(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) **EP 2 521 536 B9**

(12) **CORRECTED EUROPEAN PATENT SPECIFICATION**

(15) Correction information:
Corrected version no 2 (W2 B1)
Corrections, see
Description Paragraph(s) 71

(48) Corrigendum issued on:
23.01.2019 Bulletin 2019/04

(45) Date of publication and mention of the grant of the patent:
01.08.2018 Bulletin 2018/31

(21) Application number: **11703294.6**

(22) Date of filing: **07.01.2011**

(51) Int Cl.:
A61K 9/00 *(2006.01)* ***A61K 39/395*** *(2006.01)*
A61K 31/485 *(2006.01)* ***A61K 47/10*** *(2017.01)*
A61K 47/22 *(2006.01)* ***A61K 47/26*** *(2006.01)*
A61K 47/18 *(2017.01)*

(86) International application number:
PCT/US2011/020457

(87) International publication number:
WO 2011/085158 (14.07.2011 Gazette 2011/28)

(54) STABILIZED FORMULATIONS CONTAINING ANTI-INTERLEUKIN-6 RECEPTOR (IL-6R) ANTIBODIES

STABILISIERTE FORMULIERUNGEN MIT ANTI-INTERLEUKIN-6-REZEPTOR (IL-6R)-ANTIKÖRPERN

FORMULATIONS STABILISÉES CONTENANT DES ANTICORPS CONTRE LE RÉCEPTEUR DE L'INTERLEUKINE-6 (IL-6R)

(84) Designated Contracting States:
AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR
Designated Extension States:
BA ME

(30) Priority: **08.01.2010 US 293227 P**
07.01.2011 US 986223

(43) Date of publication of application:
14.11.2012 Bulletin 2012/46

(60) Divisional application:
18174400.4 / 3 409 269

(73) Proprietor: **Regeneron Pharmaceuticals, Inc.**
Tarrytown, NY 10591-6707 (US)

(72) Inventors:
- **DIX, Daniel, B.**
  Lagrangeville, NY 12540 (US)
- **GRAHAM, Kenneth, S.**
  Pleasant Valley, NY 12569 (US)
- **KAMEN, Douglas, E.**
  Poughquag, NY 12570 (US)
- **WALSH, Scott, M.**
  Tarrytown, NY 10591 (US)

(74) Representative: **J A Kemp**
14 South Square
Gray's Inn
London WC1R 5JJ (GB)

(56) References cited:
US-A1- 2003 113 316 **US-A1- 2003 190 316**
US-B2- 7 582 298

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to the field of therapeutic antibody formulations. More specifically, the present invention relates to the field of pharmaceutical formulations comprising a human antibody that specifically binds to human interleukin-6 receptor.

BACKGROUND

[0002] Therapeutic macromolecules (*e.g.*, antibodies) must be formulated in a manner that not only makes the molecules suitable for administration to patients, but also maintains their stability during storage. For example, therapeutic antibodies in liquid solution are prone to degradation, aggregation and/or undesired chemical modifications unless the solution is formulated properly. The stability of an antibody in liquid formulation depends not only on the kinds of excipients used in the formulation, but also on the amounts and proportions of the excipients relative to one another. Furthermore, other considerations aside from stability must be taken into account when preparing a liquid antibody formulation. Examples of such additional considerations include the viscosity of the solution and the concentration of antibody that can be accommodated by a given formulation. Thus, when formulating a therapeutic antibody, great care must be taken to arrive at a formulation that remains stable, contains an adequate concentration of antibody, and possesses a suitable viscosity as well as other properties which enable the formulation to be conveniently administered to patients.

[0003] Antibodies to the human interleukin-6 receptor (hIL-6R) are one example of a therapeutically relevant macromolecule that requires proper formulation. Anti-hIL-6R antibodies are clinically useful for the treatment and/or prevention of diseases such as rheumatoid arthritis, ankylosing spondylitis, and other conditions. Exemplary anti-IL-6R antibodies are described, *inter alia,* in US 7,582,298; 6,410,691; 5,817,790; 5,795,695; and 6,670,373. A particularly important anti-hIL-6R antibody with great therapeutic potential is the antibody referred to in US 7,582,298 as VQ8F11-21 (also referred to herein as "mAb1").

[0004] Although anti-hIL-6R antibodies are known, there remains a need in the art for novel pharmaceutical formulations comprising anti-hIL-6R antibodies which are sufficiently stable and also suitable for administration to patients.

BRIEF SUMMARY OF THE INVENTION

[0005] The present invention satisfies the aforementioned need by providing pharmaceutical formulations comprising a human antibody that specifically binds to human interleukin-6 receptor (hIL-6R).

[0006] The present invention provides a pharmaceutical formulation comprising: (i) a human antibody that specifically binds to human interleukin-6 receptor (hIL-6R), wherein the antibody is at a concentration of from 5 mg/ml to 200 mg/ml and comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO:18 and a light chain variable region having the amino acid sequence of SEQ ID NO:26; (ii) histidine at a concentration of from 10 mM to 25 mM; (iii) arginine at a concentration of from 25 mM to 50 mM; (iv) sucrose in an amount of from 5% to 10% w/v; and (v) polysorbate 20 in an amount of from 0.1% to 0.2% w/v.

[0007] The antibody formulations may be contained within any suitable container useful for storing pharmaceutical formulations. Examples of such suitable containers include, *e.g.,* glass or plastic vials, syringes and cartridges. The container may be clear or opaque (*e.g.*, amber colored).

[0008] According to certain aspects, the pharmaceutical formulations remain relatively stable following storage for several days, months or years at a given temperature. For example, in certain exemplary embodiments, a high percentage of the antibody (*e.g.*, 90%, 95%, 96% or more) is maintained in its native form following at least 3, 6, 9 or more months of storage. The percentage of native form of the antibody may be measured, *e.g.*, by SE-HPLC, or by any other method known in the art. The storage temperature at which stability of the antibody is maintained can be, *e.g.*, -80°C, -40°C, -20°C, 0°C, 5°C, 25°C, 45°C, or higher.

BRIEF DESCRIPTION OF THE FIGURES

[0009]

Figure 1 shows the percent of native mAb1 remaining, as measured by SE-HPLC, following various amounts of time of storage at -20°C (filled triangles), -30°C (filled squares), and -80°C (filled diamonds).

Figure 2 shows the percent of acidic species of mAb1, as measured by CEX-HPLC, following various amounts of time of storage at -20°C (filled triangles), -30°C (filled squares), and -80°C (filled diamonds).

Figure 3 shows the percent of native mAb1 remaining in various minimal excipient formulations, as measured by SE-HPLC, following various amounts of time of storage at - 30°C. Filled diamonds represent formulation 1 (80 mg/mL mAb1, 0.13% polysorbate 20, 6% sucrose, 10 mM histidine); filled squares represent formulation 2 (80 mg/mL mAb1, 0.13% polysorbate 20, 10 mM histidine); filled triangles represent formulation 3 (80 mg/mL mAb, 1% sucrose, 10 mM histidine); open squares represent formulation 4 (80 mg/mL mAb1, 2% sucrose, 10 mM histidine); asterisks represent formulation 5 (80 mg/mL mAb1, 4% sucrose, 10 mM histidine); filled circles represent formulation 6 (80 mg/mL mAb1, 6% sucrose, 10 mM histidine); crosses represent formulation 7 (80 mg/mL antibody, 10 mM histidine); and open circles represent formulation 8 (65 mg/mL antibody, 10 mM histidine). All formulations are set out in Table 6 (see Example 2, below).

Figure 4 shows the percent of native mAb1 remaining in various minimal excipient formulations, as measured by SE-HPLC, following various amounts of time of storage at - 20°C. Filled diamonds represent formulation 1 (80 mg/mL mAb1, 0.13% polysorbate 20, 6% sucrose, 10 mM histidine); filled squares represent formulation 2 (80 mg/mL mAb1, 0.13% polysorbate 20, 10 mM histidine); filled triangles represent formulation 3 (80 mg/mL mAb, 1% sucrose, 10 mM histidine); open squares represent formulation 4 (80 mg/mL mAb1, 2% sucrose, 10 mM histidine); asterisks represent formulation 5 (80 mg/mL mAb1, 4% sucrose, 10 mM histidine); filled circles represent formulation 6 (80 mg/mL mAb1, 6% sucrose, 10 mM histidine); crosses represent formulation 7 (80 mg/mL antibody, 10 mM histidine); and open circles represent formulation 8 (65 mg/mL antibody, 10 mM histidine). All formulations are set out in Table 6 (see Example 2, below).

DETAILED DESCRIPTION

[0010] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. As used herein, the term "about," when used in reference to a particular recited numerical value, means that the value may vary from the recited value by no more than 1%. For example, as used herein, the expression "about 100" includes 99 and 101 and all values in between (*e.g.,* 99.1, 99.2, 99.3, 99.4, etc.).

[0011] Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described.

PHARMACEUTICAL FORMULATIONS

[0012] As used herein, the expression "pharmaceutical formulation" means a combination of at least one active ingredient (*e.g.*, a small molecule, macromolecule, compound, etc. which is capable of exerting a biological effect in a human or non-human animal), and at least one inactive ingredient which, when combined with the active ingredient and/or one or more additional inactive ingredients, is suitable for therapeutic administration to a human or non-human animal. The term "formulation," as used herein, means "pharmaceutical formulation" unless specifically indicated otherwise. Specific exemplary components and formulations included within the present invention are described in detail below.

[0013] The pharmaceutical formulations may, in certain embodiments, be fluid formulations. As used herein, the expression "fluid formulation" means a mixture of at least two components that exists predominantly in the fluid state at about 5°C to about 45°C. Fluid formulations include, *inter alia,* liquid formulations. Fluid formulations may be of low, moderate or high viscosity depending on their particular constituents.

ANTIBODIES THAT BIND SPECIFICALLY TO hIL-6R

[0014] The pharmaceutical formulations comprise a human antibody, or an antigen-binding fragment thereof, that binds specifically to hIL-6R. As used herein, the term "hIL-6R" means a human cytokine receptor that specifically binds interleukin-6 (IL-6). In certain embodiments, the antibody contained within the pharmaceutical formulations of the present disclosure binds specifically to the extracellular domain of hIL-6R. The extracellular domain of hIL-6R is represented by the amino acid sequence of SEQ ID NO:74.

[0015] The term "antibody", as used herein, is generally intended to refer to immunoglobulin molecules comprising four polypeptide chains, two heavy (H) chains and two light (L) chains inter-connected by disulfide bonds, as well as multimers thereof (*e.g.*, IgM); however, immunoglobulin molecules consisting of only heavy chains (*i.e.*, lacking light chains) are also encompassed within the definition of the term "antibody." Each heavy chain comprises a heavy chain variable region (abbreviated herein as HCVR or VH) and a heavy chain constant region. The heavy chain constant region comprises three domains, CH1, CH2 and CH3. Each light chain comprises a light chain variable region (abbreviated herein as LCVR or VL) and a light chain constant region. The light chain constant region comprises one domain (CL1).

The VH and VL regions can be further subdivided into regions of hypervariability, termed complementary determining regions (CDRs), interspersed with regions that are more conserved, termed framework regions (FR). Each VH and VL is composed of three CDRs and four FRs, arranged from amino-terminus to carboxy-terminus in the following order: FR1, CDR1, FR2, CDR2, FR3, CDR3, FR4.

[0016] Unless specifically indicated otherwise, the term "antibody," as used herein, shall be understood to encompass complete antibody molecules as well as antigen-binding fragments thereof. The term "antigen-binding portion" or "antigen-binding fragment" of an antibody (or simply "antibody portion" or "antibody fragment"), as used herein, refers to one or more fragments of an antibody that retain the ability to specifically bind to hIL-6R.

[0017] An "isolated antibody", as used herein, is intended to refer to an antibody that is substantially free of other antibodies having different antigenic specificities (e.g., an isolated antibody that specifically binds hIL-6R is substantially free of antibodies that specifically bind antigens other than hIL-6R).

[0018] The term "specifically binds," or the like, means that an antibody or antigen-binding fragment thereof forms a complex with an antigen that is relatively stable under physiologic conditions. Specific binding can be characterized by a dissociation constant of at least about $1x10^{-6}$ M or greater. Methods for determining whether two molecules specifically bind are well known in the art and include, for example, equilibrium dialysis, surface plasmon resonance, and the like. An isolated antibody that specifically binds hIL-6R may, however, have cross-reactivity to other antigens, such as IL-6R molecules from other species. In the context of the present disclosure, multispecific (e.g., bispecific) antibodies that bind to hIL-6R as well as one or more additional antigens are deemed to "specifically bind" hIL-6R. Moreover, an isolated antibody may be substantially free of other cellular material and/or chemicals.

[0019] The anti-hIL-6R antibody comprises a heavy chain variable region (HCVR) having an amino acid sequence SEQ ID NO: 18. The anti-hIL-6R antibody comprises a light chain variable region (LCVR) having an amino acid sequence SEQ ID No: 26.

[0020] The non-limiting, exemplary antibody used in the Examples herein is referred to as "mAb1." This antibody is also referred to in US 7,582,298 as VQ8F11-21. mAb1 (VQ8F11-21) comprises an HCVR/LCVR amino acid sequence pair having SEQ ID NOs:18/26, and HCDR1-HCDR2-HCDR3 / LCDR1-LCDR2-LCDR3 domains represented by SEQ ID NOs:20 - 22 - 24 / SEQ ID NOs:28 - 30 - 32.

[0021] The pharmaceutical formulation according to the invention contains 5 mg/mL to 200 mg/mL of antibody; about 25 mg/mL to about 180 mg/mL of antibody; about 25 mg/mL to about 150 mg/mL of antibody; or about 50 mg/mL to about 180 mg/mL of antibody. For example, the formulations may comprise 5 mg/mL; about 10 mg/mL; about 15 mg/mL; about 20 mg/mL; about 25 mg/mL; about 30 mg/mL; about 35 mg/mL; about 40 mg/mL; about 45 mg/mL; about 50 mg/mL; about 55 mg/mL; about 60 mg/mL; about 65 mg/mL; about 70 mg/mL; about 75 mg/mL; about 80 mg/mL; about 85 mg/mL; about 86 mg/mL; about 87 mg/mL; about 88 mg/mL; about 89 mg/mL; about 90 mg/mL; about 95 mg/mL; about 100 mg/mL; about 105 mg/mL; about 110 mg/mL; about 115 mg/mL; about 120 mg/mL; about 125 mg/mL; about 130 mg/mL; about 131 mg/mL; about 132 mg/mL; about 133 mg/mL; about 134 mg/mL; about 135 mg/mL; about 140 mg/mL; about 145 mg/mL; about 150 mg/mL; about 155 mg/mL; about 160 mg/mL; about 165 mg/mL; about 170 mg/mL; about 175 mg/mL; about 180 mg/mL; about 185 mg/mL; about 190 mg/mL; about 195 mg/mL; or 200 mg/mL of an antibody that binds specifically to hIL-6R.

EXCIPIENTS and pH

[0022] The pharmaceutical formulations of the present disclosure comprise one or more excipients. The term "excipient," as used herein, means any non-therapeutic agent added to the formulation to provide a desired consistency, viscosity or stabilizing effect. The pharmaceutical formulation of the invention comprises two amino acids: histidine at a concentration of from 10 to 25 mM and arginine at a concentration of from 25 to 50 mM.

[0023] In certain embodiments, the formulations may contain histidine at a concentration of 10 mM; about 10.5 mM; about 11 mM; about 11.5 mM; about 12 mM; about 12.5 mM; about 13 mM; about 13.5 mM; about 14 mM; about 14.5 mM; about 15 mM; about 15.5 mM; 16 mM; about 16.5 mM; about 17 mM; about 17.5 mM; about 18 mM; about 18.5 mM; about 19 mM; about 19.5 mM; about 20 mM; about 20.5 mM; about 21 mM; about 21.5 mM; about 22 mM; about 22.5 mM; about 23 mM; about 23.5 mM; about 24 mM; about 24.5 mM; or 25 mM.

[0024] In certain embodiments, the formulations may contain arginine at a concentration of 25 mM; about 25.5 mM; about 26 mM; about 26.5 mM; about 27 mM; about 27.5 mM; about 28 mM; about 28.5 mM; about 29 mM; about 29.5 mM; about 30 mM; about 35 mM; about 40 mM; about 45 mM; or 50 mM.

[0025] The amount of sugar contained within the pharmaceutical formulations is from 5% to 10% w/v. For example, the pharmaceutical formulations may comprise 5.0%; about 5.5%; about 6.0%; 6.5%; about 7.0%; about 7.5%; about 8.0%; about 8.5%; about 9.0%; about 9.5%; 10%. The sugar is sucrose.

[0026] The pharmaceutical formulations comprise a surfactant, namely polysorbate 20. Polysorbate 20 is also known as TWEEN 20, sorbitan monolaurate and polyoxyethylenesorbitan monolaurate.

[0027] The amount of surfactant contained within the pharmaceutical formulations is from 0.1% to 0.2% w/v. For

example, the formulations may comprise 0.10%; about 0.11%; about 0.12%; about 0.13%; about 0.14%; about 0.15%; about 0.16%; about 0.17%; about 0.18%; about 0.19%; 0.20%.

[0028] The pharmaceutical formulations may have a pH of from about 5.0 to about 8.0. For example, the formulations may have a pH of about 5.0; about 5.2; about 5.4; about 5.6; about 5.8; about 6.0; about 6.2; about 6.4; about 6.6; about 6.8; about 7.0; about 7.2; about 7.4; about 7.6; about 7.8; or about 8.0.

EXEMPLARY FORMULATIONS

[0029] According to one aspect of the present disclosure, the pharmaceutical formulation comprises: (i) a human antibody that specifically binds to hIL-6R (*e.g.*, mAb1); (ii) an amino acid (*e.g.*, histidine); and (iii) a sugar (*e.g.*, sucrose). Specific, non-limiting exemplary embodiments encompassed by this aspect of the disclosure are set forth in Table 1. These formulations are not in the scope of the claims.

Table 1: Exemplary Pharmaceutical Formulations Comprising mAb1, Histidine and Sucrose

mAb1 (mg/ml)	25	50	100	150	25	50	100	150	25	50	100	150	25	50	100	150
histidine (mM)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
sucrose (%)	1	1	1	1	2	2	2	2	4	4	4	4	6	6	6	6

[0030] According to another aspect of the present disclosure, the pharmaceutical formulation comprises: (i) a human antibody that specifically binds to hIL-6R (e.g., mAb1); (ii) an amino acid (e.g., histidine); (iii) a sugar (e.g., sucrose); and (iv) a surfactant (e.g., polysorbate 20). Specific, non-limiting exemplary embodiments encompassed by this aspect of the disclosure are set forth in Tables 2A and 2B (not in the scope of the claims).

Table 2A: Exemplary Pharmaceutical Formulations Comprising mAb1, Histidine, Sucrose and Polysorbate 20

mAb1 (mg/ml)	25	50	100	150	25	50	100	150	25	50	100	150
histidine (mM)	10	10	10	10	10	10	10	10	10	10	10	10
sucrose (%)	2	2	2	2	5	5	5	5	10	10	10	10
polysorbate 20 (%)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Table 2B: Exemplary Pharmaceutical Formulations Comprising mAb1, Histidine, Sucrose and Polysorbate 20

mAb1 (mg/ml)	25	50	100	150	25	50	100	150	25	50	100	150
histidine (mM)	10	10	10	10	10	10	10	10	10	10	10	10
sucrose (%)	2	2	2	2	5	5	5	5	10	10	10	10
polysorbate 20 (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

[0031] According to another aspect of the present disclosure, the pharmaceutical formulation comprises: (i) a human antibody that specifically binds to hIL-6R (e.g., mAb1); (ii) a first amino acid (e.g., histidine); (iii) a sugar (e.g., sucrose); (iv) a surfactant (e.g., polysorbate 20); and (v) a second amino acid (e.g., arginine). Specific, non-limiting exemplary embodiments encompassed by this aspect of the disclosure are set forth in Tables 3A, 3B, 3C, 3D, 3E and 3F. Formulations in Tables 3A and 3C are not in the scope of the claims. Formulations in the first four columns in Tables 3B, 3D, 3E, 3F are not in the scope of the claims.

Table 3A: Exemplary Pharmaceutical Formulations Comprising mAb1, Histidine, Sucrose, Polysorbate 20 and Arginine

mAb1 (mg/ml)	25	50	100	150	25	50	100	150	25	50	100	150
histidine (mM)	10	10	10	10	10	10	10	10	10	10	10	10
sucrose (%)	2	2	2	2	5	5	5	5	10	10	10	10

(continued)

polysorbate 20 (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
arginine (mM)	10	10	10	10	10	10	10	10	10	10	10	10

Table 3B: Exemplary Pharmaceutical Formulations Comprising mAb1, Histidine, Sucrose, Polysorbate 20 and Arginine

mAb1 (mg/ml)	25	50	100	150	25	50	100	150	25	50	100	150
histidine (mM)	10	10	10	10	10	10	10	10	10	10	10	10
sucrose (%)	2	2	2	2	5	5	5	5	10	10	10	10
polysorbate 20 (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
arginine (mM)	25	25	25	25	25	25	25	25	25	25	25	25

Table 3C: Exemplary Pharmaceutical Formulations Comprising mAb1, Histidine, Sucrose, Polysorbate 20 and Arginine

mAb1 (mg/ml)	25	50	100	150	25	50	100	150	25	50	100	150
histidine (mM)	25	25	25	25	25	25	25	25	25	25	25	25
sucrose (%)	2	2	2	2	5	5	5	5	10	10	10	10
polysorbate 20 (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
arginine (mM)	10	10	10	10	10	10	10	10	10	10	10	10

Table 3D: Exemplary Pharmaceutical Formulations Comprising mAb1, Histidine, Sucrose, Polysorbate 20 and Arginine

mAb1 (mg/ml)	25	50	100	150	25	50	100	150	25	50	100	150
histidine (mM)	25	25	25	25	25	25	25	25	25	25	25	25
sucrose (%)	2	2	2	2	5	5	5	5	10	10	10	10
polysorbate 20 (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
arginine (mM)	25	25	25	25	25	25	25	25	25	25	25	25

Table 3E: Exemplary Pharmaceutical Formulations Comprising mAb1, Histidine, Sucrose, Polysorbate 20 and Arginine

mAb1 (mg/ml)	25	50	100	150	25	50	100	150	25	50	100	150
histidine (mM)	25	25	25	25	25	25	25	25	25	25	25	25
sucrose (%)	2	2	2	2	5	5	5	5	10	10	10	10
polysorbate 20 (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
arginine (mM)	50	50	50	50	50	50	50	50	50	50	50	50

Table 3F: Exemplary Pharmaceutical Formulations Comprising mAb1, Histidine, Sucrose, Polysorbate 20 and Arginine

mAb1 (mg/ml)	160	170	175	180	160	170	175	180	160	170	175	180

(continued)

histidine (mM)	25	25	25	25	25	25	25	25	25	25	25	25
sucrose (%)	2	2	2	2	5	5	5	5	10	10	10	10
polysorbate 20 (%)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
arginine (mM)	50	50	50	50	50	50	50	50	50	50	50	50

[0032] Additional non-limiting examples of pharmaceutical formulations encompassed by the present disclosure are set forth elsewhere herein, including the working Examples presented below.

STABILITY AND VISCOSITY OF THE PHARMACEUTICAL FORMULATIONS

[0033] The pharmaceutical formulations of the present disclosure typically exhibit high levels of stability. The term "stable," as used herein in reference to the pharmaceutical formulations, means that the antibodies within the pharmaceutical formulations retain an acceptable degree of structure and/or function and/or biological activity after storage for a defined amount of time. A formulation may be stable even though the antibody contained therein does not maintain 100% of its structure and/or function and/or biological activity after storage for a defined amount of time. Under certain circumstances, maintenance of about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98% or about 99% of an antibody's structure and/or function and/or biological activity after storage for a defined amount of time may be regarded as "stable."

[0034] Stability can be measured, *inter alia,* by determining the percentage of native antibody remaining in the formulation after storage for a defined amount of time at a given temperature. The percentage of native antibody can be determined by, *inter alia,* size exclusion chromatography (*e.g.*, size exclusion high performance liquid chromatography [SE-HPLC]). An "acceptable degree of stability," as that phrase is used herein, means that at least 90% of the native form of the antibody can be detected in the formulation after storage for a defined amount of time at a given temperature. In certain embodiments, at least about 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% of the native form of the antibody can be detected in the formulation after storage for a defined amount of time at a given temperature. The defined amount of time after which stability is measured can be at least 1 month, at least 2 months, at least 3 months, at least 4 months, at least 5 months, at least 6 months, at least 7 months, at least 8 months, at least 9 months, at least 10 months, at least 11 months, at least 12 months, at least 18 months, at least 24 months, or more. The temperature at which the pharmaceutical formulation may be stored when assessing stability can be any temperature from about -80°C to about 45°C, *e.g.*, storage at about -30°C, about -20°C, about 0°C, about 5°C, about 25°C, or about 45°C. For example, a pharmaceutical formulation may be deemed stable if after 3 months of storage at 5°C, greater than about 90%, 95%, 96% or 97% of native antibody is detected by SE-HPLC. A pharmaceutical formulation may also be deemed stable if after 6 months of storage at 5°C, greater than about 90%, 95%, 96% or 97% of native antibody is detected by SE-HPLC. A pharmaceutical formulation may also be deemed stable if after 9 months of storage at 5°C, greater than about 90%, 95%, 96% or 97% of native antibody is detected by SE-HPLC. A pharmaceutical formulation may also be deemed stable if after 3 months of storage at 25°C, greater than about 90%, 95%, 96% or 97% of native antibody is detected by SE-HPLC. A pharmaceutical formulation may also be deemed stable if after 6 months of storage at 25°C, greater than about 90%, 95%, 96% or 97% of native antibody is detected by SE-HPLC. A pharmaceutical formulation may also be deemed stable if after 9 months of storage at 25°C, greater than about 90%, 95%, 96% or 97% of native antibody is detected by SE-HPLC.

[0035] Other methods may be used to assess the stability of the formulations of the present disclosure such as, *e.g.*, differential scanning calorimetry (DSC) to determine thermal stability, controlled agitation to determine mechanical stability, and absorbance at about 350 nm or about 405 nm to determine solution turbidities. For example, a formulation of the present disclosure may be considered stable if, after 6 or more months of storage at about 5°C to about 25°C, the change in OD_{405} of the formulation is less than about 0.05 (*e.g.*, 0.04, 0.03, 0.02, 0.01, or less) from the OD_{405} of the formulation at t=0.

[0036] Stability may also be assessed by measuring the biological activity and/or binding affinity of the antibody to its target. For example, a formulation of the present disclosure may be regarded as stable if, after storage at *e.g.*, 5°C, 25°C, 45°C, etc. for a defined amount of time (*e.g.*, 1 to 12 months), the anti-IL-6R antibody contained within the formulation binds to IL-6R with an affinity that is at least 50%, 60%, 70%, 80%, 90%, 95%, or more of the binding affinity of the antibody prior to said storage. Additional methods for assessing the stability of an antibody in formulation are demonstrated in the Examples presented below.

[0037] In the fluid form, the pharmaceutical formulations may, in certain embodiments, exhibit low to moderate levels of viscosity. "Viscosity" as used herein may be "kinematic viscosity" or "absolute viscosity." "Kinematic viscosity" is a

measure of the resistive flow of a fluid under the influence of gravity. When two fluids of equal volume are placed in identical capillary viscometers and allowed to flow by gravity, a viscous fluid takes longer than a less viscous fluid to flow through the capillary. For example, if one fluid takes 200 seconds to complete its flow and another fluid takes 400 seconds, the second fluid is twice as viscous as the first on a kinematic viscosity scale. "Absolute viscosity", sometimes called dynamic or simple viscosity, is the product of kinematic viscosity and fluid density (Absolute Viscosity = Kinematic Viscosity x Density). The dimension of kinematic viscosity is L^2/T where L is a length and T is a time. Commonly, kinematic viscosity is expressed in centistokes (cSt). The SI unit of kinematic viscosity is mm^2/s, which is 1 cSt. Absolute viscosity is expressed in units of centipoise (cP). The SI unit of absolute viscosity is the milliPascal-second (mPa-s), where 1 cP = 1 mPa-s.

[0038] As used herein, a low level of viscosity, in reference to a fluid formulation of the present disclosure, will exhibit an absolute viscosity of less than about 20 cPoise (cP). For example, a fluid formulation of the disclosure will be deemed to have "low viscosity," if, when measured using standard viscosity measurement techniques, the formulation exhibits an absolute viscosity of about 19 cP, about 18 cP, about 17 cP, about 16 cP, about 15 cP, about 14 cP, about 13 cP, about 12 cP, about 11 cP, about 10 cP, about 9 cP, about 8 cP, about 7 cP, about 6 cP, about 5 cP, about 4 cP, or less. As used herein, a moderate level of viscosity, in reference to a fluid formulation of the present disclosure, will exhibit an absolute viscosity of between about 30 cP and about 20 cP. For example, a fluid formulation of the disclosurewill be deemed to have "moderate viscosity," if when measured using standard viscosity measurement techniques, the formulation exhibits an absolute viscosity of about 30 cP, about 29 cP, about 28 cP, about 27 cP, about 26 cP, about 25 cP, about 24 cP, about 23 cP, about 22 cP, about 21 cP or about 20 cP.

[0039] As illustrated in Example 6 below, the present inventors have made the surprising discovery that low to moderate viscosity fluid formulations comprising high concentrations of an anti-hIL-6R antibody (*e.g.*, up to at least 175 mg/mL) can be obtained by formulating the antibody with 25 mM to 100 mM histidine and 25 mM to 50 mM arginine. In addition, it was further discovered that the viscosity of the formulation could be decreased to an even greater extent by adjusting the sucrose content to less than 10%.

CONTAINERS FOR THE PHARMACEUTICAL FORMULATIONS AND METHODS OF ADMINISTRATION

[0040] The pharmaceutical formulations disclosed herein may be contained within any container suitable for storage of medicines and other therapeutic compositions. For example, the pharmaceutical formulations may be contained within a sealed and sterilized plastic or glass container having a defined volume such as a vial, ampule, syringe, cartridge, or bottle. Different types of vials can be used to contain the formulations of the present disclosureincluding, *e.g.*, clear and opaque (*e.g.*, amber) glass or plastic vials. Likewise, any type of syringe can be used to contain and/or administer the pharmaceutical formulations of the present disclosure.

[0041] The pharmaceutical formulations may be contained within "normal tungsten" syringes or "low tungsten" syringes. As will be appreciated by persons of ordinary skill in the art, the process of making glass syringes generally involves the use of a hot tungsten rod which functions to pierce the glass thereby creating a hole from which liquids can be drawn and expelled from the syringe. This process results in the deposition of trace amounts of tungsten on the interior surface of the syringe. Subsequent washing and other processing steps can be used to reduce the amount of tungsten in the syringe. As used herein, the term "normal tungsten" means that the syringe contains greater than 500 parts per billion (ppb) of tungsten. The term "low tungsten" means that the syringe contains less than 500 ppb of tungsten. For example, a low tungsten syringe, according to the present disclosure, can contain less than about 490, 480, 470, 460, 450, 440, 430, 420, 410, 390, 350, 300, 250, 200, 150, 100, 90, 80, 70, 60, 50, 40, 30, 20, 10 or fewer ppb of tungsten.

[0042] The rubber plungers used in syringes, and the rubber stoppers used to close the openings of vials, may be coated to prevent contamination of the medicinal contents of the syringe or vial and/or to preserve their stability. Thus, pharmaceutical formulations of the present disclosure, according to certain embodiments, may be contained within a syringe that comprises a coated plunger, or within a vial that is sealed with a coated rubber stopper. For example, the plunger or stopper may be coated with a fluorocarbon film. Examples of coated stoppers and/or plungers suitable for use with vials and syringes containing the pharmaceutical formulations of the present disclosure are mentioned in, *e.g.,* U.S. Patent Nos. 4,997,423; 5,908,686; 6,286,699; 6,645,635; and 7,226,554. Particular exemplary coated rubber stoppers and plungers that can be used in the context of the present disclosure are commercially available under the tradename "FluroTec®," available from West Pharmaceutical Services, Inc. (Lionville, PA).

[0043] According to certain embodiments, the pharmaceutical formulations may be contained within a low tungsten syringe that comprises a fluorocarbon-coated plunger. As discussed in the Examples section below, the combination of a low tungsten syringe and a fluorocarbon-coated plunger was observed to yield surprising stability characteristics with regard to the pharmaceutical formulations of the present disclosure.

[0044] The pharmaceutical formulations can be administered to a patient by parenteral routes such as injection (*e.g.,* subcutaneous, intravenous, intramuscular, intraperitoneal, etc.) or percutaneous, mucosal, nasal, pulmonary and/or oral administration. Numerous reusable pen and/or autoinjector delivery devices can be used to subcutaneously deliver the

pharmaceutical formulations. Examples include, but are not limited to AUTOPEN™ (Owen Mumford, Inc., Woodstock, UK), DISETRONIC™ pen (Disetronic Medical Systems, Bergdorf, Switzerland), HUMALOG MIX 75/25™ pen, HUMALOG™ pen, HUMALIN 70/30™ pen (Eli Lilly and Co., Indianapolis, IN), NOVOPEN™ I, II and III (Novo Nordisk, Copenhagen, Denmark), NOVOPEN JUNIOR™ (Novo Nordisk, Copenhagen, Denmark), BD™ pen (Becton Dickinson, Franklin Lakes, NJ), OPTIPEN™, OPTIPEN PRO™, OPTIPEN STARLET™, and OPTICLIK™ (sanofi-aventis, Frankfurt, Germany), to name only a few. Examples of disposable pen and/or autoinjector delivery devices having applications in subcutaneous delivery of a pharmaceutical composition of the present disclosureinclude, but are not limited to the SOLOSTAR™ pen (sanofi-aventis), the FLEXPEN™ (Novo Nordisk), and the KWIKPEN™ (Eli Lilly), the SURECLICK™ Autoinjector (Amgen, Thousand Oaks, CA), the PENLET™ (Haselmeier, Stuttgart, Germany), the EPIPEN (Dey, L.P.), and the HUMIRA™ Pen (Abbott Labs, Abbott Park, IL), to name only a few.

[0045] The use of a microinfusor to deliver the pharmaceutical formulations is also contemplated herein. As used herein, the term "microinfusor" means a subcutaneous delivery device designed to slowly administer large volumes (*e.g.,* up to about 2.5 mL or more) of a therapeutic formulation over a prolonged period of time (*e.g.,* about 10, 15, 20, 25, 30 or more minutes). *See, e.g.,* U.S. 6,629,949; US 6,659,982; and Meehan et al., J. Controlled Release 46:107-116 (1996). Microinfusors are particularly useful for the delivery of large doses of therapeutic proteins contained within high concentration (*e.g.,* about 100, 125, 150, 175, 200 or more mg/mL) and/or viscous solutions.

THERAPEUTIC USES OF THE PHARMACEUTICAL FORMULATIONS

[0046] The pharmaceutical formulations of the present invention are useful, *inter alia,* for the treatment, prevention and/or amelioration of any disease or disorder associated with IL-6 activity, including diseases or disorders mediated by activation of the IL-6 receptor. Exemplary, non-limiting diseases and disorders that can be treated and/or prevented by the administration of the pharmaceutical formulations of the present invention include, *e.g.,* rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis, pancreatitis, juvenile idiopathic arthritis, vasculitis, Kawasaki disease, systemic lupus erythematosis, psoriasis, psoriatic arthritis, Sjogren syndrome, Still's disease, Castleman's disease, multiple sclerosis, diseases associated with abnormal blood coagulation or fibrinolysis (*e.g.*, thrombosis), cancer (*e.g.*, breast cancer, leukemia, ovarian cancer, melanoma, prostate cancer, pancreatic cancer, lymphoma, lung cancer, renal cell carcinoma, colorectal cancer, multiple myeloma, *etc.*), cachexia, chronic rejection of transplanted organs and cells, cardiopathy, viral infection (*e.g.*, HIV infection, EBV infection, etc.), plasmacytosis, hyperimmunoglobulinemia, anemia, nephritis, mesothelioma, and hearing loss and other inner ear disorders.

[0047] Thus, the present disclosureincludes methods of treating, preventing, and/or ameliorating any disease or disorder associated with IL-6 activity or IL-6R activation (including any of the above mentioned exemplary diseases, disorders and conditions). The therapeutic methods disclosed herein comprise administering to a subject any formulation comprising an anti-hIL-6R antibody as disclosed herein. The subject to which the pharmaceutical formulation is administered can be, *e.g.,* any human or non-human animal that is in need of such treatment, prevention and/or amelioration, or who would otherwise benefit from the inhibition or attenuation of IL-6 and/or IL-6R-mediated activity. For example, the subject can be an individual that is diagnosed with, or who is deemed to be at risk of being afflicted by any of the aforementioned diseases or disorders. The present disclosurefurther includes the use of any of the pharmaceutical formulations disclosed herein in the manufacture of a medicament for the treatment, prevention and/or amelioration of any disease or disorder associated with IL-6 activity or IL-6R activation (including any of the above mentioned exemplary diseases, disorders and conditions).

EXAMPLES

[0048] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the methods and compositions of the invention, and are not intended to limit the scope of what the inventors regard as their invention. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

Example 1. Stability of a Fully Human Anti-Human Interleukin-6 Receptor (IL-6R) Antibody ("mAb1") After Storage at Low Temperatures (reference example)

[0049] In this Example, various formulations were created containing an anti-human IL-6R antibody without excipients. The exemplary antibody used in this and all subsequent Examples set forth below is an antibody comprising a heavy chain variable region (HCVR) with the amino acid sequence of SEQ ID NO:18, and a light chain variable region (LCVR) with the amino acid sequence of SEQ ID NO:26. This antibody is referred to herein as "mAb1".

[0050] As a preliminary experiment, the stability of mAb1 in liquid solution was determined following various amounts of time in frozen storage at -20°C, -30°C and -80°C. The concentration of mAb1 used in this Example was 128 mg/mL. At various time points, the stability of mAb1 was determined by size exclusion high performance liquid chromatography (SE-HPLC) and by cation exchange high performance liquid chromatography (CEX-HPLC). Stability was assessed based on the percentage of native mAb1 remaining in the sample (by SE-HPLC; Table 4) and by the percentage of acidic species observed in the sample (by CEX-HPLC; Table 5) (An increase in percent acidic species is consistent with deamidation of the antibody and is thus considered an undesired phenomenon with respect to the pharmaceutical formulations of the present disclosure).

Table 4: % Native mAb1 Remaining (SE-HPLC)

	Storage Temperature		
Time (months)	-80°C	-30°C	-20°C
0	95.9	95.9	95.9
1	95.7	94.3	93.2
3	95.6	93.6	89.3
6	96.1	96.0	88.9
9	95.6	91.6	87.9

Table 5: % Acidic Species (CEX-HPLC)

	Storage Temperature		
Time (months)	-80°C	-30°C	-20°C
0	28.6	28.6	28.6
1	27.3	28.0	28.1
3	27.3	27.7	28.3
6	28.6	29.6	29.3
9	29.0	28.8	29.0

[0051] The results of Tables 3 and 4 are depicted in Figures 1 and 2, respectively. These results show that mAb1 can remain stable at a concentration of 128 mg/mL for at least 9 months when stored at -80°C.

Example 2. Stability of mAb1 Formulations Containing Minimal Excipients (reference example)

[0052] Eight different formulations containing mAb1 and minimal excipients as shown in Table 6 were prepared.

Table 6: mAb1 Minimal Excipient Formulations

Formulation	Excipient	mAb1 (mq/mL)
1	0.13% polysorbate 20 6% sucrose	80
2	0.13% polysorbate 20	80
3	1% sucrose	80
4	2% sucrose	80
5	4% sucrose	80
6	6% sucrose	80
7	none	80
8	none	65
All formulations contain 10 mM histidine, pH 6.0		

[0053] The formulations were tested for stability by SE-HPLC after various amounts of time at -30°C and -20°C. The results, expressed in percent of native mAb1 remaining, are shown in Tables 7 (-30°C storage) and 8 (-20°C).

Table 7: % Native mAb1 Remaining (SE-HPLC) After Storage at -30°C

	Formulation # (see Table 6)							
Time (months)	1	2	3	4	5	6	7	8
0	96.4	96.2	96.4	96.5	96.5	96.6	96.2	96.5
1	96.4	95.1	96.3	96.3	96.4	96.6	95.1	95.3
2	96.4	94.7	96.0	96.4	96.5	96.0	95.0	95.4
3	96.5	94.7	96.3	96.7	96.7	96.7	94.4	94.9
4	97.2	95.2	96.7	97.4	97.3	97.3	95.1	95.7
6	97.0	94.2	96.2	96.8	97.1	96.9	94.0	94.5
9	96.7	93.6	96.0	96.6	96.5	96.9	93.4	93.8

Table 8: % Native mAb1 Remaining (SE-HPLC) After Storage at -20°C

	Formulation # (see Table 6)							
Time (months)	1	2	3	4	5	6	7	8
0	96.4	96.2	96.4	96.5	96.5	96.6	96.2	96.5
1	96.7	94.5	96.0	96.8	96.5	96.3	94.1	94.5
2	96.4	90.9	95.3	96.4	96.4	96.4	90.9	91.8
3	96.9	90.1	95.1	96.6	96.6	96.7	90.5	90.9
4	97.2	90.7	95.8	97.4	97.1	97.1	91.4	91.8
6	96.9	86.9	94.1	96.9	96.9	97.1	87.5	88.5
9	96.5	86.0	93.3	96.6	96.6	96.7	86.7	87.5

[0054] The results of Tables 7 and 8 are depicted in Figures 3 and 4, respectively. As shown in this Example, the stability of mAb1 was maintained to a significant extent in formulations 1, 4, 5 and 6 after several months of storage at -20°C and -30°C. These results indicate that the stability of mAb1 at -20°C and -30°C can be enhanced by the addition of at least 2% sucrose.

Example 3. Stabilized Formulation of mAb1 (reference example)

[0055] A stabilized formulation containing various concentrations of mAb1 was prepared for use in Examples 4 and 5 below. This formulation, designated "Formulation **A**", is shown in Table 9.

Table 9: Stabilized mAb1 Formulation "A"

Component	Formulation A
mAb1	25 - 100 mg/mL
Histidine	10 mM
Polysorbate 20	0.2%
Sucrose	10%
pH adjusted to 6.0	

Example 4. Stability of Formulation A After Storage at 5°C

[0056] Formulation A (see Example 3) containing 25, 50 or 100 mg/mL mAb1 was tested for stability after several months of storage at 5°C in clear vials. Stability was assessed by the following parameters: (a) visual appearance; (b) turbidity (OD 405 nm); (c) pH; (d) percent total mAb1 recovered (as measured by RP-HPLC); (d) percent native mAb1 recovered (as measured by SE-HPLC); (e) percent main peak mAb1 recovered (as measured by CEX-HPLC); and (f) percent acidic species mAb1 recovered (as measured by CEX-HPLC). The stability results for Formulation A containing 25, 50 and 100 mg/mL of mAb1 are summarized in Tables 10, 11 and 12, respectively.

Table 10: Stability of Formulation A Containing 25 mg/mL mAb1 After Storage at 5°C in Clear Vials

Parameter	Length of 5°C Storage (months)						
	0	1	2	3	6	9	12
Visual Appearance	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Turbidity (OD 405 nm)	0.00	0.00	0.00	0.00	0.00	0.00	0.00
pH	6.0	6.1	6.1	6.1	6.1	6.1	6.1
% Total mAb1 Recovered	100	99	101	112	103	94	101
% Native mAb1 Recovered	97.5	98.0	97.5	97.6	97.5	97.5	97.8
% Main Peak mAb1 Recovered	58.4	57.9	58.7	58.1	57.9	57.9	58.4
% Acidic Species mAb1 Recovered	26.5	28.0	26.5	28.0	27.3	28.0	27.9

Table 11A: Stability of Formulation A Containing 50 mg/mL mAb1 After Storage at 5°C in Clear Vials (0-9 months)

Parameter	Length of 5°C Storage (months)					
	0	1	2	3	6	9
Visual Appearance	Pass	Pass	Pass	Pass	Pass	Pass
Turbidity (OD 405 nm)	0.00	0.00	0.00	0.00	0.00	0.00
pH	5.8	5.9	5.8	5.9	5.9	6.0
% Total mAb1 Recovered	100	99	104	106	100	109
% Native mAb1 Recovered	97.4	97.5	97.3	97.2	97.3	97.2
% Main Peak mAb1 Recovered	57.1	56.7	58.0	54.2	53.3	57.9
% Acidic Species mAb1 Recovered	27.6	26.7	27.6	28.5	26.8	26.9

Table 11B: Stability of Formulation A Containing 50 mg/mL mAb1 After Storage at 5°C in Clear Vials (12 - 24 months)

Parameter	Length of 5°C Storage (months)		
	12	18	24
Visual Appearance	Pass	Pass	Pass
Turbidity (OD 405 nm)	0.00	0.00	0.00
pH	5.9	6.0	5.9
% Total mAb1 Recovered	103	107	105
% Native mAb1 Recovered	97.1	97.1	96.9
% Main Peak mAb1 Recovered	56.4	57.1	56.4

(continued)

Parameter	Length of 5°C Storage (months)		
	12	18	24
% Acidic Species mAb1 Recovered	28.1	28.3	29.0

Table 12A: Stability of Formulation A Containing 100 mg/mL mAb1 After Storage at 5°C in Clear Vials (0 - 9 months)

Parameter	Length of 5°C Storage (months)					
	0	1	2	3	6	9
Visual Appearance	Pass	Pass	Pass	Pass	Pass	Pass
Turbidity (OD 405 nm)	0.00	0.00	0.00	0.00	0.00	0.00
pH	5.9	6.0	5.9	5.9	5.9	5.9
% Total mAb1 Recovered	100	99	100	107	101	106
% Native mAb1 Recovered	97.3	97.0	97.0	97.1	96.9	96.9
% Main Peak mAb1 Recovered	55.1	55.5	57.9	55.9	55.4	56.8
% Acidic Species mAb1 Recovered	27.6	26.9	27.4	29.6	27.4	27.4

Table 12B: Stability of Formulation A Containing 100 mg/mL mAb1 After Storage at 5°C in Clear Vials (12 - 24 months)

Parameter	Length of 5°C Storage (months)		
	12	18	24
Visual Appearance	Pass	Pass	Pass
Turbidity (OD 405 nm)	0.00	0.00	0.00
pH	6.0	6.0	6.0
% Total mAb1 Recovered	101	102	103
% Native mAb1 Recovered	96.8	96.7	96.5
% Main Peak mAb1 Recovered	57.3	57.5	56.7
% Acidic Species mAb1 Recovered	27.3	28.1	28.7

[0057] The results of this Example demonstrate that Formulation A containing 25, 50 or 100 mg/mL mAb1 remained stable after at least 9 months of storage, at 5°C in clear vials, with about 97% or more of native mAb1 remaining in all samples after 9 months of storage under such conditions. For the 50 and 100 mg/mL formulations, 96.9% and 96.5% of native mAb1, respectively, was detected after up to 24 months of storage at 5°C. In addition, the percent acidic species remained at 29% or lower for all time points analyzed, thus confirming the stability of the formulations.

[0058] Similar stability studies were also carried out using Formulation A containing 75 mg/mL mAb1 following storage at 2-8°C. No significant degradation was observed for any of the concentrations tested after 24 months of 2-8°C storage as determined by SE-HPLC and CEX-HPLC (data not shown).

Table 13: Stability of Formulation A Containing 25 mg/mL mAb1 After Storage at 5°C in 5 mL clear Vials

Parameter	Storage at 5°C (months)						
	t=0 0	1	2	3	6	9	12
Visual Appearance	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Turbidity (OD 405 nm)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
pH	6.0	6.0	6.0	6.0	6.0	6.0	6.1
% Total mAb1 Recovered	100	106	103	98	100	100	101
% Native mAb1 Recovered	97.1	97.0	96.9	96.9	97.0	96.4	96.6
% Main Peak mAb1 Recovered	57.8	56.8	56.2	54.2	56.4	56.4	56.8
% Acidic Species mAb1 Recovered	27.9	30.7	30.8	33.0	30.6	29.8	30.1

Example 5. Stability of Formulation A Manufactured in Clear and Amber Glass Vials

[0059] Additional experiments were conducted to compare the stability of Formulation A (see Example 3) containing 25 and 100 mg/mL mAb1 manufactured in amber glass vials to the same formulation manufactured in clear vials. Two types of amber vials were used in this Example: 5 mL and 20 mL amber vials. Stability was assessed following storage at 5°C, 25°C or 45°C based on the same parameters as used in Example 4. The results for the 25 mg/mL and 100 mg/mL formulations are summarized in Tables 13 through 21.

Table 14: Stability of Formulation A Containing 100 mg/mL mAb1 After Storage at 5°C in 5 mL Clear Vials

Parameter	Storage at 5°C (months)						
	t=0 0	1	2	3	6	9	12
Visual Appearance	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Turbidity (OD 405 nm)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
pH	6.0	6.1	6.0	6.1	6.0	6.1	6.1
% Total mAb1 Recovered	100	106	104	97	100	99	100
% Native mAb1 Recovered	96.2	96.3	96.1	96.0	95.9	95.5	95.4
% Main Peak mAb1 Recovered	57.6	57.3	57.9	55.5	56.2	56.4	55.4
% Acidic Species mAb1 Recovered	28.2	30.2	29.4	31.1	30.7	30.0	32.2

Table 15: Stability of Formulation A Containing 25 mg/mL mAb1 After Storage at 5°C in 5 mL Amber Vials

Parameter	Storage at 5°C (months)						
	t=0 0	1	2	3	6	9	12
Visual Appearance	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Turbidity (OD 405 nm)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
pH	6.0	6.0	6.0	6.0	6.0	6.0	6.0
% Total mAb1 Recovered	100	104	104	98	99	97	101
% Native mAb1 Recovered	97.1	97.4	96.8	96.7	96.7	96.1	96.3
% Main Peak mAb1 Recovered	57.8	56.4	56.3	56.1	55.7	55.9	55.2
% Acidic Species mAb1 Recovered	27.9	30.4	30.6	31.8	31.0	30.5	32.9

Table 16: Stability of Formulation A Containing 100 mg/mL mAb1 After Storage at 5°C in 5 mL Amber Vials

Parameter	Storage at 5°C (months)						
	0	1	2	3	6	9	12
Visual Appearance	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Turbidity (OD 405 nm)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
pH	6.0	6.0	6.0	6.0	6.0	6.0	6.1
% Total mAb1 Recovered	100	102	104	97	101	100	100
% Native mAb1 Recovered	96.2	95.0	96.0	96.0	95.8	95.0	95.3
% Main Peak mAb1 Recovered	57.6	56.9	58.0	55.6	56.3	56.5	55.1
% Acidic Species mAb1 Recovered	28.2	30.1	29.4	31.4	30.4	30.0	32.3

Table 17: Stability of Formulation A Containing 25 mg/mL mAb1 After Storage at 5°C in 20 mL Amber Vials

Parameter	Storage at 5°C (months)						
	0	1	2	3	6	9	12
Visual Appearance	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Turbidity (OD 405 nm)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
pH	6.0	6.0	6.0	6.0	6.0	6.0	6.0

Table 17, cont ...: Stability of Formulation A Containing 25 mg/mL mAb1 After Storage at 5°C in 20 mL Amber Vials

	Storage at 5°C (months)						
Parameter	0	1	2	3	6	9	12
% Total mAb1 Recovered	100	105	103	97	101	98	101
% Native mAb1 Recovered	97.1	96.9	97.0	96.8	97.0	96.2	96.6
% Main Peak mAb1 Recovered	57.8	56.4	57.1	55.9	55.6	56.1	55.2
% Acidic Species mAb1 Recovered	27.9	20.9	30.2	30.5	30.7	30.0	31.9

Table 18: Stability of Formulation A Containing 100 mg/mL mAb1 After Storage at 5°C in 20 mL Amber Vials

Parameter	Storage at 5°C months						
	0	1	2	3	6	9	12
Visual Appearance	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Turbidity (OD 405 nm)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
pH	6.0	6.0	6.0	6.0	6.0	6.0	6.0
% Total mAb1 Recovered	100	105	103	97	99	98	100
% Native mAb1 Recovered	96.2	96.2	96.0	96.0	95.8	95.4	95.5

(continued)

Parameter	Storage at 5°C months 0	1	2	3	6	9	12
% Main Peak mAb1 Recovered	57.6	57.9	56.3	56.5	56.5	56.4	55.3
% Acidic Species mAb1 Recovered	28.2	29.8	30.4	30.3	30.6	30.0	30.9

Table 19: Stability of Formulation A Containing 100 mg/mL mAb1 After Storage at 25°C and 45°C in Clear Vials

Parameter	0	Storage at 45°C (days) 7	14	28	Storage at 25°C (months) 1	2	3	6
Visual Appearance	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Turbidity (OD 405 nm)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
pH	6.0	6.1	6.1	6.1	6.1	6.1	6.1	6.1
% Total mAb1 Recovered	100	101	97	105	105	102	97	101
% Native mAb1 Recovered	95.6	94.8	93.8	91.2	94.6	93.7	93.1	93.4
% Main Peak mAb1 Recovered	57.6	45.7	34.9	22.3	53.1	49.0	43.0	37.9
% Acidic Species mAb1 Recovered	28.2	37.3	49.8	70.8	32.5	36.8	42.4	53.8

Table 20: Stability of Formulation A Containing 100 mg/mL mAb1 After Storage at 25°C and 45°C in 5 mL Amber Vials

Parameter	t=0 0	Storage at 45°C (days) 7	14	28	Storage at 25°C (months) 1	2	3	6
Visual Appearance	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Turbidity (OD 405 nm)	0.00	0.00	0.01	0.02	0.00	0.00	0.01	0.02
pH	6.0	6.1	6.1	6.1	6.1	6.1	6.1	6.0
% Total mAb1 Recovered	100	101	100	105	106	103	97	100
% Native mAb1 Recovered	95.6	94.6	93.6	90.9	94.5	93.7	93.4	92.7
% Main Peak mAb1 Recovered	57.6	46.1	35.2	21.6	52.7	46.3	42.0	34.2
% Acidic Species mAb1 Recovered	28.2	37.3	50.1	70.9	32.8	39.6	43.4	57.3

Table 21: Stability of Formulation A Containing 100 mg/mL mAb1 After Storage at 25°C and 45°C in 20 mL Amber Vials

	t=0	Storage at 45°C (days)			Storage at 25°C months			
Parameter	0	7	14	28	1	2	3	6
Visual Appearance	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Turbidity (OD 405 nm)	0.00	0.01	0.00	0.02	0.00	0.01	0.00	0.02
pH	6.0	6.0	6.1	6.1	6.0	6.0	6.0	6.0
% Total mAb1 Recovered	100	101	101	105	104	103	96	100
% Native mAb1 Recovered	95.6	94.9	93.8	91.5	94.3	94.0	93.6	93.5
% Main Peak mAb1 Recovered	57.6	45.7	34.2	23.3	52.7	49.3	43.5	36.7
% Acidic Species mAb1 Recovered	28.2	36.7	51.1	68.6	32.5	35.8	41.3	55.0

[0060] As shown in this Example, Formulation A containing 25 mg/mL or 100 mg/mL mAb1 exhibited equivalent stability profiles when stored in either clear or amber vials. Moreover, as demonstrated in Example 4 for storage in clear vials, relatively high stability of mAb1 was maintained in Formulation A when stored in either clear or amber vials at 5°C for up to 12 months.

Example 6. Effect of Arginine, Histidine and Sucrose Concentrations on Viscosity and Stability of Formulations Containing 150 mg/mL mAb1

[0061] Several formulations were prepared containing 150 mg/mL, 175 mg/mL and 200 mg/mL mAb1 and various quantities of histidine, arginine and sucrose. Viscosity and osmolality were measured for each formulation. Additionally, the stability of the 150 mg/mL formulations after 4 weeks of storage at 45°C was assessed in terms of percent native mAb1 remaining (by SE-HPLC) and percent main peak remaining (by CEX-HPLC). The results are summarized in Table 22 (reference examples).

Table 22: Effect of Arginine, Histidine and Sucrose on Viscosity and Stability of mAb1 Formulations

mAb1 (mq/mL)	[Histidine] (mM)	[Arginine] (mM)	[Sucrose] (%)	Viscosity (cPoise)	Osmolality (mOsm)	% native mAb1 remaining*	% acidic species
150	10	0	10	~ 15	375	90.8	19.9
150	25	25	10	~ 11.5	500	91.6	19.5
150	25	25	5	~ 8.5	305	91.8	19.8
150	25	25	2.5	~ 8.0	220	91.1	19.9
150	25	25	0	~ 8.5	115	90.3	20.6
175	10	0	10	~ 27	395		
175	25	25	10	~ 20.5	415		
175	25	25	5	~ 19	300		
175	25	50	5	~ 14.5	390		
175	100	0	5	~ 12.5	415		

(continued)

mAb1 (mq/mL)	[Histidine] (mM)	[Arginine] (mM)	[Sucrose] (%)	Viscosity (cPoise)	Osmolality (mOsm)	% native mAb1 remaining*	% acidic species
175	100	50	5	~ 10	515		
200	10	0	10	~ 44	410		
200	25	25	10	~ 35	480		
200	25	25	5	~ 30	300		
200	25	25	0	~ 28	130		
200	100	0	10	~ 27	570		
200	100	50	10	~ 21	670		
* Initial % native mAb1 = 96.5% (SE-HPLC)							

[0062] The results presented in Table 16 indicate that increasing the histidine concentration to 25 mM or 100 mM and adding arginine to the formulation (25 mM or 50 mM) significantly reduced the viscosity of the formulation as compared to formulations containing only 10 mM histidine and no arginine. Furthermore, reducing the sucrose concentration from 10% to 5% with the added histidine and arginine decreased the viscosity of the formulation to an even greater extent.

[0063] Based at least in part on the foregoing, the following Formulations (designated "Formulation B" and "Formulation C") set forth in Table 23 were prepared.

Table 23: Stabilized mAb1 Formulations "B" and "C"

Component	Formulation B	Formulation C
mAb1	25 - 200 mg/mL	25 - 200 mg/mL
Histidine	25 mM	25 mM
Polysorbate 20	0.2%	0.2%
Sucrose	5%	5%
Arginine	25 mM	50 mM
pH adjusted to 6.0		

Example 7. Stability of Formulation B Containing 150 mg/mL mAb1 When Manufactured in a Vial and Syringes

[0064] Formulation B (see Table 23) containing 150 mg/mL mAb1 was prepared in a 2 mL glass vial and in two different syringes: regular and low tungsten. The preparations were stored at 5, 25 and 45°C for various amounts of time. The stability of mAb1 following storage was measured by SE-HPLC and CEX-HPLC. The results are shown in Table 24. (An increase in percent acidic species is consistent with deamidation of the antibody and is thus considered an undesired phenomenon with respect to the pharmaceutical formulations of the present disclosure).

Table 24: Stability of Formulation B Containing 150 mg/mL mAb1 in Vial and Syringe

		2 mL Glass Vial		Regular Syringe		Low Tungsten Syringe	
Temp	Time	% Native (SE-HPLC)	% Acidic (CEX-HPLC)	% Native (SE-HPLC)	% Acidic (CEX-HPLC)	% Native (SE-HPLC)	% Acidic (CEX-HPLC)
-	Start	96.7	32.2	96.5	32.3	96.7	31.7
45°C	14 days	94.1	52.7	94.3	54.5	94.3	56.1
45°C	28 days	92.7	69.7	92.7	69.7	92.5	70.8

(continued)

		2 mL Glass Vial		Regular Syringe		Low Tungsten Syringe	
Temp	Time	% Native (SE-HPLC)	% Acidic (CEX-HPLC)	% Native (SE-HPLC)	% Acidic (CEX-HPLC)	% Native (SE-HPLC)	% Acidic (CEX-HPLC)
45°C	56 days	86.7	84.7	87.8	82.6	86.9	83.5
25°C	1 month	95.1	31.2	95.7	30.6	95.6	31.1
25°C	2 month	95.3	34.6	94.7	37.4	96.0	36.3
25°C	3 month	94.3	40.6	93.9	43.7	94.1	42.6
5°C	1 month	96.2	30.2	96.5	29.1	96.4	29.3
5°C	2 month	96.3	29.3	96.4	29.0	96.4	29.1
5°C	3 month	95.7	29.4	95.8	29.6	95.8	29.6

[0065] As shown in this table, Formulation B containing 150 mg/mL mAb1, stored at 5°C in a glass vial or syringe, remained relatively stable for at least 3 months.

Example 8: Stability of mAb1 Formulations in Prefilled Syringes

[0066] A series of experiments was carried out to assess the stability of different mAb1 formulations in prefilled syringes. For these experiments various luer and staked needle, regular-tungsten and low-tungsten syringes were used in combination with different types of plungers (coated and uncoated) and tip-caps. The formulations were tested for stability after storage in prefilled syringes at 45°C, 25°C and 5°C for various amounts of time (ranging from 14 days to 12 months, depending on the conditions tested).

[0067] Six different formulations of mAb1 were tested for stability in prefilled syringes in this Example: (1) Formulation A (see Table 9) containing 100 mg/mL mAb1; (2) Formulation A (see Table 9) containing 25 mg/mL mAb1; (3) Formulation B (see Table 23) containing 150 mg/mL mAb1; (4) Formulation B (see Table 23) containing 25 mg/mL mAb1; (5) Formulation C (see Table 23) containing 175 mg/mL of mAb1; and (6) Formulation C (see Table 23) containing 25 mg/mL of mAb1. Formulation A is not in the scope of the claims.

[0068] Stability was assessed by the following parameters: (a) visual analysis; (b) turbidity (OD_{405nm}); (c) percent recovery by RP-HPLC; (d) percent native mAb1 by SE-HPLC; (e) percent main peak mAb1 by CEX-HPLC; and (f) percent acidic species by CEX-HPLC.

[0069] The results from a representative experiment assessing the stability of Formulation A, containing 100 mg/mL mAb1 in two different syringes (Syringe #1 and Syringe #2) are shown in Tables 25 and 26 below.

Table 25: Stability of Formulation A containing 100 mg/mL mAb1 in Staked Needle Prefilled Syringe #1

Syringe #1 Description:							
Syringe:		BD 1 mL long 29ga x 1/2" Physiolis, Low Tungsten					
Plunger:		West FluroTec® 4023/50					
Tip Cap:		BD 260					
Siliconization:		Sprayed					
Temp	**Time**	Visual Analysis	Turbidity ($OD_{405\ nm}$)	% Recovery	% Native mAb1	% Main Peak	% Acidic Species
--	Start	Pass	0.00	100	96.6	56.9	28.7

(continued)

Temp	Time	Visual Analysis	Turbidity ($OD_{405\ nm}$)	% Recovery	% Native mAb1	% Main Peak	% Acidic Species
45°C	14 days	Pass	0.00	99	95.1	32.7	50.7
45°C	28 days	Pass	0.01	103	92.6	20.9	66.1
45°C	56 days	Pass	0.03	105	88.8	9.9	80.9
25°C	1 month	Pass	0.00	106	95.6	52.4	32.0
25°C	2 months	Pass	0.00	107	95.2	48.0	37.0
25°C	3 months	Pass	0.00	106	94.2	44.8	41.8
25°C	6 months	Pass	0.01	101	93.7	34.8	53.9
25°C	9 months	Pass	0.03	98	91.4	26.1	64.6
25°C	12 months	Pass	0.03	101	89.9	21.3	69.4

Table 25 cont...: Stability of Formulation A containing 100 mg/mL mAb1 in Staked Needle Prefilled Syringe #1

Syringe #1 Description:							
Syringe:		BD 1 mL long 29ga x 1/2" Physiolis, Low Tungsten					
Plunger:		West FluroTec® 4023/50					
Tip Cap:		BD 260					
Siliconization:		Sprayed					
5°C	1 month	Pass	0.00	110	96.4	56.8	29.9
5°C	2 months	Pass	0.00	108	96.2	55.7	31.1
5°C	3 months	Pass	0.00	104	96.0	56.3	30.0
5°C	6 months	Pass	0.00	100	96.5	55.0	31.3
5°C	9 months	Pass	0.00	98	96.2	56.7	30.3
5°C	12 months	Pass	0.00	101	95.4	57.3	30.2

Table 26: Stability of Formulation A containing 100 mg/mL mAb1 in Staked Needle Prefilled Syringe #2

Syringe #2 Description:							
Syringe:		Schott 1 mL Long SN CF 29ga x 1/2"					
Plunger:		West FluroTec® 4023/50					
Tip Cap:		Stelmi 4800 w/RNS					
Siliconization:		Sprayed					
Temp	**Time**	Visual Analysis	Turbidity ($OD_{405\ nm}$)	% Recovery	% Native mAb1	% Main Peak	% Acidic Species
--	Start	Pass	0.00	100	96.3	57.5	28.0
45°C	14 days	Pass	0.00	100	95.2	33.7	49.6

(continued)

Temp	Time	Visual Analysis	Turbidity ($OD_{405\ nm}$)	% Recovery	% Native mAb1	% Main Peak	% Acidic Species
45°C	28 days	Pass	0.00	103	93.3	22.8	64.7
45°C	56 days	Pass	0.03	107	88.0	9.9	81.1
25°C	1 month	Pass	0.00	108	95.5	52.5	31.8
25°C	2 months	Pass	0.00	107	95.2	49.2	35.7
25°C	3 months	Fail	0.00	106	93.9	43.1	42.0
25°C	6 months	Fail	0.00	102	92.9	34.4	54.0
25°C	9 months	Pass	0.02	100	92.3	26.9	63.5
25°C	12 months	Pass	0.03	103	90.0	20.0	70.2
5°C	1 month	Pass	0.00	111	96.3	56.7	29.9
5°C	2 months	Pass	0.00	112	95.6	55.9	31.1
5°C	3 months	Pass	0.00	106	96.1	57.2	29.4
5°C	6 months	Pass	0.00	102	96.0	54.9	31.6
5°C	9 months	Pass	0.00	100	95.9	56.7	30.2
5°C	12 months	Pass	0.00	102	95.4	56.0	30.7

[0070] The results from another representative experiment assessing the stability of Formulation C, containing 175 mg/mL mAb1 in two different syringes (Syringe #1 and Syringe #3) are shown in Tables 27 and 28 below.

[0071] The results from this set of experiments demonstrate that the different formulations remain relatively stable in prefilled syringes, especially when stored at temperatures of 25°C and below, for one month or greater. Moreover, the various formulations disclosed herein appeared to have enhanced stability when contained in low tungsten syringes containing fluorocarbon-coated plungers.

Table 27: Stability of Formulation C containing 175 mg/mL mAb1 in Staked Needle Prefilled Syringe #1

Syringe #1 Description:							
Syringe:	BD 1 mL long 29ga x 1/2" Physiolis, Low Tungsten						
Plunger:	West FluroTec® 4023/50						
Tip Cap:	BD 260						
Siliconization:	Sprayed						
Temp	**Time**	Visual Analysis	Turbidity ($OD_{405\ nm}$)	% Recovery	% Native mAb1	% Main Peak	% Acidic Species
--	Start	Pass	0.00	100	96.7	59.7	32.4
45°C	7 days	Pass	0.01	102	96.1	48.6	39.5
45°C	14 days	Pass	0.03	97	95.0	36.9	50.0

(continued)

Temp	Time	Visual Analysis	Turbidity ($OD_{405\ nm}$)	% Recovery	% Native mAb1	% Main Peak	% Acidic Species
45°C	28 days	Pass	0.03	98	91.9	24.7	66.0
45°C	56 days	Pass	0.05	97	91.9	12.3	83.3
25°C	1 month	Pass	0.02	99	95.4	56.9	33.8
25°C	2 months	Pass	0.00	100	95.0	51.1	39.8
5°C	1 month	Pass	0.00	98	96.1	59.5	32.7
5°C	2 months	Pass	0.00	101	96.4	56.3	37.1

Table 28: Stability of Formulation C containing 175 mg/mL mAb1 in Staked Needle Prefilled Syringe #3

Syringe #1 Description:	
Syringe:	Daikyo Seiko CZ 1 mL std 30ga x 1/2 "
Plunger:	Daikyo D-21-6-1 FluroTec® Coated
Tip Cap:	7028
Siliconization:	N/A

Temp	Time	Visual Analysis	Turbidity ($OD_{405\ nm}$)	% Recovery	% Native mAb1	% Main Peak	% Acidic Species
--	Start	Pass	0.00	100	96.4	58.2	33.6
45°C	7 days	Pass	0.00	101	95.7	45.4	40.4
45°C	14 days	Pass	0.01	101	94.8	37.5	48.8
45°C	28 days	Pass	0.04	96	94.0	29.4	59.4
45°C	56 days	Pass	0.06	99	85.9	7.8	87.0
25°C	1 month	N/D	N/D	N/D	N/D	N/D	N/D
5°C	1 month	Pass	0.00	100	96.4	56.7	34.0
5°C	2 months	Pass	0.00	101	96.2	54.7	34.0

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Tyr Gly Ala Ser Thr Arg Ala Thr Gly Ile Pro Ala Arg Phe Ser Gly
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Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Ser
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    50                  55                  60
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gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120
gggaaagccc ctaagctcct gatctatggt gcatccagtt tggaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caagttatta ttgtcaacag gctaacagtt tcccgtacac ttttggccag 300
gggaccaagc tggagatcaa ac 322

<210> 26
<211> 107
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 26

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Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Val Ser Ala Ser Val Gly
 1               5                  10                  15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Gly Ile Ser Ser Trp
            20                  25                  30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
        35                  40                  45
Tyr Gly Ala Ser Ser Leu Glu Ser Gly Val Pro Ser Arg Phe Ser Gly
    50                  55                  60
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65                  70                  75                  80
Glu Asp Phe Ala Ser Tyr Tyr Cys Gln Gln Ala Asn Ser Phe Pro Tyr
                85                  90                  95
Thr Phe Gly Gln Gly Thr Lys Leu Glu Ile Lys
            100                 105
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<210> 27
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 27
cagggtatta gcagctgg 18

<210> 28
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 28

```
Gln Gly Ile Ser Ser Trp
 1               5
```

<210> 29
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 29
ggtgcatcc 9

<210> 30
<211> 3
<212> PRT

<213> Artificial Sequence

<220>
<223> Synthetic

<400> 30

Gly Ala Ser
1

<210> 31
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 31
caacaggcta acagtttccc gtacact 27

<210> 32
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 32

Gln Gln Ala Asn Ser Phe Pro Tyr Thr
1 5

<210> 33
<211> 349
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 33

gaagtgcagc tggtggagtc tgggggaggc ttggtacagc ctggcaggtc cctgagactc 60
tcctgtgcag cctctggatt cacctttgat gattatgccc tgcactgggt ccggcaagct 120
ccagggaagg gcctggagtg ggtctcaggt gttagttgga atggtggtag aataggctat 180
gcggactctg tgaaaggccg attcaccatc tccagagaca acgccaagaa ctccctcttt 240
ctgcaaatga acagtctgag agttgaggac acggccttgt attattgtgc aaaaggccgg 300

gatgcttttg atatctgggg ccaagggaca ttggtcaccg tctcttcag 349

<210> 34

<211> 116
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 34

```
Glu Val Gln Leu Val Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Arg
 1               5                  10                  15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Asp Asp Tyr
            20                  25                  30
Ala Leu His Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
        35                  40                  45
Ser Gly Val Ser Trp Asn Gly Gly Arg Ile Gly Tyr Ala Asp Ser Val
    50                  55                  60
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ala Lys Asn Ser Leu Phe
65                  70                  75                  80
Leu Gln Met Asn Ser Leu Arg Val Glu Asp Thr Ala Leu Tyr Tyr Cys
                85                  90                  95
Ala Lys Gly Arg Asp Ala Phe Asp Ile Trp Gly Gln Gly Thr Leu Val
            100                 105                 110
Thr Val Ser Ser
        115
```

<210> 35
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 35
ggattcacct ttgatgatta tgcc 24

<210> 36
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 36

```
Gly Phe Thr Phe Asp Asp Tyr Ala
 1               5
```

<210> 37
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 37
gttagttgga atggtggtag aata 24

<210> 38
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 38

Val Ser Trp Asn Gly Gly Arg Ile
1 5

<210> 39
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 39
gcaaaaggcc gggatgcttt tgatatc 27

<210> 40
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 40

Ala Lys Gly Arg Asp Ala Phe Asp Ile
1 5

<210> 41
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 41

gacatccaga tgacccagtc tccatcttcc gtgtctgcat ctgtaggaga cagagtcacc 60
atcacttgtc gggcgagtca gggtattagc agctggttag cctggtatca gcagaaacca 120
gggaaagccc ctaaactcct gatctatgct gcatccagtt tgcaaagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagat ttcactctca ccatcagcag cctgcagcct 240
gaagattttg caacttacta ttgtcaacat gcttacagtt tcccgtacac ttttggccag 300
gggaccaagc tggagatcaa ac 322

<210> 42
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 42

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Val	Ser	Ala	Ser	Val	Gly
1				5				10					15		
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Gly	Ile	Ser	Ser	Trp
			20					25					30		
Leu	Ala	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
		35					40					45			
Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
	50					55					60				
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65					70					75					80
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	His	Ala	Tyr	Ser	Phe	Pro	Tyr
				85					90					95	
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Leu	Glu	Ile	Lys					
			100					105							

<210> 43
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 43
cagggtatta gcagctgg 18

<210> 44
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 44

Gln	Gly	Ile	Ser	Ser	Trp
1				5	

<210> 45

<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 45
gctgcatcc 9

<210> 46
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 46

Ala Ala Ser
1

<210> 47
<211> 27
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 47
caacatgctt acagtttccc gtacact 27

<210> 48
<211> 9
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 48

Gln His Ala Tyr Ser Phe Pro Tyr Thr
1 5

<210> 49
<211> 361
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 49

caggtgcagc tggtgcagtc tggggctgag gtgaaagagc ctggggcctc agtgaaggtc 60
tcctgcaagg cttctggata caccttcacc tcttatgata tcatctgggt gcgacaggcc 120
actggacaag ggcttgagtg gatgggatgg atgaacccaa acagtggtaa cacaggctat 180
acacagaacc tccagggcag agtcaccttg accaggaaca cctccataac tacagtctac 240
atggaactga gcagcctgag ctctgaggac acggccgttt attactgtgc gcgagactac 300
agtagccact actacggttt ggacgtctgg ggccaaggga ccacggtcac cgtctcctca 360
a 361

<210> 50
<211> 120
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 50

Gln Val Gln Leu Val Gln Ser Gly Ala Glu Val Lys Glu Pro Gly Ala
1 5 10 15
Ser Val Lys Val Ser Cys Lys Ala Ser Gly Tyr Thr Phe Thr Ser Tyr
20 25 30
Asp Ile Ile Trp Val Arg Gln Ala Thr Gly Gln Gly Leu Glu Trp Met
35 40 45
Gly Trp Met Asn Pro Asn Ser Gly Asn Thr Gly Tyr Thr Gln Asn Leu
50 55 60

Gln Gly Arg Val Thr Leu Thr Arg Asn Thr Ser Ile Thr Thr Val Tyr
65 70 75 80
Met Glu Leu Ser Ser Leu Ser Ser Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95
Ala Arg Asp Tyr Ser Ser His Tyr Tyr Gly Leu Asp Val Trp Gly Gln
100 105 110
Gly Thr Thr Val Thr Val Ser Ser
115 120

<210> 51
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 51
ggatacacct tcacctctta tgat 24

<210> 52
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 52

Gly Tyr Thr Phe Thr Ser Tyr Asp
1 5

<210> 53
<211> 24
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 53
atgaacccaa acagtggtaa caca 24

<210> 54
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 54

Met Asn Pro Asn Ser Gly Asn Thr
1 5

<210> 55
<211> 39
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 55
gcgcgagact acagtagcca ctactacggt ttggacgtc 39

<210> 56
<211> 13
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 56

Ala Arg Asp Tyr Ser Ser His Tyr Tyr Gly Leu Asp Val
1 5 10

<210> 57
<211> 322
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 57

gacatccagt tgacccagtc tccatccttc ctgtctacat ctataggaga cagagtcacc 60
atcacttgct gggccagtca ggacattagc aattatttag cctggtatca gcaaaaacca 120
gggaaagccc ctaagctcct gatctttgtt gcatccactt tgcagagtgg ggtcccatca 180
aggttcagcg gcagtggatc tgggacagaa ttcactctca caatcagtag cctgcagcct 240
gaggattttg caacttatta ctgtcaacag tttaatagtt acccgctcac tttcggcgga 300
gggaccaagg tggaaatcaa ac 322

<210> 58
<211> 107
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 58

Asp Ile Gln Leu Thr Gln Ser Pro Ser Phe Leu Ser Thr Ser Ile Gly
1 5 10 15
Asp Arg Val Thr Ile Thr Cys Trp Ala Ser Gln Asp Ile Ser Asn Tyr
20 25 30
Leu Ala Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45
Phe Val Ala Ser Thr Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60
Ser Gly Ser Gly Thr Glu Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Phe Asn Ser Tyr Pro Leu
85 90 95
Thr Phe Gly Gly Gly Thr Lys Val Glu Ile Lys
100 105

<210> 59
<211> 18
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 59
caggacatta gcaattat 18

<210> 60
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 60

Gln Asp Ile Ser Asn Tyr
1 5

<210> 61
<211> 9
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 61
gttgcatcc 9

<210> 62
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 62

Val Ala Ser
1

<210> 63
<211> 30
<212> DNA
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 63
caacagttta atagttaccc gctcactttc 30

<210> 64
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 64

Gln Gln Phe Asn Ser Tyr Pro Leu Thr Phe
1 5 10

<210> 65
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> VARIANT
<222> (1)...(1)
<223> Xaa = Gly or Arg

<220>
<221> VARIANT
<222> (2)...(2)
<223> Xaa = Phe or Tyr

<220>
<221> VARIANT
<222> (3)...(3)
<223> Xaa = Ile or Thr

<220>
<221> VARIANT
<222> (4)...(4)
<223> Xaa = Phe

<220>
<221> VARIANT
<222> (5)...(5)
<223> Xaa = Asp or Thr

<220>
<221> VARIANT
<222> (6)...(6)
<223> Xaa = Asp or Ser

<220>
<221> VARIANT
<222> (7)...(7)
<223> Xaa = Tyr

<220>
<221> VARIANT
<222> (8)...(8)
<223> Xaa = Ala or Asp

<400> 65

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 66
<211> 8
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>

<221> VARIANT
<222> (1)...(1)
<223> Xaa = Ile, Val or Met

<220>
<221> VARIANT
<222> (2)...(2)
<223> Xaa = Ser or Asn

<220>
<221> VARIANT
<222> (3)...(3)
<223> Xaa = Thr or Pro

<220>
<221> VARIANT
<222> (4)...(4)
<223> Xaa = Asn

<220>
<221> VARIANT
<222> (5)...(5)
<223> Xaa = Ser or Gly

<220>
<221> VARIANT
<222> (6)...(6)
<223> Xaa = Gly

<220>
<221> VARIANT
<222> (7)...(7)
<223> Xaa = Ser, Arg or Asn

<220>
<221> VARIANT
<222> (8)...(8)
<223> Xaa = Ile or Thr

<400> 66

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 67
<211> 19
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> VARIANT
<222> (1)...(1)
<223> Xaa = Ala

<220>
<221> VARIANT
<222> (2)...(2)
<223> Xaa = Lys or Arg

<220>
<221> VARIANT
<222> (3)...(3)
<223> Xaa = Asp or Gly

<220>
<221> VARIANT
<222> (4)...(4)
<223> Xaa = Gly, Arg or Tyr

<220>
<221> VARIANT
<222> (5)...(5)
<223> Xaa = Gly, Asp or Ser

<220>
<221> VARIANT
<222> (6)...(6)
<223> Xaa = Ser or Ala

<220>
<221> VARIANT
<222> (7)...(7)
<223> Xaa = Ser, Phe or His

<220>
<221> VARIANT
<222> (8)...(8)
<223> Xaa = Trp, Asp or Tyr

<220>
<221> VARIANT
<222> (9)...(9)
<223> Xaa = Leu, Ile or Tyr

<220>
<221> VARIANT
<222> (10)...(10)
<223> Xaa = Pro, Gly or absent

<220>
<221> VARIANT
<222> (11)...(11)
<223> Xaa = Phe, Leu or absent

<220>
<221> VARIANT
<222> (12)...(12)
<223> Xaa = Val, Asp or absent

<220>
<221> VARIANT
<222> (13)...(13)

<223> Xaa = Tyr, Val or absent

<220>
<221> VARIANT
<222> (14)...(14)
<223> Xaa = Tyr or absent

<220>
<221> VARIANT
<222> (15)...(15)
<223> Xaa = Tyr or absent

<220>
<221> VARIANT
<222> (16)...(16)
<223> Xaa = Gly or absent

<220>
<221> VARIANT
<222> (17)...(17)
<223> Xaa = Met or absent

<220>
<221> VARIANT
<222> (18)...(18)
<223> Xaa = Asp or absent

<220>
<221> VARIANT
<222> (19)...(19)
<223> Xaa = Val or absent

<400> 67

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1               5                  10                  15
Xaa Xaa Xaa
```

<210> 68
<211> 6
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> VARIANT
<222> (1)...(1)
<223> Xaa = Gln

<220>
<221> VARIANT
<222> (2)...(2)
<223> Xaa = Ser, Gly or Asp

<220>
<221> VARIANT

<222> (3)...(3)
<223> Xaa = Ile

<220>
<221> VARIANT
<222> (4)...(4)
<223> Xaa = Ser

<220>
<221> VARIANT
<222> (5)...(5)
<223> Xaa = Ser or Asn

<220>
<221> VARIANT
<222> (6)...(6)
<223> Xaa = Asn, Trp or Tyr

<400> 68

Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> 69
<211> 3
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> VARIANT
<222> (1)...(1)
<223> Xaa = Gly, Ala or Val

<220>
<221> VARIANT
<222> (2)...(2)
<223> Xaa = Ala

<220>
<221> VARIANT
<222> (3)...(3)
<223> Xaa = Ser

<400> 69

Xaa Xaa Xaa
1

<210> 70
<211> 10
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<220>
<221> VARIANT
<222> (1)...(1)
<223> Xaa = Gln

<220>
<221> VARIANT
<222> (2)...(2)
<223> Xaa = Gln or His

<220>
<221> VARIANT
<222> (3)...(3)
<223> Xaa = Tyr, Ala or Phe

<220>
<221> VARIANT
<222> (4)...(4)
<223> Xaa = Ser, Asn or Tyr

<220>
<221> VARIANT
<222> (5)...(5)
<223> Xaa = Ser

<220>
<221> VARIANT
<222> (6)...(6)
<223> Xaa = Trp, Phe or Tyr

<220>
<221> VARIANT
<222> (7)...(7)
<223> Xaa = Pro

<220>
<221> VARIANT
<222> (8)...(8)
<223> Xaa = Pro, Tyr or Leu

<220>
<221> VARIANT
<222> (9)...(9)
<223> Xaa = Tyr or Thr

<220>
<221> VARIANT
<222> (10)...(10)
<223> Xaa = Thr or absent

<400> 70

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5 10

<210> 71
<211> 330
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 71

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Ser Ser Lys
 1               5                  10                  15
Ser Thr Ser Gly Gly Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Gln Thr
65                  70                  75                  80
Tyr Ile Cys Asn Val Asn His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95
Lys Val Glu Pro Lys Ser Cys Asp Lys Thr His Thr Cys Pro Pro Cys
            100                 105                 110
Pro Ala Pro Glu Leu Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro
        115                 120                 125
Lys Pro Lys Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys
    130                 135                 140
Val Val Val Asp Val Ser His Glu Asp Pro Glu Val Lys Phe Asn Trp
145                 150                 155                 160
Tyr Val Asp Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu
                165                 170                 175
Glu Gln Tyr Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu
            180                 185                 190
His Gln Asp Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn
        195                 200                 205
Lys Ala Leu Pro Ala Pro Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly
    210                 215                 220
Gln Pro Arg Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Arg Asp Glu
225                 230                 235                 240
Leu Thr Lys Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr
                245                 250                 255
Pro Ser Asp Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn
            260                 265                 270
Asn Tyr Lys Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe
        275                 280                 285
Leu Tyr Ser Lys Leu Thr Val Asp Lys Ser Arg Trp Gln Gln Gly Asn
    290                 295                 300
Val Phe Ser Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr
305                 310                 315                 320
Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
                325                 330
```

<210> 72
<211> 327
<212> PRT
<213> Artificial Sequence

<220>

<223> Synthetic

<400> 72

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Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
 1               5                  10                  15
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60

Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95
Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Ser Cys Pro Ala Pro
            100                 105                 110
Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125
Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205
Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
305                 310                 315                 320
Leu Ser Leu Ser Leu Gly Lys
                325
```

<210> 73
<211> 327
<212> PRT
<213> Artificial Sequence

<220>
<223> Synthetic

<400> 73

```
Ala Ser Thr Lys Gly Pro Ser Val Phe Pro Leu Ala Pro Cys Ser Arg
 1               5                  10                  15
Ser Thr Ser Glu Ser Thr Ala Ala Leu Gly Cys Leu Val Lys Asp Tyr
            20                  25                  30
Phe Pro Glu Pro Val Thr Val Ser Trp Asn Ser Gly Ala Leu Thr Ser
        35                  40                  45
Gly Val His Thr Phe Pro Ala Val Leu Gln Ser Ser Gly Leu Tyr Ser
    50                  55                  60
Leu Ser Ser Val Val Thr Val Pro Ser Ser Ser Leu Gly Thr Lys Thr
65                  70                  75                  80
Tyr Thr Cys Asn Val Asp His Lys Pro Ser Asn Thr Lys Val Asp Lys
                85                  90                  95
Arg Val Glu Ser Lys Tyr Gly Pro Pro Cys Pro Pro Cys Pro Ala Pro
            100                 105                 110
Glu Phe Leu Gly Gly Pro Ser Val Phe Leu Phe Pro Pro Lys Pro Lys
        115                 120                 125

Asp Thr Leu Met Ile Ser Arg Thr Pro Glu Val Thr Cys Val Val Val
    130                 135                 140
Asp Val Ser Gln Glu Asp Pro Glu Val Gln Phe Asn Trp Tyr Val Asp
145                 150                 155                 160
Gly Val Glu Val His Asn Ala Lys Thr Lys Pro Arg Glu Glu Gln Phe
                165                 170                 175
Asn Ser Thr Tyr Arg Val Val Ser Val Leu Thr Val Leu His Gln Asp
            180                 185                 190
Trp Leu Asn Gly Lys Glu Tyr Lys Cys Lys Val Ser Asn Lys Gly Leu
        195                 200                 205
Pro Ser Ser Ile Glu Lys Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg
    210                 215                 220
Glu Pro Gln Val Tyr Thr Leu Pro Pro Ser Gln Glu Glu Met Thr Lys
225                 230                 235                 240
Asn Gln Val Ser Leu Thr Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp
                245                 250                 255
Ile Ala Val Glu Trp Glu Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys
            260                 265                 270
Thr Thr Pro Pro Val Leu Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser
        275                 280                 285
Arg Leu Thr Val Asp Lys Ser Arg Trp Gln Glu Gly Asn Val Phe Ser
    290                 295                 300
Cys Ser Val Met His Glu Ala Leu His Asn His Tyr Thr Gln Lys Ser
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Leu Ser Leu Ser Leu Gly Lys
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<212> PRT
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<400> 74

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 1               5                  10                  15
Gly Ala Ala Leu Ala Pro Arg Arg Cys Pro Ala Gln Glu Val Ala Arg
            20                  25                  30
Gly Val Leu Thr Ser Leu Pro Gly Asp Ser Val Thr Leu Thr Cys Pro
        35                  40                  45
Gly Val Glu Pro Glu Asp Asn Ala Thr Val His Trp Val Leu Arg Lys
    50                  55                  60
Pro Ala Ala Gly Ser His Pro Ser Arg Trp Ala Gly Met Gly Arg Arg
65                  70                  75                  80
Leu Leu Leu Arg Ser Val Gln Leu His Asp Ser Gly Asn Tyr Ser Cys
                85                  90                  95
Tyr Arg Ala Gly Arg Pro Ala Gly Thr Val His Leu Leu Val Asp Val
            100                 105                 110
Pro Pro Glu Glu Pro Gln Leu Ser Cys Phe Arg Lys Ser Pro Leu Ser
        115                 120                 125
Asn Val Val Cys Glu Trp Gly Pro Arg Ser Thr Pro Ser Leu Thr Thr
    130                 135                 140
Lys Ala Val Leu Leu Val Arg Lys Phe Gln Asn Ser Pro Ala Glu Asp
145                 150                 155                 160
Phe Gln Glu Pro Cys Gln Tyr Ser Gln Glu Ser Gln Lys Phe Ser Cys
                165                 170                 175
Gln Leu Ala Val Pro Glu Gly Asp Ser Ser Phe Tyr Ile Val Ser Met
            180                 185                 190
Cys Val Ala Ser Ser Val Gly Ser Lys Phe Ser Lys Thr Gln Thr Phe
        195                 200                 205
Gln Gly Cys Gly Ile Leu Gln Pro Asp Pro Pro Ala Asn Ile Thr Val

    210                 215                 220
Thr Ala Val Ala Arg Asn Pro Arg Trp Leu Ser Val Thr Trp Gln Asp
225                 230                 235                 240
Pro His Ser Trp Asn Ser Ser Phe Tyr Arg Leu Arg Phe Glu Leu Arg
                245                 250                 255
Tyr Arg Ala Glu Arg Ser Lys Thr Phe Thr Thr Trp Met Val Lys Asp
            260                 265                 270
Leu Gln His His Cys Val Ile His Asp Ala Trp Ser Gly Leu Arg His
        275                 280                 285
Val Val Gln Leu Arg Ala Gln Glu Glu Phe Gly Gln Gly Glu Trp Ser
    290                 295                 300
Glu Trp Ser Pro Glu Ala Met Gly Thr Pro Trp Thr Glu Ser Arg Ser
305                 310                 315                 320
Pro Pro Ala Glu Asn Glu Val Ser Thr Pro Met Gln Ala Leu Thr Thr
                325                 330                 335
Asn Lys Asp Asp Asp Asn Ile Leu Phe Arg Asp Ser Ala Asn Ala Thr
            340                 345                 350
Ser Leu Pro Val Gln Asp
        355
```

Claims

1. A pharmaceutical formulation comprising:

(i) a human antibody that specifically binds to human interleukin-6 receptor (hIL-6R), wherein the antibody is at a concentration of from 5 mg/ml to 200 mg/ml and comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO:18 and a light chain variable region having the amino acid sequence of SEQ ID NO:26;
(ii) histidine at a concentration of from 10 mM to 25 mM;

(iii) arginine at a concentration of from 25 mM to 50 mM;
(iv) sucrose in an amount of from 5% to 10% w/v; and
(v) polysorbate 20 in an amount of from 0.1% to 0.2% w/v.

2. The pharmaceutical formulation of claim 1, wherein the formulation has a pH of about 6.

3. The pharmaceutical formulation of claim 1 or 2, wherein at least 90% of native form of said antibody is recovered after nine months of storage at 5°C, as determined by size exclusion-high performance liquid chromatography (SE-HPLC).

4. The pharmaceutical formulation of claim 1 or 2, wherein at least 95% of native form of said antibody is recovered after nine months of storage at 5°C, as determined by size exclusion-high performance liquid chromatography (SE-HPLC).

5. The pharmaceutical formulation of claim 1 or 2, wherein at least 96% of native form of said antibody is recovered after nine months of storage at 5°C, as determined by size exclusion-high performance liquid chromatography (SE-HPLC).

6. The pharmaceutical formulation of any one of claims 1 to 5 which is contained in a glass vial.

7. The pharmaceutical formulation of any one of claims 1 to 5 which is contained in a syringe.

8. The pharmaceutical formulation of claim 7 wherein said syringe comprises a fluorocarbon-coated plunger or said syringe is a low tungsten syringe.

9. The pharmaceutical formulation of any one of claims 1 to 5 which is contained in a microinfusor.

10. The pharmaceutical formulation of claim 1, comprising:

(i) 25 to 200 mg/mL of a human antibody that specifically binds to human interleukin-6 receptor (hIL-6R), wherein the antibody comprises a heavy chain variable region having the amino acid sequence of SEQ ID NO:18 and a light chain variable region having the amino acid sequence of SEQ ID NO:26;
(ii) about 25 mM histidine;
(iii) about 5% w/v sucrose; and
(iv) about 0.2% w/v polysorbate 20; and
(v) about 50 mM arginine.

11. The pharmaceutical formulation of claim 1, comprising (i) about 175 mg/mL of a human antibody that specifically binds to human interleukin-6 receptor (hIL-6R), wherein said antibody comprises a heavy chain and light chain variable region (HCVR / LCVR) amino acid sequence pair of SEQ ID NOs: 18/26;

(ii) about 25 mM histidine;
(iii) about 5% sucrose;
(iv) about 0.2% polysorbate 20; and
(v) about 50 mM arginine.

12. The pharmaceutical formulation of claim 11, wherein the formulation is contained in a staked needle prefilled syringe.

Patentansprüche

1. Pharmazeutische Formulierung, umfassend:

(i) einen humanen Antikörper, der spezifisch an humanen Interleukin-6-Rezeptor (hIL-6R) bindet, wobei der Antikörper in einer Konzentration von 5 mg/ml bis 200 mg/ml ist und eine variable Region der schweren Kette, die die Aminosäuresequenz von SEQ ID NO: 18 hat, und eine variable Region der leichten Kette, die die Aminosäuresequenz von SEQ ID NO: 26 hat, umfasst;
(ii) Histidin in einer Konzentration von 10 mM bis 25 mM;

(iii) Arginin in einer Konzentration von 25 mM bis 50 mM;
(iv) Saccharose in einer Menge von 5 % bis 10 % Gew./Vol.; und
(iv) Polysorbat 20 in einer Menge von 0,1 % bis 0,2 % Gew./Vol.

2. Pharmazeutische Formulierung nach Anspruch 1, wobei die Formulierung einen pH-Wert von etwa 6 hat.

3. Pharmazeutische Formulierung nach Anspruch 1 oder 2, wobei mindestens 90 % der nativen Form des Antikörpers nach neun Monaten Lagerung bei 5 °C rückgewonnen werden, wie durch Größenausschluss-Hochleistungs-Flüssigkeitschromatographie (size exclusion-high performance liquid chromatography, SE-HPLC) bestimmt.

4. Pharmazeutische Formulierung nach Anspruch 1 oder 2, wobei mindestens 95 % der nativen Form des Antikörpers nach neun Monaten Lagerung bei 5 °C rückgewonnen werden, wie durch Größenausschluss-Hochleistungs-Flüssigkeitschromatographie (size exclusion-high performance liquid chromatography, SE-HPLC) bestimmt.

5. Pharmazeutische Formulierung nach Anspruch 1 oder 2, wobei mindestens 96 % der nativen Form des Antikörpers nach neun Monaten Lagerung bei 5 °C rückgewonnen werden, wie durch Größenausschluss-Hochleistungs-Flüssigkeitschromatographie (size exclusion-high performance liquid chromatography, SE-HPLC) bestimmt.

6. Pharmazeutische Formulierung nach einem der Ansprüche 1 bis 5, die in einer Glasampulle enthalten ist.

7. Pharmazeutische Formulierung nach einem der Ansprüche 1 bis 5, die in einer Spritze enthalten ist.

8. Pharmazeutische Formulierung nach Anspruch 7, wobei die Spritze einen mit Fluorkohlenstoff beschichteten Kolben umfasst oder die Spritze eine Spritze mit wenig Wolfram ist.

9. Pharmazeutische Formulierung nach einem der Ansprüche 1 bis 5, die in einem Mikroinfusor enthalten ist.

10. Pharmazeutische Formulierung nach Anspruch 1, umfassend:

(i) 25 bis 200 mg/ml eines humanen Antikörpers, der spezifisch an humanen Interleukin-6-Rezeptor (hIL-6R) bindet, wobei der Antikörper eine variable Region der schweren Kette, die die Aminosäuresequenz von SEQ ID NO: 18 hat, und eine variable Region der leichten Kette, die die Aminosäuresequenz von SEQ ID NO: 26 hat, umfasst;
(ii) etwa 25 mM Histidin;
(iii) etwa 5 % Gew./Vol. Saccharose; und
(iv) etwa 0,2 % Gew./Vol. Polysorbat 20; und
(v) etwa 50 mM Arginin.

11. Pharmazeutische Formulierung nach Anspruch 1, umfassend (i) etwa 175 mg/ml eines humanen Antikörpers, der spezifisch an humanen Interleukin-6-Rezeptor (hIL-6R) bindet, wobei der Antikörper ein Paar der variablen Region der schweren Kette und der leichten Kette (heavy chain variable region, light chain variable region, HCVR/LCVR) von SEQ ID NO: 18/26 umfasst;

(ii) etwa 25 mM Histidin;
(iii) etwa 5 % Saccharose;
(iv) etwa 0,2 % Polysorbat 20; und
(v) etwa 50 mM Arginin.

12. Pharmazeutische Formulierung nach Anspruch 11, wobei die Formulierung in einer Fertigspritze mit eingesetzter Nadel enthalten ist.

Revendications

1. Formulation pharmaceutique comprenant :

(i) un anticorps humain qui se lie spécifiquement au récepteur d'interleukine 6 humaine (hIL-6R), l'anticorps étant à une concentration de 5 mg/mL à 200 mg/mL et comprenant une région variable de chaîne lourde ayant

la séquence d'acides aminés de SEQ ID NO : 18 et une région variable de chaîne légère ayant la séquence d'acides aminés de SEQ ID NO : 26 ;
(ii) de l'histidine à une concentration de 10 mM à 25 mM ;
(iii) de l'arginine à une concentration de 25 mM à 50 mM ;
(iv) du saccharose dans une quantité de 5 % à 10 % p/v ; et
(v) du polysorbate 20 dans une quantité de 0,1 % à 0,2 % p/v.

2. Formulation pharmaceutique de la revendication 1, la formulation ayant un pH d'environ 6.

3. Formulation pharmaceutique de la revendication 1 ou 2, dans laquelle au moins 90% de la forme native dudit anticorps sont récupérés après neuf mois de stockage à 5 °C, comme déterminé par chromatographie d'exclusion stérique haute performance (SE-HPLC).

4. Formulation pharmaceutique de la revendication 1 ou 2, dans laquelle au moins 95% de la forme native dudit anticorps sont récupérés après neuf mois de stockage à 5 °C, comme déterminé par chromatographie d'exclusion stérique haute performance (SE-HPLC).

5. Formulation pharmaceutique de la revendication 1 ou 2, dans laquelle au moins 96% de la forme native dudit anticorps sont récupérés après neuf mois de stockage à 5 °C, comme déterminé par chromatographie d'exclusion stérique haute performance (SE-HPLC).

6. Formulation pharmaceutique de l'une quelconque des revendications 1 à 5 qui est contenue dans une fiole en verre.

7. Formulation pharmaceutique de l'une quelconque des revendications 1 à 5 qui est contenue dans une seringue.

8. Formulation pharmaceutique de la revendication 7, dans laquelle ladite seringue comprend un piston revêtu de fluorocarbone ou ladite seringue est une seringue à faible teneur en tungstène.

9. Formulation pharmaceutique de l'une quelconque des revendications 1 à 5 qui est contenue dans un microperfuseur.

10. Formulation pharmaceutique de la revendication 1, comprenant :

(i) 25 à 200 mg/mL d'un anticorps humain qui se lie spécifiquement au récepteur d'interleukine 6 humaine (hIL-6R), l'anticorps comprenant une région variable de chaîne lourde ayant la séquence d'acides aminés de SEQ ID NO : 18 et une région variable de chaîne légère ayant la séquence d'acides aminés de SEQ ID NO : 26 ;
(ii) de l'histidine à environ 25 mM ;
(iii) du saccharose à environ 5 % p/v ; et
(iv) du polysorbate 20 à environ 0,2 % p/v ; et
(v) de l'arginine à environ 50 mM.

11. Formulation pharmaceutique de la revendication 1, comprenant (i) environ 175 mg/mL d'un anticorps humain qui se lie spécifiquement au récepteur d'interleukine 6 humaine (hIL-6R), ledit anticorps comprenant une paire de séquences d'acides aminés de région variable de chaîne lourde et de région variable de chaîne légère (HCVR / LCVR) de SEQ ID NO : 18/26;

(ii) de l'histidine à environ 25 mM ;
(iii) du saccharose à environ 5 % ;
(iv) du polysorbate 20 à environ 0,2 % ; et
(v) de l'arginine à environ 50 mM.

12. Formulation pharmaceutique de la revendication 11, la formulation étant contenue dans une seringue préremplie avec aiguille fixe.

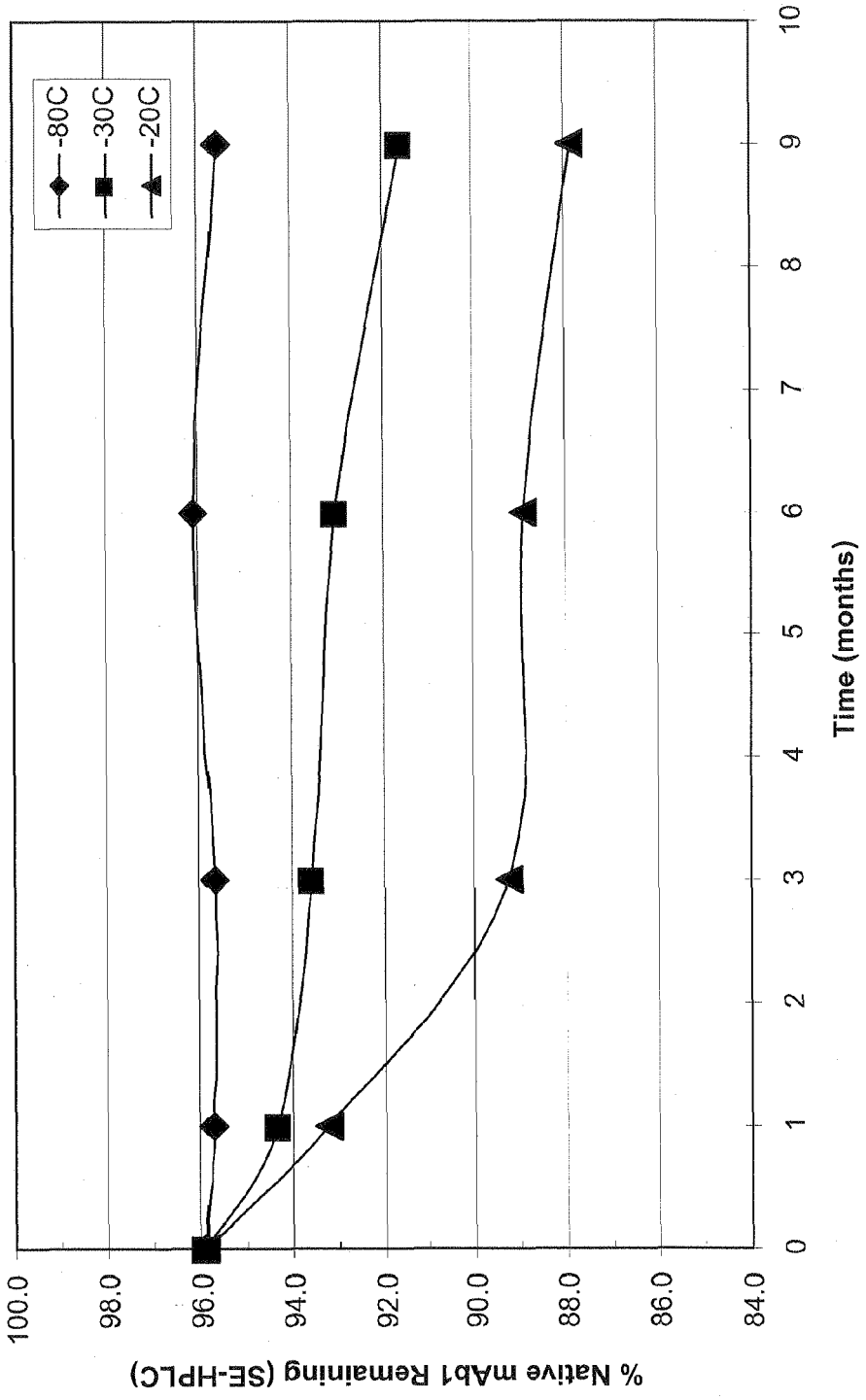

-80C
-30C
-20C
% Native mAb1 Remaining (SE-HPLC)
100.0
98.0
96.0
94.0
92.0
90.0
88.0
86.0
84.0
0
1
2
3
4
5
6
7
8
9
10
Time (months)

Figure 1

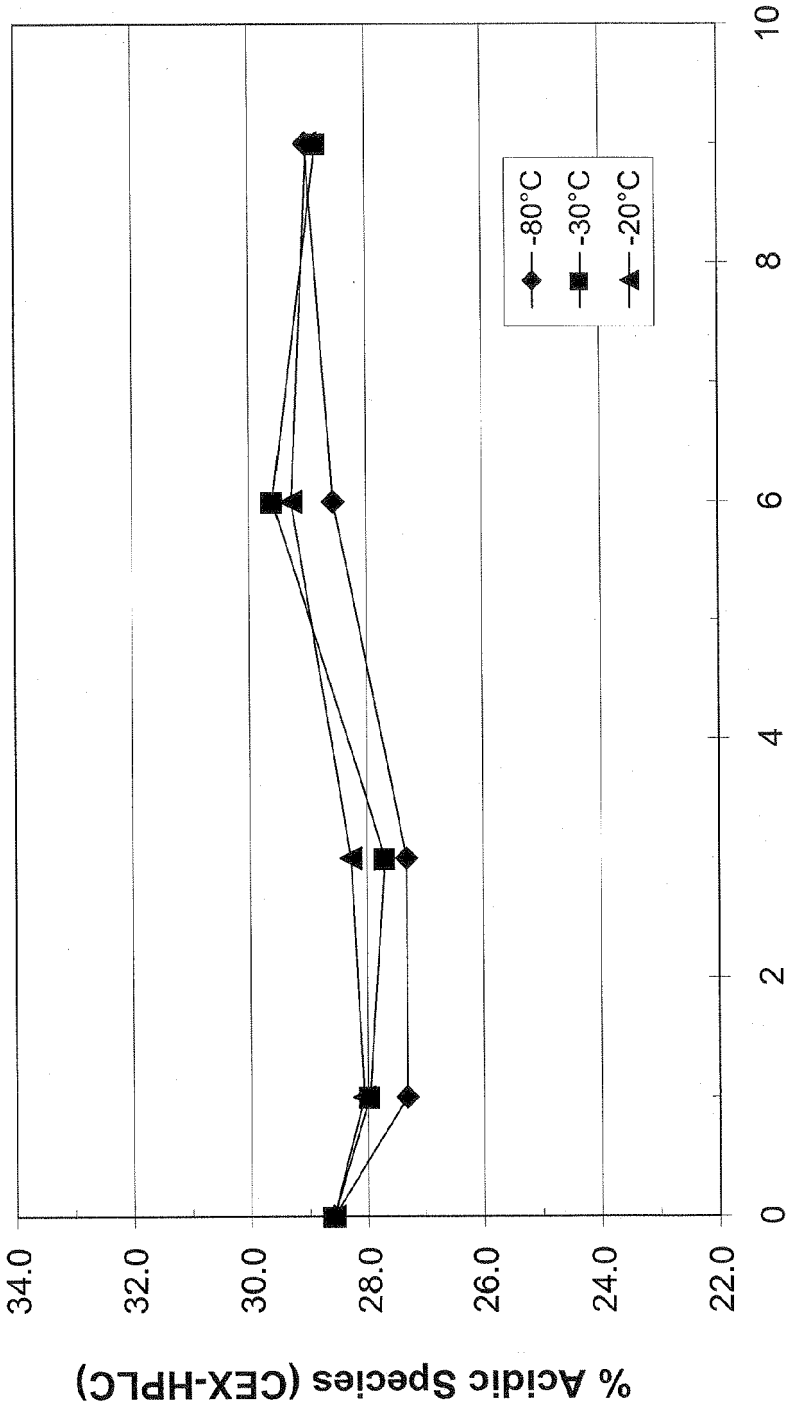

% Acidic Species (CEX-HPLC)
34.0
32.0
30.0
28.0
26.0
24.0
22.0
0
2
4
6
8
10
Time (months)
-80°C
-30°C
-20°C

Figure 2

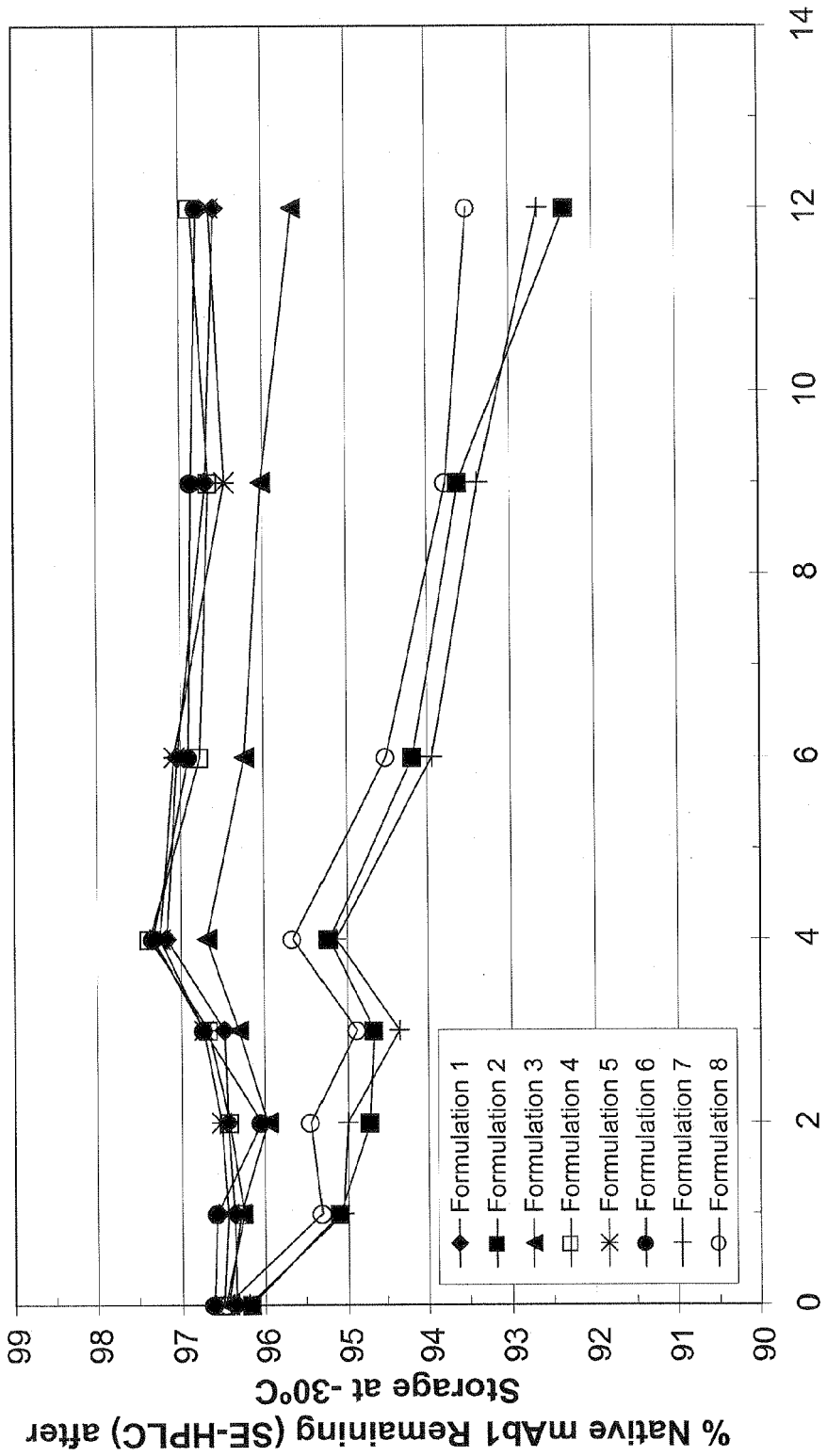
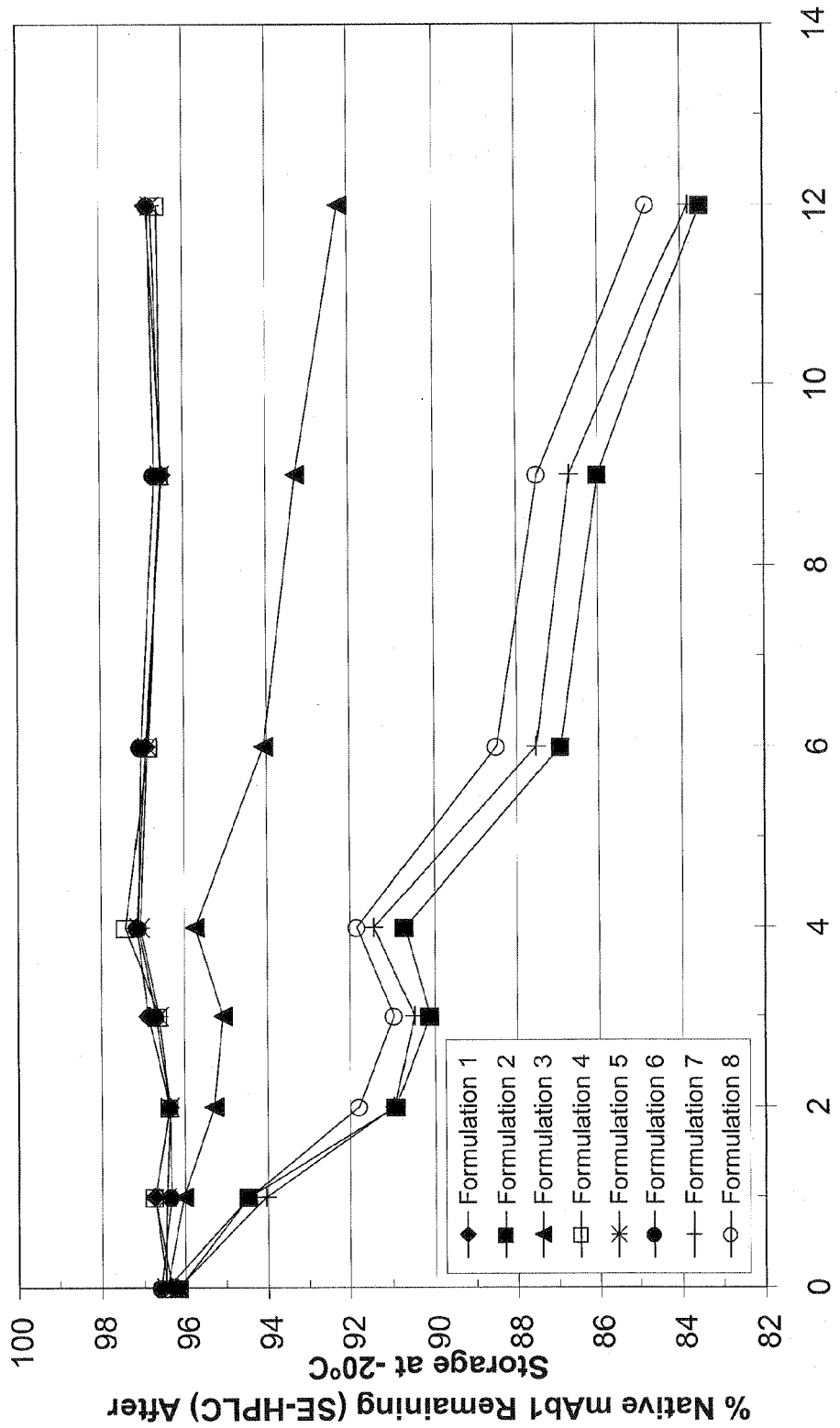

% Native mAb1 Remaining (SE-HPLC) after Storage at -30°C
99
98
97
96
95
94
93
92
91
90
0
2
4
6
8
10
12
14
Time (months)
Formulation 1
Formulation 2
Formulation 3
Formulation 4
Formulation 5
Formulation 6
Formulation 7
Formulation 8

Figure 3


% Native mAb1 Remaining (SE-HPLC) After Storage at -20°C
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98
96
94
92
90
88
86
84
82
0
2
4
6
8
10
12
14
Time (months)
Formulation 1
Formulation 2
Formulation 3
Formulation 4
Formulation 5
Formulation 6
Formulation 7
Formulation 8

Figure 4

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- US 7582298 B **[0003] [0020]**
- US 6410691 B **[0003]**
- US 5817790 A **[0003]**
- US 5795695 A **[0003]**
- US 6670373 B **[0003]**
- US 4997423 A **[0042]**
- US 5908686 A **[0042]**
- US 6286699 B **[0042]**
- US 6645635 B **[0042]**
- US 7226554 B **[0042]**
- US 6629949 B **[0045]**
- US 6659982 B **[0045]**
- US 61293227 B **[0072]**

Non-patent literature cited in the description

- **MEEHAN et al.** *J. Controlled Release,* 1996, vol. 46, 107-116 **[0045]**