through fraction without binding to the hydrophobic adsorbent, wherein the loading condition comprises a pH of from **[**about 5**]** *5.5* to about 8.6;

b) allowing the *recombinant* target protein to pass through the hydrophobic adsorbent in the flow-through fraction portion of the mixture; and

c) collecting the flow-through fraction portion of the mixture containing the *recombinant* target protein that does not bind to the hydrophobic adsorbent *to separate the recombinant target protein from the cell culture protein contaminants*.

3. A method for separating a recombinant Fc fusion target protein, produced as a product of cell culture expression in a host cell, from a mixture containing the *recombinant Fc fusion* target protein and non-target protein contaminants, comprising:

a) contacting the mixture *containing the recombinant Fc fusion target protein and non-target protein contaminants* with a hydrophobic adsorbent comprising branched alkyl functional groups having from 4 to about 8 carbon atoms, at least one of which is a tertiary carbon atom, in an aqueous salt solution under loading conditions that permit the non-target protein contaminants to bind to the adsorbent and the *recombinant Fc fusion* target protein to pass through the hydrophobic adsorbent in a flow-through fraction without binding to the hydrophobic adsorbent, wherein the loading condition comprises a pH of from **[**about 5**]** *5.5* to about 8.6;

b) allowing the *recombinant Fc fusion* target protein to pass through the hydrophobic adsorbent in the flow-through fraction portion of the mixture; and

c) collecting the flow-through fraction portion of the mixture containing the *recombinant Fc fusion* target protein that does not bind to the hydrophobic adsorbent *to separate the recombinant Fc fusion protein from the non-target protein contaminants*.

5. A method for removing Protein A from a mixture containing **[**a**]** *an antibody* target protein and Protein A contaminants, comprising:

a) contacting the mixture *containing an antibody target protein and Protein A contaminants* with a hydrophobic adsorbent comprising branched alkyl functional groups having from 4 to about 8 carbon atoms, at least one of which is a tertiary carbon atom, in an aqueous salt solution under loading conditions that permit the Protein A contaminants to bind to the adsorbent and the *antibody* target protein to pass though the hydrophobic adsorbent in a flow-through fraction without binding to the hydrophobic adsorbent, wherein the loading condition comprises a pH of from **[**about 5**]** *5.5* to about 8.6;

b) allowing the *antibody* target protein to pass through the hydrophobic adsorbent in the flow- through fraction portion of the mixture; and

c) collecting the flow-through fraction portion of the mixture containing the *antibody* target protein that does not bind to the hydrophobic adsorbent *to remove Protein A contaminants from the mixture*.

7. A method for removing a misfolded variant of a recombinant target protein from a mixture containing a combination of correctly folded variants and misfolded variants of the *recombinant* target protein, comprising:

a) contacting the mixture *containing a combination of correctly folded and misfolded variants of the recombinant target protein* with a hydrophobic adsorbent comprising branched alkyl functional groups having from 4 to about 8 carbon atoms, at least one of which is a tertiary carbon atom, in an aqueous salt solution under loading conditions that permit the misfolded variants of the *recombinant* target protein to bind to the adsorbent and the *correctly folded variants of the recombinant* target protein to pass through the hydrophobic adsorbent in a flow-through fraction without binding to the hydrophobic adsorbent, wherein the loading condition comprises a pH of from **[**about 5**]** *5.5* to about 8.6;

b) allowing the *correctly folded variants of the recombinant* target protein to pass through the hydrophobic adsorbent in the flow-through fraction portion of the mixture; and

c) collecting the flow-through fraction portion of the mixture containing a correctly folded variant of the *recombinant* target protein that does not bind to the hydrophobic adsorbent *to remove the misfolded variant of the recombinant target protein from the mixture*.

9. A method for removing aggregated forms of a recombinant target protein from a mixture containing individual forms and aggregated forms of the *recombinant* target protein, comprising:

a) contacting the mixture *containing individual and aggregated forms of the recombinant target protein* with a hydrophobic adsorbent comprising branched alkyl functional groups having from 4 to about 8 carbon atoms, at least one of which is a tertiary carbon atom, in an aqueous salt solution under loading conditions that permit the aggregated forms of the target *recombinant* protein to bind to the adsorbent and the *individual form of the*

recombinant target protein to pass through the hydrophobic adsorbent in a flow-through fraction without binding to the hydrophobic adsorbent; wherein the loading condition comprises a pH of from **[**about 5**]** *5.5* to about 8.6;

b) allowing the *individual form of the recombinant* target protein to pass through the hydrophobic adsorbent in the flow-through fraction portion of the mixture; and

c) collecting the flow-through fraction portion of the mixture containing the individual form of the *recombinant* target protein that does not bind to the hydrophobic adsorbent *to remove the aggregated forms of the recombinant target protein from the mixture*.

11. A process for separating a recombinant target protein from a mixture containing the *recombinant* target protein and cell culture contaminants produced by cell culture expression of the recombinant protein in a Chinese Hamster Ovary host cell, comprising:

a) contacting the mixture *containing the recombinant target protein and Chinese Hamster Ovary host cell culture contaminants* with a hydrophobic adsorbent comprising branched alkyl functional groups having from 4 to about 8 carbon atoms, at least one of which is a tertiary carbon atom, in an aqueous salt solution under loading conditions that permit the *Chinese Hamster Ovary host* cell culture contaminants to bind to the adsorbent and the *recombinant* target protein to pass through the hydrophobic adsorbent in a flow-through fraction without binding to the hydrophobic adsorbent, wherein the loading condition comprises a pH of from **[**about 5**]** *5.5* to about 8.6;

b) allowing the *recombinant* target protein to pass through the hydrophobic adsorbent in the flow-through fraction portion of the mixture; and

c) collecting the flow-through fraction portion of the mixture containing the *recombinant* target protein that does not bind to the hydrophobic adsorbent *to separate the recombinant target protein from the cell culture contaminants*.

13. The method of claim 1, 3, 7, 9, or 11 wherein the loading condition comprises a pH of from about 6.0 to about 8.6.

14. The method of claim 13, wherein the loading condition comprises a pH of from about 6.5 to about 7.5.

15. The method of claim 1, 3, 7, 9, or 11, wherein the separation method is further combined with a method of protein purification of the target protein.

16. The method of claim 11, wherein the amount of Chinese Hamster Ovary host cell culture contaminants in the flow-through fraction is not more than about 2500 ppm.

17. The method of claim 16, wherein the amount of Chinese Hamster Ovary host cell culture contaminants in the flow-through fraction is not more than about 400 ppm.

18. The method of claim 11, wherein the amount of Chinese Hamster Ovary host cell culture contaminants in the flow-through fraction is not more than about 100 ppm.

19. The method of claim 11, wherein the cell culture contaminants are selected from the group of a recombinant target protein aggregate, a misfolded recombinant target protein, and mixtures thereof.

20. The method of claim 7, wherein the recombinant target protein is a Fc fusion protein.

21. The method of claim 20, wherein the Fc fusion protein is selected from the group consisting of receptor activator of NF-kappa B:Fc (RANK:Fc) and human p75 tumor necrosis factor receptor:Fc (p75 TNFR:Fc).

* * * * *

Any remaining allegations of this paragraph are denied.

50. Amgen admits that during prosecution of the ’659 Patent, the applicant’s remarks dated 2006-05-22 states that “the claimed invention is directed to an HIC protein purification process in which the target protein passes through in a flow-through column without binding to the HIC column.” Any remaining allegations of this paragraph are denied.

U.S. Patent No. 7,662,930 (“the ’930 Patent”)

51. Admitted.

52. Admitted.

53. Admitted.

54. Amgen admits that the claims of the ’930 Patent state:

The invention claimed is:

1. A method for removing residual impurities from a first target-molecule solution, the method comprising:

loading the target-molecule solution onto a cation-exchange-chromatography column;

eluting the target molecule as a second target-molecule solution from the cation-exchange-chromatography column using a time dependent pH gradient buffer eluant to remove impurities from the first target molecule solution; and

passing the second target-molecule, diluted one-fold or less, solution through a Q membrane at a flow rate of between 400 and 600 cm/h to remove residual impurities from the second target-molecule solution.

2. The method of claim 1 wherein the target molecule is an Fc-region-containing protein.

3. The method of claim 1 wherein the target molecule is one of:

an Fc-containing, naturally occurring antibody;

an Fc-containing, synthetic antibody; and

an Fc-containing, recombinant antibody.

4. The method of claim 3 wherein the target molecule is initially purified in an affinity-chromatography capture step comprising:

loading a target-molecule sample solution onto a chromatography column prepared with a protein-A chromatography resin; and

eluting the target-molecule in the first target-molecule solution from the chromatography column.

5. The method of claim 1 wherein the second target-molecule solution is diluted one-fold prior to applying the second target-molecule solution to the membrane.

6. The method of claim 1 wherein residual impurities may include one or more of:

host-cell proteins;

host DNA;

viral DNA;

host RNA;

viral RNA;

target-molecule aggregates;

viral fragments;

intact viruses; and

endotoxins.

7. The method of claim 1 wherein the membrane passes neutral or positively charged molecules with smallest dimensions less than a threshold length, while retaining negatively charged molecules and molecules with a smallest dimension greater than a threshold length.

8. A method for removing residual impurities selected from the from consisting of host-cell proteins, DNA, RNA, antibody aggregates, virus particles, virus fragments, and endotoxins from an antibody solution initially purified in an affinity-chromatography capture step, the method comprising:

loading the antibody solution onto a cation-exchange-chromatography column;

eluting the antibody as a second antibody solution from the cation-exchange-chromatography column using a time dependent pH gradient buffer eluant to remove residual impurities from the antibody solution; and

passing the second antibody solution, diluted one-fold or less, through a selectively permeable Q membrane, at a flow rate of between 400 and 600 cm/h to remove the residual impurities from the second antibody solution while passing between 95% and 100% of natively folded and non-aggregated antibody into a resultant, purified antibody solution.

* * * * *

Any remaining allegations of this paragraph are denied.

55. Amgen admits that the ’930 Patent specification at 6:40-50 states:

> One family of anion exchangers used in various embodiments of the present invention, referred to as “Q-anion exchangers,” includes Q membranes and Q chromatography columns. Q membranes and Q chromatography resins operate as basic anion-exchange adsorbers, and are based on quaternary ammonium salts. Q membranes have large surface to volume ratios, and comprise a thin, microporous adsorptive layer bound to a cellulose matrix. A Sartobind® Q membrane may be employed as the Q membrane in certain embodiments of the present invention.

Any remaining allegations of this paragraph are denied.

56. Amgen admits that during prosecution of the ’930 Patent, the applicant’s remarks dated 2009-01-06 stated, “A Q-membrane is not used for sterilization, which can be performed in another subsequent step, but for removing charged contaminants such as relatively large host cell proteins, DNA, RNA, intact viruses and endotoxins.” Any remaining allegations of this paragraph are denied.

U.S. Patent No. 7,735,525 (“the ‘525 Patent”)

57. Admitted.

58. Admitted.

59. Admitted.

60. Amgen admits that the claims of the ’930 Patent state:

We claim:

1. A thermally insulated apparatus, comprising:

(a) an elongated metallic body having an exterior portion, a hollow interior portion and two openings located at opposing ends of a longitudinal axis;

(b) an insulating material contacting the exterior of the elongated metallic body of (a); and

(c) two capping members having a design that allows the capping members to substantially cover the openings located at opposing ends of the longitudinal axis of the metallic body of (a), and

wherein each of the two capping members comprise an opening or slit that allows tubing, which carries mobile phase into and out of a analytical separation column, to pass therethrough,

wherein the insulation material substantially surrounds the entire outer surface of the elongated metallic body with the exception of those portions that contact a heating source.

2. The thermally insulated apparatus of claim 1 further including a chromatography column situated within the elongated metallic body of the thermally insulated apparatus.

3. The thermally insulated apparatus of claim 2, wherein the column is 300sb-C18, 3.5 micron, 4.6×150 mm; Poly 4.6 mm id×150 mm, 5 micron, 200 Å pore size; or C4 bonded phase silica column, 4.6 mm id×150 mm, 5 micron, 300 Å pore size.

4. The thermally insulated apparatus of claim 1 having a size such that it may be placed within a chromatography column compartment of a liquid chromatography system.

5. A method for maintaining an elevated set point temperature in liquid chromatography applications comprising:

(a) providing a mobile phase inlet conduit configured to convey mobile phase from a mobile phase source to a chromatographic column;

(b) providing a pre-heater apparatus operably coupled to said mobile phase inlet conduit for heating the mobile phase to an elevated set point temperature;

(c) providing a chromatographic column operably coupled to, and disposed downstream from, said pre-heater apparatus such that the mobile phase exiting said pre-heater apparatus is directed to said column, said column including the thermally insulated apparatus of claim 1 for maintaining said column at temperatures consistent set point temperature of the mobile phase; and

(d) chromatographically separating the liquid mobile phase in said column at an elevated temperature maintained in a substantially adiabatic state throughout an entire length of said column.

6. A thermally insulated apparatus comprising:

(a) an elongated, cylindrical copper tube having a hollow interior portion and two openings located at opposing ends of a longitudinal axis;

(b) a polyethylene foam insulating material contacting the outer surface of the copper tube of (a), wherein the polyethylene foam is removed from portions of the outer surface of the copper tube in areas that contact a heating source; and

(c) two capping members having a design that allows the capping members to substantially cover the openings located at opposing ends of the longitudinal axis of the metallic cylindrical tube of (a), and

wherein each of the two capping members comprise an opening or slit that allows tubing, which carries mobile phase into and out of the analytical separation column, to pass therethrough;

wherein the thermally insulated apparatus has a size that allows it to fit within the column compartment of a liquid chromatography system.

* * * * *

Any remaining allegations of this paragraph are denied.

U.S. Patent No. 7,781,395 ("the '395 Patent")

61. Admitted.

62. Admitted.

63. Admitted.

64. Amgen admits that the claims of the '395 Patent state:

What is claimed is:

1. A process for purifying a protein on a hydrophobic interaction chromatography column such that the dynamic capacity of the column is increased for that protein comprising mixing a preparation containing the protein with a combination of a first salt and a second salt, loading the mixture onto a hydrophobic interaction chromatography column, and eluting the protein, wherein the first and second salts are citrate and phosphate salts, and wherein the concentration of each of the first salt and the second salt in the mixture is between about 0.1 M and about 1.0.

2. The process of claim 1 wherein the pH of the mixture loaded onto the column is between about pH 5 and about pH 7.

3. The process of claim 1 wherein the column is eluted with a solution having a pH between about pH 5 and about pH 7.

4. The process of claim 1 wherein the citrate and phosphate salts are selected from the group consisting of sodium, potassium and ammonium salts.

5. The process of claim 1 wherein the protein is a fusion protein or an antibody.

6. The process of claim 1, further comprising diluting the protein.

7. The process of claim 1, further comprising filtering the protein.

8. The process of claim 1, further comprising formulating the protein.

9. The process of claim 1, further comprising lyophilizing the protein.

10. A process of increasing the dynamic capacity of a hydrophobic interaction chromatography column for a particular protein, comprising mixing a preparation containing the protein with a combination of a first salt and a second salt, and loading the mixture onto a hydrophobic interaction chromatography column, wherein the first and second salts are citrate and phosphate salts, and wherein the concentration of each of the first and second salts in the mixture is between about 0.1M and about 1.0 M.

11. The process of claim 10 wherein the pH of the mixture loaded onto the column is between about pH 5 and about pH 7.

12. The process of claim 10, wherein the citrate and phosphate salts are selected from the group consisting of sodium, potassium and ammonium salts.

13. The process of claim 10 wherein the protein is a fusion protein or an antibody.

* * * * *

Any remaining allegations of this paragraph are denied.

65. Denied.

U.S. Patent No. 8,191,566 (“the ‘566 Patent”)

66. Admitted.

67. Admitted.

68. Amgen admits that Claim 1 of the ’566 Patent states:

1. A method of fluid transfer using a conduit assembly including a conduit defining a channel and also including a rupture valve dividing the channel into an inlet portion and an outlet portion, the rupture valve having an inlet side and an outlet side, the method comprising:

applying steam to the outlet portion of the channel with the rupture valve restricting entry of the steam into the inlet portion;

rupturing the rupture valve by increasing a pressure exerted on at least a portion of the inlet side of the rupture valve to create a passageway through the rupture valve; and

adding a fluid reagent to a receiver vessel connected to the conduit assembly, from a supply vessel containing the fluid reagent and through the passageway of the rupture valve.

69. Amgen admits that the claims of the ’566 Patent state:

The invention claimed is:

1. A method of fluid transfer using a conduit assembly including a conduit defining a channel and also including a rupture valve dividing the channel into an inlet portion and an outlet portion, the rupture valve having an inlet side and an outlet side, the method comprising:

applying steam to the outlet portion of the channel with the rupture valve restricting entry of the steam into the inlet portion;

rupturing the rupture valve by increasing a pressure exerted on at least a portion of the inlet side of the rupture valve to create a passageway through the rupture valve; and

adding a fluid reagent to a receiver vessel connected to the conduit assembly, from a supply vessel containing the fluid reagent and through the passageway of the rupture valve.

2. The method of claim **1**, wherein the step of adding a fluid reagent includes a step of adding a fluid reagent that is substantially liquid.

3. The method of claim **1**, wherein the step of rupturing includes a step of exerting pressure on the rupture valve via gas disposed downstream of the fluid reagent in the inlet portion.

4. The method of claim **1**, wherein the step of rupturing includes a step of exerting pressure on the rupture valve directly with the fluid reagent.

5. The method of claim **1**, further comprising a step of connecting the conduit assembly to the receiver vessel.

6. The method of claim **5**, wherein the step of connecting includes a step of connecting the conduit assembly such that the receiver vessel is farther downstream from the inlet portion than the outlet portion.

7. The method of claim **5**, wherein the receiver vessel is a bioreactor, and wherein the step of adding a fluid reagent includes a step of adding a medium for growing biological cells.

8. The method of claim **1**, wherein the conduit is a main conduit, wherein the conduit assembly also includes an ancillary conduit that branches from the main conduit, further comprising a step of removing steam condensate from the main conduit via the ancillary conduit during the step of applying steam.

9. The method of claim 1, wherein the conduit assembly includes a filter operatively connected to the conduit, further comprising a step of filtering the fluid reagent to remove microorganisms from the fluid reagent during the step of adding.

10. The method of claim 1, further comprising a step of sterilizing the inlet portion of the channel prior to the step of applying steam.

11. A method of fluid transfer using a conduit assembly including a main conduit defining a channel and also including an ancillary conduit that branches from the main conduit, the conduit assembly further including a rupture valve dividing the channel into an inlet portion and an outlet portion, the method comprising:

applying steam to the outlet portion of the channel with the rupture valve restricting entry of the steam into the inlet portion;

removing steam condensate from the main conduit via the ancillary conduit during the step of applying steam; and

rupturing the rupture valve with pressure exerted on the rupture valve from the inlet portion to create a passageway through the rupture valve for fluid flow.

12. The method of claim 11, further comprising a step of connecting the conduit assembly to a receiver vessel and a step of adding a fluid reagent to the receiver vessel through the rupture valve.

13. The method of claim 12, wherein the step of connecting includes a step of connecting the conduit assembly such that the receiver vessel is farther downstream from the inlet portion than the outlet portion.

14. The method of claim 12, wherein the receiver vessel is a bioreactor, and wherein the step of adding a fluid reagent includes a step of adding a medium for growing biological cells.

15. The method of claim 12, further comprising (1) a step of connecting the conduit assembly to a supply vessel containing a fluid reagent, and (2) a step of adding the fluid reagent to the receiver vessel through the rupture valve after the step of rupturing.

16. The method of claim 15, wherein the conduit assembly includes a filter operatively connected to the conduit, further comprising a step of filtering the fluid reagent upstream of the rupture valve in the conduit assembly.

17. The method of claim 11, further comprising a step of sterilizing the conduit assembly prior to the step of applying steam.

18. A method of fluid transfer using a conduit assembly including a conduit defining a channel and also including a rupture valve dividing the channel into an inlet portion and an outlet portion, the rupture valve having an inlet side and an outlet side, the method comprising:

applying steam to the outlet portion of the channel with the rupture valve restricting entry of the steam into the inlet portion;

rupturing the rupture valve by increasing a pressure exerted on at least a portion of the inlet side of the rupture valve to create a passageway through the rupture valve; and

flowing a fluid reagent through the passageway of the rupture valve.

19. The method of claim 18, wherein the step of flowing a fluid reagent includes a step of flowing a fluid reagent that is substantially liquid.

20. The method of claim 18, further comprising a step of sterilizing the inlet portion of the channel prior to the step of applying steam.

* * * * *

Any remaining allegations of this paragraph are denied.

U.S. Patent No. 8,273,707 ("the '707 Patent")

70. Admitted.

71. Admitted.

72. Admitted.

73. Amgen admits that the claims of the '707 Patent state:

within the scope of the invention. Indeed, various modifications of the invention, in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and accompanying drawings. Such modifications are intended to fall within the scope of the appended claims.

What is claimed is:

1. A process for purifying a protein on a hydrophobic interaction chromatography column such that the dynamic capacity of the column is increased for the protein comprising mixing a preparation containing the protein with a combination of a first salt and a second salt, loading the mixture onto a hydrophobic interaction chromatography column, and eluting the protein, wherein the first and second salts are selected from the group consisting of citrate and sulfate, citrate and acetate, and sulfate and acetate, respectively, and wherein the concentration of each of the first salt and the second salt in the mixture is between about 0.1 M and about 1.0.

2. The process of claim **1** wherein the pH of the mixture loaded onto the column is between about pH 5 and about pH 7.

3. The process of claim **1** wherein the column is eluted with a solution having a pH between about pH 5 and pH 7.

4. The process of claim **1** wherein the first and second salts are selected from the group consisting of sodium, potassium and ammonium salts.

5. The process of claim **1** wherein the protein is a fusion protein or an antibody.

6. The process of claim **1**, further comprising diluting the protein.

7. The process of claim **1**, further comprising filtering the protein.

8. The process of claim **1**, further comprising formulating the protein.

9. The process of claim **1**, further comprising lyophilizing the protein.

10. A method of increasing the dynamic capacity of a hydrophobic interaction chromatography column for a protein, comprising mixing a preparation containing the protein with a combination of a first salt and a second salt, and loading the mixture onto a hydrophobic interaction chromatography column, wherein the first and second salts are selected from the group consisting of citrate and sulfate, citrate and acetate and sulfate and acetate, respectively, and wherein the concentration of each of the first and second salts in the mixture is between about 0.1 M and about 1.0 M.

11. The method of claim **10** wherein the pH of the mixture loaded onto the column is between about pH 5 and about pH 7.

12. The method process of claim **10**, wherein the first and second salts are selected from the group consisting of sodium, potassium and ammonium salts.

13. The method of claim **10** wherein the protein is a fusion protein or an antibody.

* * * * *

Any remaining allegations of this paragraph are denied.

74. Denied.

U.S. Patent No. 8,940,878 ("the '878 Patent")

75. Admitted.

76. Admitted.

77. Amgen admits that Claims 1-6, and 18-25 of the '878 Patent state:

What is claimed is:

1. A method of purifying a protein expressed in a non-native soluble form in a non-mammalian expression system comprising:

(a) lysing a non-mammalian cell in which the protein is expressed in a non-native soluble form to generate a cell lysate;

(b) contacting the cell lysate with a separation matrix under conditions suitable for the protein to associate with the separation matrix;

(c) washing the separation matrix; and

(d) eluting the protein from the separation matrix, wherein the separation matrix is an affinity resin selected from the group consisting of Protein A, Protein G and a synthetic mimetic affinity resin.

2. The method of claim **1**, wherein the protein is a complex protein.

3. The method of claim **2**, wherein the complex protein is selected from the group consisting of a multimeric protein, an antibody and an Fc fusion protein.

4. The method of claim **1**, wherein the non-mammalian expression system comprises bacteria or yeast cells.

5. The method of claim **1**, wherein the cell lysate is filtered before it is contacted with the separation matrix.

6. The method of claim **1**, further comprising refolding the protein to its native form after it is eluted.

18. The method of claim **1** or **7**, further comprising the step of washing the separation matrix with a regeneration reagent.

19. The method of claim **18**, wherein the regeneration reagent is one of a strong base or a strong acid.

20. The method of claim **19**, wherein the strong acid is phosphoric acid.

21. The method of claim **19**, wherein the strong base is sodium hydroxide.

22. The method of claim **18**, wherein the regenerating comprises washing the separation matrix with a solution comprising one or both of a chaotrope present at a concentration of 4-6 M and a reductant.

23. The method of claim **22**, wherein the chaotrope is one of urea, dimethyl urea, methylurea, ethylurea, and guanidinium.

24. The method of claim **22**, wherein the reductant is one of cysteine, dithiothreitol (DTT), beta-mercaptoethanol and glutathione.

25. The method of claim **18**, wherein the regenerating comprises washing the separation matrix with a solution comprising 50 mM Tris, 10 mM citrate, 6 M urea, 50 mM dithiothreitol (DTT) at pH 7.4.

* * * * *

Any remaining allegations of this paragraph are denied.

78. Amgen admits that Claim 7 recites:

> 7. A method of purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system comprising:
> (a) expressing a protein in a non-native limited solubility form in a non-mammalian cell;
> (b) lysing a non-mammalian cell;
> (c) solubilizing the expressed protein in a solubilization solution comprising one or more of the following:
> (i) a denaturant;
> (ii) a reductant; and
> (iii) a surfactant;
> (d) forming a refold solution comprising the solubilization solution and a refold buffer, the refold buffer comprising one or more of the following:
> (i) a denaturant;
> (ii) an aggregation suppressor;
> (iii) a protein stabilizer; and
> (iv) a redox component;
> (e) directly applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix;
> (f) washing the separation matrix; and
> (g) eluting the protein from the separation matrix, wherein the separation matrix is a non-affinity resin selected from the group consisting of ion exchange, mixed mode, and a hydrophobic interaction resin.

Amgen admits that Claims 8-17 are dependent on Claim 7. Amgen admits that Claims 18-25 state:

18. The method of claim **1** or **7**, further comprising the step of washing the separation matrix with a regeneration reagent.

19. The method of claim **18**, wherein the regeneration reagent is one of a strong base or a strong acid.

20. The method of claim **19**, wherein the strong acid is phosphoric acid.

21. The method of claim **19**, wherein the strong base is sodium hydroxide.

22. The method of claim **18**, wherein the regenerating comprises washing the separation matrix with a solution comprising one or both of a chaotrope present at a concentration of 4-6 M and a reductant.

23. The method of claim **22**, wherein the chaotrope is one of urea, dimethyl urea, methylurea, ethylurea, and guanidinium.

24. The method of claim **22**, wherein the reductant is one of cysteine, dithiothreitol (DTT), beta-mercaptoethanol and glutathione.

25. The method of claim **18**, wherein the regenerating comprises washing the separation matrix with a solution comprising 50 mM Tris, 10 mM citrate, 6 M urea, 50 mM dithiothreitol (DTT) at pH 7.4.

* * * * *

Any remaining allegations of this paragraph are denied.

79. Amgen admits that Claim 7 of the '878 Patent states:

> 7. A method of purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system comprising:
> (a) expressing a protein in a non-native limited solubility form in a non-mammalian cell;
> (b) lysing a non-mammalian cell;
> (c) solubilizing the expressed protein in a solubilization solution comprising one or more of the following:
> (i) a denaturant;
> (ii) a reductant; and
> (iii) a surfactant;
> (d) forming a refold solution comprising the solubilization solution and a refold buffer, the refold buffer comprising one or more of the following:
> (i) a denaturant;
> (ii) an aggregation suppressor;
> (iii) a protein stabilizer; and
> (iv) a redox component;
> (e) directly applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix;
> (f) washing the separation matrix; and

(g) eluting the protein from the separation matrix, wherein the separation matrix is a non-affinity resin selected from the group consisting of ion exchange, mixed mode, and a hydrophobic interaction resin.

Amgen admits that Claims 8-17 are dependent on Claim 7. Amgen admits that Claims 18-25 of the '878 Patent state:

18. The method of claim **1** or **7**, further comprising the step of washing the separation matrix with a regeneration reagent.

19. The method of claim **18**, wherein the regeneration reagent is one of a strong base or a strong acid.

20. The method of claim **19**, wherein the strong acid is phosphoric acid.

21. The method of claim **19**, wherein the strong base is sodium hydroxide.

22. The method of claim **18**, wherein the regenerating comprises washing the separation matrix with a solution comprising one or both of a chaotrope present at a concentration of 4-6 M and a reductant.

23. The method of claim **22**, wherein the chaotrope is one of urea, dimethyl urea, methylurea, ethylurea, and guanidinium.

24. The method of claim **22**, wherein the reductant is one of cysteine, dithiothreitol (DTT), beta-mercaptoethanol and glutathione.

25. The method of claim **18**, wherein the regenerating comprises washing the separation matrix with a solution comprising 50 mM Tris, 10 mM citrate, 6 M urea, 50 mM dithiothreitol (DTT) at pH 7.4.

* * * * *

Any remaining allegations of this paragraph are denied.

80. Amgen admits that on January 9, 2014, Amgen submitted an amendment to claim 9 of the '990 application to read as follows:

A method of purifying a protein expressed in a non-native limited solubility form in a non-mammalian expression system comprising:

(a) expressing a protein in a non-native limited solubility form in a non-mammalian cell;

(b) lysing a non-mammalian cell;

(c) solubilizing the expressed protein in a solubilization solution comprising one or more of the following:

(i) a denaturant;

(ii) a reductant; and

(iii)a surfactant;

(d) forming a refold solution comprising the solubilization solution and a refold buffer, the refold buffer comprising one or more of the following:

(i) a denaturant;
(ii) an aggregation suppressor;
(iii)a protein stabilizer; and
(iv)a redox component;

(e) directly applying the refold solution to a separation matrix under conditions suitable for the protein to associate with the matrix;
(f) washing the separation matrix; and
(g) eluting the protein from the separation matrix, wherein the separation matrix is a non-affinity resin selected from the group consisting of ion exchange, mixed mode, and a hydrophobic interaction resin.

Any remaining allegations of this paragraph are denied.

U.S. Patent No. 8,952,138 ("the '138 Patent")

81. Admitted.

82. Admitted.

83. Admitted.

84. Admitted.

85. Amgen admits that the United States Patent and Trademark Office issued a Final Written Decision in IPR2016-01542 on February 15, 2018 determining that claims 1-17 and 19-24 of the '138 Patent are unpatentable.

U.S. Patent No. 9,418,416 ("the '416 Patent")

86. Admitted.

87. Admitted.

88. Admitted.

89. Amgen admits that the claims of the '416 Patent state:

What is claimed is:

1. A method of nondestructive counting and sizing of undissolved particles in a vessel that is at least partially filled with a fluid, the method comprising:

(a) receiving, by a sensor of an imaging system, at least one image of the particles in the vessel obtained under specified imaging conditions; and analyzing the at least one image by a processor of the imaging system, the analyzing including (b)-(d):

(b) detecting the particles and determining information indicative of an apparent size of the detected particles in the image;

(c) determining apparent particle size population information indicative of an apparent particle size distribution of the detected particles; and

(d) determining actual particle size population information indicative of an actual particle size distribution of the detected particles based on:

(i) the apparent particle size population information; and

(ii) calibration population information indicative of the apparent size distribution of one or more sets of standard sized particles imaged under conditions corresponding to the specified imaging conditions;

wherein (d) comprises fitting a superposition of apparent size distributions for a plurality of the sets of standard sized particles to the apparent particle size population of the detected particles; and

wherein fitting the superposition of apparent size distributions for the plurality of sets of standard sized particles conditions to the apparent particle size population of the detected particles comprises: minimizing a difference between the superposition and the apparent particle size population of the detected particles by adjusting the weighting of the apparent size distributions for the plurality of sets of standard sized particles.

2. A method of nondestructive counting and sizing of undissolved particles in a vessel that is at least partially filled with a fluid, the method comprising:

(a) receiving, by a sensor of an imaging system, at least one image of the particles in the vessel obtained under specified imaging conditions; and analyzing the at least one image by a processor of the imaging system, the analyzing including (b)-(d):

(b) detecting the particles and determining information indicative of an apparent size of the detected particles in the image;

(b1) selecting a first set of particles for counting based on the apparent size of the particles;

(c) determining apparent particle size population information indicative of an apparent particle size distribution of the first set of particles; and

(d) determining actual particle size population information indicative of an actual particle size distribution of the first set of particles based on:

(i) the apparent particle size population information; and

(ii) calibration population information indicative of the apparent size distribution of one or more sets of standard sized particles imaged under conditions corresponding to the specified imaging conditions.

3. The method of claim **2**, wherein the particles in the first set of particles are selected based on an apparent size threshold.

4. The method of claim **2**, wherein the at least one image comprises a time-series of images, and comprising:

detecting or counting particles of a second set of particles different from the first by determining trajectories of the second set of particles based on the time-series of images.

5. An apparatus for counting and sizing undissolved particles in a vessel that is at least partially filled with a fluid, the apparatus comprising a memory and at least one processor configured to execute instructions from the memory, the instructions when executed configuring the processor to:

(a) receive from the memory at least one image of the particles in the vessel obtained under specified imaging conditions;

(b) based on the at least one image, detect the particles and determine information indicative of an apparent size of the detected particles in the image;

(c) determine apparent particle size population information indicative of an apparent particle size distribution of the detected particles; and

(d) determine actual particle size population information indicative of an actual particle size distribution of the detected particles based on:

(i) the apparent particle size population information; and

(ii) calibration population information indicative of the apparent size distribution of one or more sets of standard sized particles imaged under conditions corresponding to the specified imaging conditions;

wherein the instructions when executed further configure the processor to fit the superposition of apparent size distributions for the plurality of sets of standard sized particles to the apparent particle size population of the detected particles by: minimizing a difference between the superposition and the apparent particle size population of the detected particles by adjusting the weighting of the apparent size distributions for the plurality of sets of standard sized particles.

6. An apparatus for counting and sizing undissolved particles in a vessel that is at least partially filled with a fluid, the apparatus comprising a memory and at least one processor configured to execute instructions from the memory, the instructions when executed configuring the processor to:

(a) receive from the memory at least one image of the particles in the vessel obtained under specified imaging conditions;

(b) based on the at least one image, detect the particles and determine information indicative of an apparent size of the detected particles in the image;

(c) determine apparent particle size population information indicative of an apparent particle size distribution of the detected particles; and

(d) determine actual particle size population information indicative of an actual particle size distribution of the detected particles based on:

(i) the apparent particle size population information; and

(ii) calibration population information indicative of the apparent size distribution of one or more sets of standard sized particles imaged under conditions corresponding to the specified imaging conditions;

wherein the instructions when executed further configure the processor to preprocess the at least one image to select a first set of particles for counting based on the apparent size of the particles, wherein (c) and (d) is applied only to the first set of particles.

7. The apparatus of claim **6**, wherein the particles in the first set of particles are selected based on an apparent size threshold.

8. The apparatus of claim **7**, wherein the at least one image comprises a time-series of images, and wherein the processor is configured to detect or count particles of a second set of particles different from the first by determining trajectories of the second set of particles based on the time-series of images.

* * * * *

Any remaining allegations of this paragraph are denied.

U.S. Patent No. 9,632,095 ("the '095 Patent")

90. Admitted.

91. Admitted.

92. Amgen admits that Claim 1 of the '095 Patent states:

1. A method of determining the reaction rate coefficient (k_{obs}) for the degradation of a chemical species at each of a plurality of constant temperatures, comprising in sequence the steps of

a) simultaneously incubating a plurality of samples of the chemical species in a single unitary device at said plurality of constant temperatures T, wherein the incubation of each of the plurality of samples is performed for an incubation time t selected to result in loss of a portion of the chemical species, said portion being at most 20 mol % of the amount originally present, where the choice of t might or might not be the same for each value of T;

b) quenching each of the samples in a manner sufficient to stop degradation;

c) determining the mole fraction m of the chemical species remaining in each of the quenched samples, relative to the amount present before incubating; and

d) determining for each sample a reaction rate coefficient k_{obs} according to the equation

$$k_{obs}(T) = \frac{1 - m(T)}{t}.$$

93. Amgen admits that the claims of the '095 Patent state:

What is claimed is:

1. A method of determining the reaction rate coefficient (k_{obs}) for the degradation of a chemical species at each of a plurality of constant temperatures, comprising in sequence the steps of

a) simultaneously incubating a plurality of samples of the chemical species in a single unitary device at said plurality of constant temperatures T, wherein the incubation of each of the plurality of samples is performed for an incubation time t selected to result in loss of a portion of the chemical species, said portion being at most 20 mol % of the amount originally present, where the choice of t might or might not be the same for each value of T;

b) quenching each of the samples in a manner sufficient to stop degradation;

c) determining the mole fraction m of the chemical species remaining in each of the quenched samples, relative to the amount present before incubating; and

d) determining for each sample a reaction rate coefficient k_{obs} according to the equation

$$k_{obs}(T) = \frac{1 - m(T)}{t}.$$

2. The method of claim **1**, wherein the chemical species is a pharmaceutical product.

3. The method of claim **1**, wherein the chemical species is a protein.

4. The method of claim **3**, wherein the degradation comprises aggregation.

5. The method of claim **3**, wherein the degradation comprises non-native aggregation.

6. The method of claim **3**, wherein the degradation comprises chemical degradation.

7. The method of claim **1**, wherein the loss of the chemical species is at most 10 mol %.

8. The method of claim **1**, further comprising e) performing numerical regression of the k_{obs} values obtained in step d) and the corresponding temperatures T in ° K to derive the activation energy E_a of the degradation of the chemical species according to the following equation

$$k_{obs} = k_0 \exp\left(\frac{E_a}{R}\left(\frac{1}{T} - \frac{1}{T_0}\right)\right)$$

wherein k_0 is the value of k_{obs} for T_0, one of the plurality of temperatures in ° K.

9. The method of claim **8**, wherein the chemical species is a pharmaceutical product.

10. The method of claim **8**, wherein the chemical species is a protein.

11. The method of claim **10**, wherein the degradation comprises aggregation.

12. The method of claim **10**, wherein the degradation comprises non-native aggregation.

13. The method of claim **10**, wherein the degradation comprises chemical degradation.

14. The method of claim **8**, wherein the loss of the chemical species is at most 10 mol %.

* * * * *

Any remaining allegations of this paragraph are denied.

U.S. Patent No. 9,643,997 ("the '997 Patent")

94. Admitted.

95. Admitted.

96. Admitted.

97. Amgen admits that Claims 1-8 of the '997 Patent state:

What is claimed is:

1. A method of purifying a protein expressed in a non-native soluble form in a non-mammalian expression system comprising:

(a) lysing a non-mammalian cell in which the protein is expressed in a nonnative soluble form to generate a cell lysate;

(b) contacting the cell lysate with a separation matrix under conditions suitable for the protein to associate with the separation matrix;

(c) washing the separation matrix; and

(d) eluting the protein from the separation matrix.

2. The method of claim **1**, wherein the protein is a complex protein.

3. The method of claim **2**, wherein the complex protein is selected from the group consisting of a multimeric protein, an antibody and an Fc fusion protein.

4. The method of claim **1**, wherein the non-mammalian expression system comprises bacteria or yeast cells.

5. The method of claim **1**, wherein the separation matrix is an affinity resin.

6. The method of claim **1**, wherein the separation matrix is a non-affinity resin selected from the group consisting of ion exchange, mixed mode, and a hydrophobic interaction resin.

7. The method of claim **1**, wherein the cell lysate is filtered before it is contacted with the separation matrix.

8. The method of claim **1**, further comprising refolding the protein to its native form after it is eluted.

Amgen admits that Claim 22 states: "The method of claim 8, wherein the protein is isolated after refolding." Any remaining allegations of this paragraph are denied.

98. Amgen admits that the '997 Patent specification at 7:51-59 states:

> As used herein, the term "non-native soluble form" when used in the context of a protein of interest, such as a protein comprising a Fc domain, means that the protein lacks at least one formed structure attribute found in a form of the protein that is biologically active in an appropriate in vivo or in vitro assay designed to assess the protein's biological activity, but in which the protein is expressed in a form or state that is soluble intracellularly (for example in the cell's cytoplasm) or extracellularly (for example, in a lysate pool).

Any remaining allegations of this paragraph are denied.

99. Amgen admits that the '997 Patent specification at 7:60-8:4 states:

> As used herein, the term "non-native limited solubility form" when used in the context of a protein of interest, such as a protein comprising a Fc domain, means any form or state

> in which the protein lacks at least one formed structural feature found in a form of the protein that (a) is biologically active in an appropriate in vivo or in vitro assay designed to assess the protein's biological activity and/or (b) forms aggregates that require treatment, such as chemical treatment to become soluble. The term specifically includes proteins existing in inclusion bodies, such as those sometimes found when a recombinant protein is expressed in a non-mammalian expression system.

Any remaining allegations of this paragraph are denied.

U.S. Patent No. 9,704,239 ("the '239 Patent")

100. Admitted.

101. Admitted.

102. Admitted.

103. Amgen admits that the claims of the '239 Patent state:

What is claimed is:

1. A method comprising:

during an agitation period of an agitation profile, applying a motion to a transparent vessel containing a fluid

acquiring, via one or more imagers while applying the motion, a sequence of original images of a portion of the transparent vessel, the acquisition of the sequence of original images being synchronized to the agitation profile such that each original image in the sequence of original images corresponds to the transparent vessel being in the same position;

generating, via one or more processors, a background image from the sequence of original images;

generating, via one or more processors, a resultant image from the background image and an original image in the sequence of original images; and

identifying, via one or more processors, a particle in the fluid from the resultant image.

2. The method of claim 1, wherein:

the agitation period includes a first agitation period and a second agitation period that is subsequent to the first agitation period,

the first agitation period includes applying a first motion, and

the second agitation period includes applying a second motion.

3. The method of claim 2, wherein the first motion or the second motion comprises spinning, rotating, shaking, oscillating or flipping the transparent vessel.

4. The method of claim 3, wherein the first motion includes spinning the transparent vessel at a first rate.

5. The method of claim 4, wherein the second motion includes spinning the transparent vessel at a second rate that is slower than the first rate.

6. The method of claim 1, wherein the agitation profile further comprises applying acoustic energy or ultrasonic energy to the transparent vessel prior to the agitation period.

7. The method of claim 1, further comprising:

rotating the transparent vessel by an integer multiple of 360 degrees between acquiring sequential images from among the sequence of original images.

8. The method of claim 7, wherein the integer multiple of 360 degrees varies between acquiring sequential images from among the sequence of original images.

9. The method of claim 1, wherein the transparent vessel is a syringe.

10. The method of claim 1, wherein the fluid substantially fills the transparent vessel such that the transparent vessel does not include an air gap.

11. The method of claim 1, wherein the transparent vessel is asymmetrical about a long axis of the transparent vessel.

12. The method of claim 1, wherein a cross-section of the transparent vessel varies along a length of the transparent vessel.

13. The method of claim 1, wherein the transparent vessel is non-cylindrical.

14. An inspection system comprising:

an agitator configured to receive a transparent vessel containing a fluid and to apply a motion to the transparent vessel during an agitation period of an agitation profile;

an imager configured to acquire a sequence of original images of the transparent vessel as the agitator applies the motion, the imager being synchronized to the agitation profile such that each original image in the sequence of original images corresponds to the transparent vessel being in the same position; and

a controller configured to:

receive from the imager the sequence of original images;

identify common features of at least two original images in the sequence of original images;

generate a background image including the common features;

generate one or more resultant images from the background image and the sequence of original images; and

identify, from the background image, a particle in the fluid.

15. The system of claim **14**, wherein the agitator is configured to spin, rotate, oscillate, or flip the transparent vessel.

16. The system of claim **14**, wherein the agitator is configured to apply at least one of acoustic energy or ultrasonic energy to the transparent vessel.

17. The system of claim **14**, wherein:

the agitation period includes a first agitation period and a second agitation period, the first agitation period being subsequent to the second agitation period, and

the agitator is configured to spin the transparent vessel at a first rotational velocity during the first agitation period and to spin the transparent vessel at a second, slower rotational velocity, during the second agitation period.

18. The system of claim **14**, wherein the agitator is further configured to flip the transparent vessel prior to the agitation period.

19. The system of claim **18**, wherein the agitator is further configured to spin the transparent vessel during the flipping of the transparent vessel.

20. The system of claim **14**, wherein the agitator comprises a motor, the system further comprising:

a triggering circuit configured to receive rotational information from the motor and to provide a trigger signal to initiate the imager to acquire an image of the transparent vessel to facilitate the acquisition of the sequence of original images being synchronized to the agitation profile.

21. A method comprising:

during an agitation period of an agitation profile, acquiring a sequence of original images of a portion of a transparent vessel via one or more imagers, the acquisition of the sequence of original images being synchronized to the agitation profile such that each original image in the sequence of original images corresponds to the transparent vessel being in the same position;

determining, via one or more processors, a background image from the sequence of original images;

generating, via one or more processors, at least one resultant image from the background image and the sequence of original images; and

identifying, via one or more processors, at least one particle in the fluid from the resultant image.

22. The method of claim **21**, wherein the sequence of original images is a sequence of two original images.

23. The method of claim **21**, wherein:

the agitation profile includes a first agitation period and a second agitation period, the first agitation period being prior to the second agitation period.

24. The method of claim **23**, further comprising:

applying a violent motion to the transparent vessel during the first agitation period.

* * * * *

Any remaining allegations of this paragraph are denied.

104. Amgen admits that the claims of the ’239 Patent are as stated in its answer to the allegations in Paragraph 103 and incorporates the claims of the ’239 Patent herein. Any remaining allegations of this paragraph are denied.

U.S. Patent No. 9,856,287 (“the ’287 Patent”)

105. Admitted.

106. Admitted.

107. Admitted.

COUNT I: DECLARATORY JUDGMENT
(NON-INFRINGEMENT OF U.S. PATENT NO. 6,180,391)

108. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-107 as if fully set forth herein.

109. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Adello declined to produce its aBLA to Amgen pursuant to the 42 U.S.C. § 262(l)(1). Adello has since produced its aBLA during the course of this litigation and Amgen is now in the process of reviewing Adello's aBLA after the parties' agreement to a protective order, which the Court so ordered on June 6, 2018. *See* D.E. No. 34.

110. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 109.

111. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 109.

112. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 109.

113. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 109.

114. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 109.

115. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraphs 109-114.

116. Admitted.

117. Denied.

COUNT II: DECLARATORY JUDGMENT
(INVALIDITY OF U.S. PATENT NO. 6,180,391)

118. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-117 as if fully set forth herein.

119. Denied.

120. Denied.

121. Denied.

COUNT III: DECLARATORY JUDGMENT
(NON-INFRINGEMENT OF U.S. PATENT NO. 7,083,948)

122. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-121 as if fully set forth herein.

123. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Adello declined to produce its aBLA to Amgen pursuant to the 42 U.S.C. § 262(l)(1). Adello has since produced its aBLA during the course of this litigation and Amgen is now in the process of reviewing Adello's aBLA after the parties' agreement to a protective order, which the Court so ordered on June 6, 2018. *See* D.E. No. 34.

124. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 123.

125. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraphs 123-124.

126. Admitted.

127. Denied.

COUNT IV: DECLARATORY JUDGMENT
(INVALIDITY OF U.S. PATENT NO. 7,083,948)

128. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-127 as if fully set forth herein.

129. Denied.

130. Denied.

131. Denied.

COUNT V: DECLARATORY JUDGMENT
(NON-INFRINGEMENT OF U.S. PATENT NO. 7,118,884)

132. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-131 as if fully set forth herein.

133. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Adello declined to produce its aBLA to Amgen pursuant to the 42 U.S.C. § 262(l)(1). Adello has since produced its aBLA during the course of this litigation and Amgen is now in the process of reviewing Adello's aBLA after the parties' agreement to a protective order, which the Court so ordered on June 6, 2018. *See* D.E. No. 34.

134. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 133.

135. Admitted.

136. Denied.

COUNT VI: DECLARATORY JUDGMENT
(INVALIDITY OF U.S. PATENT NO. 7,118,884)

137. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-136 as if fully set forth herein.

138. Denied.

139. Denied.

140. Denied.

COUNT VII: DECLARATORY JUDGMENT
(NON-INFRINGEMENT OF U.S. PATENT NO. 7,384,765)

141. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-140 as if fully set forth herein.

142. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Adello declined to produce its aBLA to Amgen pursuant to the 42 U.S.C. § 262(l)(1). Adello has since produced its aBLA during the course of this litigation and Amgen is now in the process of reviewing Adello's aBLA after the parties' agreement to a protective order, which the Court so ordered on June 6, 2018. *See* D.E. No. 34.

143. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 142.

144. Admitted.

145. Denied.

COUNT VIII: DECLARATORY JUDGMENT
(INVALIDITY OF U.S. PATENT NO. 7,384,765)

146. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-145 as if fully set forth herein.

147. Denied.

148. Denied.

149. Denied.

COUNT IX: DECLARATORY JUDGMENT
(NON-INFRINGEMENT OF U.S. PATENT NO. 7,427,659)

150. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-149 as if fully set forth herein.

151. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Adello declined to produce its aBLA to Amgen pursuant to the 42 U.S.C. § 262(l)(1). Adello has since produced its aBLA during the course of this litigation and Amgen is now in the process of reviewing Adello's aBLA after the parties' agreement to a protective order, which the Court so ordered on June 6, 2018. *See* D.E. No. 34.

152. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 151.

153. Admitted.

154. Denied.

COUNT X: DECLARATORY JUDGMENT
(INVALIDITY OF U.S. PATENT NO. 7,427,659)

155. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-154 as if fully set forth herein.

156. Denied.

157. Denied.

158. Denied.

COUNT XI: DECLARATORY JUDGMENT
(NON-INFRINGEMENT OF U.S. PATENT NO. 7,662,930)

159. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-158 as if fully set forth herein.

160. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Adello declined to produce its aBLA to Amgen pursuant to the 42 U.S.C. § 262(l)(1). Adello has since produced its aBLA during the course of this litigation and Amgen is now in the process of reviewing Adello's aBLA after the parties' agreement to a protective order, which the Court so ordered on June 6, 2018. *See* D.E. No. 34.

161. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 160.

162. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 160.

163. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraphs 160-162.

164. Admitted.

165. Denied.

COUNT XII: DECLARATORY JUDGMENT
(INVALIDITY OF U.S. PATENT NO. 7,662,930)

166. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-165 as if fully set forth herein.

167. Denied.

168. Denied.

169. Denied.

COUNT XIII: DECLARATORY JUDGMENT
(NON-INFRINGEMENT OF U.S. PATENT NO. 7,735,525)

170. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-169 as if fully set forth herein.

171. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Adello declined to produce its aBLA to Amgen pursuant to the 42 U.S.C. § 262(l)(1). Adello has since produced its aBLA during the course of this litigation and Amgen is now in the process of reviewing Adello's aBLA after the parties' agreement to a protective order, which the Court so ordered on June 6, 2018. *See* D.E. No. 34.

172. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 171.

173. Admitted.

174. Denied.

COUNT XIV: DECLARATORY JUDGMENT
(INVALIDITY OF U.S. PATENT NO. 7,735,525)

175. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-174 as if fully set forth herein.

176. Denied.

177. Denied.

178. Denied.

COUNT XV: DECLARATORY JUDGMENT
(NON-INFRINGEMENT OF U.S. PATENT NO. 7,781,395)

179. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-178 as if fully set forth herein.

180. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Adello declined to produce its aBLA to Amgen pursuant to the 42 U.S.C. § 262(l)(1). Adello has since produced its aBLA during the course of this litigation and Amgen is now in the process of reviewing Adello's aBLA after the parties' agreement to a protective order, which the Court so ordered on June 6, 2018. *See* D.E. No. 34.

181. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 180.

182. Admitted.

183. Denied.

COUNT XVI: DECLARATORY JUDGMENT
(INVALIDITY OF U.S. PATENT NO. 7,781,395)

184. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-183 as if fully set forth herein.

185. Denied.

186. Denied.

187. Denied.

COUNT XVII: DECLARATORY JUDGMENT
(NON-INFRINGEMENT OF U.S. PATENT NO. 8,191,566)

188. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-187 as if fully set forth herein.

189. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Adello declined to produce its aBLA to Amgen pursuant to the 42 U.S.C. § 262(l)(1). Adello has since produced its aBLA during the course of this litigation and Amgen is now in the process of reviewing Adello's aBLA after the parties' agreement to a protective order, which the Court so ordered on June 6, 2018. *See* D.E. No. 34.

190. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 189.

191. Admitted.

192. Denied.

COUNT XVIII: DECLARATORY JUDGMENT
(INVALIDITY OF U.S. PATENT NO. 8,191,566)

193. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-192 as if fully set forth herein.

194. Denied.

195. Denied.

196. Denied.

COUNT XIX: DECLARATORY JUDGMENT
(NON-INFRINGEMENT OF U.S. PATENT NO. 8,273,707)

197. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-196 as if fully set forth herein.

198. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Adello declined to produce its aBLA to Amgen pursuant to the 42 U.S.C. § 262(l)(1). Adello has since produced its aBLA during the course of this litigation and Amgen is now in the process of reviewing Adello's aBLA after the parties' agreement to a protective order, which the Court so ordered on June 6, 2018. *See* D.E. No. 34.

199. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 198.

200. Admitted.

201. Denied.

COUNT XX: DECLARATORY JUDGMENT
(INVALIDITY OF U.S. PATENT NO. 8,273,707)

202. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-201 as if fully set forth herein.

203. Denied.

204. Denied.

205. Denied.

COUNT XXI: DECLARATORY JUDGMENT
(NON-INFRINGEMENT OF U.S. PATENT NO. 8,940,878)

206. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-205 as if fully set forth herein.

207. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Adello declined to produce its aBLA to Amgen pursuant to the 42 U.S.C. § 262(l)(1). Adello has since produced its aBLA during the course of this litigation and Amgen

is now in the process of reviewing Adello's aBLA after the parties' agreement to a protective order, which the Court so ordered on June 6, 2018. *See* D.E. No. 34.

208. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 207.

209. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 207.

210. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraphs 207-209.

211. Admitted.

212. Denied.

COUNT XXII: DECLARATORY JUDGMENT
(INVALIDITY OF U.S. PATENT NO. 8,940,878)

213. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-212 as if fully set forth herein.

214. Denied.

215. Denied.

216. Denied.

COUNT XXIII: DECLARATORY JUDGMENT
(NON-INFRINGEMENT OF U.S. PATENT NO. 8,952,138)

217. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-216 as if fully set forth herein.

218. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Adello declined to produce its aBLA to Amgen pursuant to the 42 U.S.C. § 262(l)(1). Adello has since produced its aBLA during the course of this litigation and Amgen is now in the process of reviewing Adello's aBLA after the parties' agreement to a protective order, which the Court so ordered on June 6, 2018. *See* D.E. No. 34.

219. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 218.

220. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraphs 218-219.

221. Admitted.

222. Denied.

COUNT XXIV: DECLARATORY JUDGMENT
(INVALIDITY OF U.S. PATENT NO. 8,952,138)

223. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-222 as if fully set forth herein.

224. Denied.

225. Denied.

226. Denied.

COUNT XV: DECLARATORY JUDGMENT
(NON-INFRINGEMENT OF U.S. PATENT NO. 9,418,416)

227. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-226 as if fully set forth herein.

228. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Adello declined to produce its aBLA to Amgen pursuant to the 42 U.S.C. § 262(l)(1). Adello has since produced its aBLA during the course of this litigation and Amgen is now in the process of reviewing Adello's aBLA after the parties' agreement to a protective order, which the Court so ordered on June 6, 2018. *See* D.E. No. 34.

229. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 228.

230. Admitted.

231. Denied.

COUNT XVI: DECLARATORY JUDGMENT
(INVALIDITY OF U.S. PATENT NO. 9,418,416)

232. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-231 as if fully set forth herein.

233. Denied.

234. Denied.

235. Denied.

COUNT XVII: DECLARATORY JUDGMENT
(NON-INFRINGEMENT OF U.S. PATENT NO. 9,632,095)

236. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-235 as if fully set forth herein.

237. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Adello declined to produce its aBLA to Amgen pursuant to the 42 U.S.C. § 262(l)(1). Adello has since produced its aBLA during the course of this litigation and Amgen

is now in the process of reviewing Adello's aBLA after the parties' agreement to a protective order, which the Court so ordered on June 6, 2018. *See* D.E. No. 34.

238. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 237.

239. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraphs 237-238.

240. Admitted.

241. Denied.

COUNT XXVIII: DECLARATORY JUDGMENT
(INVALIDITY OF U.S. PATENT NO. 9,632,095)

242. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-241 as if fully set forth herein.

243. Denied.

244. Denied.

245. Denied.

COUNT XXIX: DECLARATORY JUDGMENT
(NON-INFRINGEMENT OF U.S. PATENT NO. 9,643,997)

246. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-245 as if fully set forth herein.

247. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Adello declined to produce its aBLA to Amgen pursuant to the 42 U.S.C. § 262(l)(1). Adello has since produced its aBLA during the course of this litigation and Amgen

is now in the process of reviewing Adello's aBLA after the parties' agreement to a protective order, which the Court so ordered on June 6, 2018. *See* D.E. No. 34.

248. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 247.

249. Admitted.

250. Denied.

COUNT XXX: DECLARATORY JUDGMENT
(INVALIDITY OF U.S. PATENT NO. 9,643,997)

251. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-250 as if fully set forth herein.

252. Denied.

253. Denied.

254. Denied.

COUNT XXXI: DECLARATORY JUDGMENT
(NON-INFRINGEMENT OF U.S. PATENT NO. 9,704,239)

255. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-254 as if fully set forth herein.

256. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Adello declined to produce its aBLA to Amgen pursuant to the 42 U.S.C. § 262(l)(1). Adello has since produced its aBLA during the course of this litigation and Amgen is now in the process of reviewing Adello's aBLA after the parties' agreement to a protective order, which the Court so ordered on June 6, 2018. *See* D.E. No. 34.

257. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraph 256.

258. At this stage of the proceeding, Amgen can neither admit nor deny the allegations of this paragraph. Amgen incorporates by reference its answer to the allegations of Paragraphs 256-257.

259. Admitted.

260. Denied.

COUNT XXXII: DECLARATORY JUDGMENT
(INVALIDITY OF U.S. PATENT NO. 9,704,239)

261. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-260 as if fully set forth herein.

262. Denied.

263. Denied.

264. Denied.

COUNT XXXIII: DECLARATORY JUDGMENT
(NON-INFRINGEMENT OF U.S. PATENT NO. 9,856,287)

265. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-264 as if fully set forth herein.

266. Denied. Amgen notes that Adello has not provided any specific reasons why it believes it does not infringe the ’287 Patent.

267. Admitted.

268. Denied.

COUNT XXXIV: DECLARATORY JUDGMENT
(INVALIDITY OF U.S. PATENT NO. 9,856,287)

269. Amgen incorporates by reference its answer to the allegations of Paragraphs 1-268 as if fully set forth herein.

270. Denied.

271. Denied.

272. Denied.

Dated: June 21, 2018

Respectfully submitted,

s/Liza M. Walsh

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IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

AMGEN INC. and AMGEN MANUFACTURING LIMITED, Plaintiffs, v. ADELLO BIOLOGICS, LLC, Defendant.	Civil Action No. 2:18-cv-03347 **CERTIFICATE OF SERVICE** *Filed Electronically*

I, Liza M. Walsh, hereby certify that, on the date set forth below, I caused a true and correct copy of the following documents submitted on behalf of Plaintiffs Amgen Inc. and Amgen Manufacturing Limited (collectively, "Plaintiffs") to be filed and served on the Office of the Clerk, United States District Court District of New Jersey, Martin Luther King, Jr. Building & U.S. Courthouse, 50 Walnut Street, Newark, New Jersey in accordance with the Court's electronic filing procedures:

- Plaintiffs Amgen Inc.'s and Amgen Manufacturing Limited's Answer to Defendant Adello Biologics, LLC's Counterclaims; and
- This Certificate of Service.

I further certify that, on the date set forth below, I caused a true and correct copy of the foregoing documents to be served via the Court's electronic filing system upon all parties registered to receive electronic filings.

I certify that the foregoing is true and correct.

Dated: June 21, 2018

s/ Liza M. Walsh
Liza M. Walsh