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

FIELD OF THE INVENTION

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.

SEQUENCE LISTING

A WIPO Standard ST.25 (1998) compliant text file of a sequence listing is filed concurrently with the present specification. The contents of the text file are herein incorporated by reference. The text file containing the sequence listing is named "IL6RAbFormulationSeqList," was created on January 7, 2010, and contains 37,387 bytes.

BACKGROUND

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.

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").

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

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). The formulations of the invention may comprise excipients in addition to the anti-hIL-6R antibody. For example, in certain embodiments, the formulation may comprise (i) a human antibody that specifically binds to hIL-6R; (ii) at least one amino acid; and (iii) at least one carbohydrate. The amino acid can be, *e.g.*, histidine and/or arginine. The carbohydrate can be a sugar such as, *e.g.*, sucrose, glucose, mannitol, lactose or trehalose.

According to certain embodiments of the present invention, the formulation further comprises a non-ionic surfactant. The non-ionic surfactant can be, *e.g.*, polysorbate 20, polysorbate 80, polyoxyethylene sorbitan monooleate, polyethylene glycol, etc.

The antibody contained within the pharmaceutical formulations of the present invention can be any antibody which specifically binds to hIL-6R. Exemplary antibodies that may be contained within the formulations of the invention are antibodies comprising a heavy chain variable region (HCVR) and a light chain variable region (LCVR), wherein the HCVR comprises a heavy chain complementary determining region (HCDR) 1 having the amino acid sequence of SEQ ID NO: 20, a HCDR2 having the amino acid sequence of SEQ ID NO:22, and a HCDR3 having the amino acid sequence of SEQ ID NO:24; and wherein the LCVR comprises a light chain complementary determining region (LCDR) 1 having the amino acid sequence of SEQ ID NO: 28, a LCDR2 having the amino acid sequence of SEQ ID NO:30, and a LCDR3 having the amino acid sequence of SEQ ID NO:32. In certain embodiments, the antibody contained within the formulations of the present invention are antibodies comprising a HCVR having the amino acid sequence of SEQ ID NO:18 and a LCVR having the amino acid sequence of SEQ ID NO:26.

The antibody formulations of the present invention 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).

According to certain aspects of the present invention, the pharmaceutical formulations remain relatively stable following storage for several days, months or years at a given

temperature. For example, in certain exemplary embodiments of the present invention, 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.

Other embodiments of the present invention will become apparent from a review of the ensuing detailed description.

BRIEF DESCRIPTION OF THE FIGURES

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

Before the present invention is described, it is to be understood that this invention is not limited to particular methods and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only by the appended claims.

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.).

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. All publications mentioned herein are incorporated herein by reference to describe in their entirety.

PHARMACEUTICAL FORMULATIONS

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. The present invention provides pharmaceutical formulations comprising at least one therapeutic polypeptide. According to certain embodiments of the present invention, the therapeutic polypeptide is an antibody that binds specifically to human interleukin-6 receptor (hIL-6R) or an antigen-binding fragment thereof. More specifically, the present invention includes pharmaceutical formulations that comprise:

(i) a human antibody that specifically binds to hIL-6R; (ii) histidine; and (iii) a carbohydrate. Additional components may be included in the formulations of the present invention such as, *e.g.*, at least one non-ionic surfactant, and at least one additional amino acid. Specific exemplary components and formulations included within the present invention are described in detail below.

The pharmaceutical formulations of the present invention 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

The pharmaceutical formulations of the present invention may 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 invention 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.

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.

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.

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).

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 invention, 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.

Exemplary anti-hIL-6R antibodies that may be included in the pharmaceutical formulations of the present invention are set forth in US 7,582,298, the disclosure of which is incorporated by reference in its entirety.

According to certain embodiments of the present invention, the anti-hIL-6R antibody, or antigen-binding fragment thereof, comprises a heavy chain complementary determining region (HCDR) 1 having an amino acid sequence selected from the group consisting of SEQ ID NO: 4, 20, 36 and 52; a HCDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:6, 22, 38 and 54; and a HCDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:2, 18, 34 and 50. In certain embodiments, the anti-hIL-6R antibody, or antigen-binding fragment thereof, comprises HCDR1-HCDR2-HCDR3 domains, respectively, selected from the group consisting of: (i) SEQ ID NOs:4 – 6 – 8; (ii) SEQ ID NOs:20 – 22 – 24; (iii) SEQ ID NOs:36 – 38 – 40; and (iv) SEQ ID NOs:52 – 54 – 56.

According to certain embodiments of the present invention, the anti-hIL-6R antibody, or antigen-binding fragment thereof, comprises a light chain complementary determining region (LCDR) 1 having an amino acid sequence selected from the group consisting of SEQ ID NO: 12, 28, 44 and 60; a LCDR2 having an amino acid sequence selected from the group consisting of SEQ ID NO:14, 30, 46 and 62; and a LCDR3 having an amino acid sequence selected from the group consisting of SEQ ID NO:16, 32, 48 and 64. In certain

embodiments, the anti-hIL-6R antibody, or antigen-binding fragment thereof, comprises LCDR1-LCDR2-LCDR3 domains, respectively, selected from the group consisting of: (i) SEQ ID NOs:12 – 14 – 16; (ii) SEQ ID NOs:28 – 30 – 32; (iii) SEQ ID NOs:44 – 46 – 48; and (iv) SEQ ID NOs:60 – 62 – 64.

In certain embodiments, the anti-hIL-6R antibody, or antigen-binding fragment thereof, comprises HCDR1-HCDR2-HCDR3 / LCDR1-LCDR2-LCDR3 domains, respectively, selected from the group consisting of: (i) SEQ ID NOs:4 – 6 – 8 / SEQ ID NOs:12 – 14 – 16; (ii) SEQ ID NOs:20 – 22 – 24 / SEQ ID NOs:28 – 30 – 32; (iii) SEQ ID NOs:36 – 38 – 40 / SEQ ID NOs:44 – 46 – 48; and (iv) SEQ ID NOs:52 – 54 – 56 / SEQ ID NOs:60 – 62 – 64.

In certain embodiments, the anti-hIL-6R antibody, or antigen-binding fragment thereof, comprises a heavy chain variable region (HCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO:2, 18, 34 and 50. In certain embodiments, the anti-hIL-6R antibody, or antigen-binding fragment thereof, comprises a light chain variable region (LCVR) having an amino acid sequence selected from the group consisting of SEQ ID NO:10, 26, 42 and 58. In certain embodiments, the anti-hIL-6R antibody, or antigen-binding fragment thereof, comprises a HCVR/LCVR amino acid sequence pair selected from the group consisting of SEQ ID NO:2/10; 18/26; 34/42 and 50/58.

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.

The amount of antibody, or antigen-binding fragment thereof, contained within the pharmaceutical formulations of the present invention may vary depending on the specific properties desired of the formulations, as well as the particular circumstances and purposes for which the formulations are intended to be used. In certain embodiments, the pharmaceutical formulations may contain about 1 mg/mL to about 500 mg/mL of antibody; about 5 mg/mL to about 400 mg/mL of antibody; about 5 mg/mL to about 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 of the present invention may comprise about 1 mg/mL; about 2 mg/mL; about 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 about 200 mg/mL of an antibody or an antigen-binding fragment thereof, that binds specifically to hIL-6R.

EXCIPIENTS and pH

The pharmaceutical formulations of the present invention 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.

In certain embodiments, the pharmaceutical formulation of the invention comprises at least one amino acid. Exemplary amino acids suitable for use in the formulations of the present invention include, *inter alia*, arginine and/or histidine.

The amount of amino acid contained within the pharmaceutical formulations of the present invention may vary depending on the specific properties desired of the formulations, as well as the particular circumstances and purposes for which the formulations are intended to be used. In certain embodiments, the formulations may contain about 1 mM to about 200 mM of an amino acid; about 2 mM to about 100 mM of an amino acid; about 5 mM to about 50 mM of an amino acid; or about 10 mM to about 25 mM of an amino acid. For example, the pharmaceutical formulations of the present invention may comprise about 1 mM; about 1.5 mM; about 2 mM; about 2.5 mM; about 3 mM; about 3.5 mM; about 4 mM; about 4.5 mM; about 5 mM; about 5.5 mM; about 6 mM; about 6.5 mM; about 7 mM; about 7.5 mM; about 8 mM; about 8.5 mM; about 9 mM; about 9.5 mM; about 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; about 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 about 50 mM of an amino acid (*e.g.*, histidine and/or arginine).

The pharmaceutical formulations of the present invention may also comprise one or more carbohydrate, *e.g.*, one or more sugar. The sugar can be a reducing sugar or a non-reducing sugar. "Reducing sugars" include, *e.g.*, sugars with a ketone or aldehyde group

and contain a reactive hemiacetal group, which allows the sugar to act as a reducing agent. Specific examples of reducing sugars include fructose, glucose, glyceraldehyde, lactose, arabinose, mannose, xylose, ribose, rhamnose, galactose and maltose. Non-reducing sugars can comprise an anomeric carbon that is an acetal and is not substantially reactive with amino acids or polypeptides to initiate a Maillard reaction. Specific examples of non-reducing sugars include sucrose, trehalose, sorbose, sucralose, melezitose and raffinose. Sugar acids include, for example, saccharic acids, gluconate and other polyhydroxy sugars and salts thereof.

The amount of sugar contained within the pharmaceutical formulations of the present invention will vary depending on the specific circumstances and intended purposes for which the formulations are used. In certain embodiments, the formulations may contain about 0.1% to about 20% sugar; about 0.5% to about 20% sugar; about 1% to about 20% sugar; about 2% to about 15% sugar; about 3% to about 10% sugar; about 4% to about 10% sugar; or about 5% to about 10% sugar. For example, the pharmaceutical formulations of the present invention may comprise about 0.5%; about 1.0%; about 1.5%; about 2.0%; about 2.5%; about 3.0%; about 3.5%; about 4.0%; about 4.5%; about 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%; about 10.0%; about 10.5%; about 11.0%; about 11.5%; about 12.0%; about 12.5%; about 13.0%; about 13.5%; about 14.0%; about 14.5%; about 15.0%; about 15.5%; about 16.0%; 16.5%; about 17.0%; about 17.5%; about 18.0%; about 18.5%; about 19.0%; about 19.5%; or about 20.0% sugar (*e.g.*, sucrose).

The pharmaceutical formulations of the present invention may also comprise one or more surfactant. As used herein, the term "surfactant" means a substance which reduces the surface tension of a fluid in which it is dissolved and/or reduces the interfacial tension between oil and water. Surfactants can be ionic or non-ionic. Exemplary non-ionic surfactants that can be included in the formulations of the present invention include, *e.g.*, alkyl poly(ethylene oxide), alkyl polyglucosides (*e.g.*, octyl glucoside and decyl maltoside), fatty alcohols such as cetyl alcohol and oleyl alcohol, cocamide MEA, cocamide DEA, and cocamide TEA. Specific non-ionic surfactants that can be included in the formulations of the present invention include, *e.g.*, polysorbates such as polysorbate 20, polysorbate 28, polysorbate 40, polysorbate 60, polysorbate 65, polysorbate 80, polysorbate 81, and polysorbate 85; poloxamers such as poloxamer 188, poloxamer 407; polyethylene-polypropylene glycol; or polyethylene glycol (PEG). Polysorbate 20 is also known as TWEEN 20, sorbitan monolaurate and polyoxyethylenesorbitan monolaurate.

The amount of surfactant contained within the pharmaceutical formulations of the present invention may vary depending on the specific properties desired of the formulations, as well

as the particular circumstances and purposes for which the formulations are intended to be used. In certain embodiments, the formulations may contain about 0.05% to about 5% surfactant; or about 0.1% to about 0.2% surfactant. For example, the formulations of the present invention may comprise about 0.05%; about 0.06%; about 0.07%; about 0.08%; about 0.09%; about 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%; about 0.20%; about 0.21%; about 0.22%; about 0.23%; about 0.24%; about 0.25%; about 0.26%; about 0.27%; about 0.28%; about 0.29%; or about 0.30% surfactant (*e.g.*, polysorbate 20).

The pharmaceutical formulations of the present invention may have a pH of from about 5.0 to about 8.0. For example, the formulations of the present invention 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

According to one aspect of the present invention, 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 invention are set forth in Table 1.

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

According to another aspect of the present invention, 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 invention are set forth in Tables 2A and 2B.

According to another aspect of the present invention, 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 invention are set forth in Tables 3A, 3B, 3C, 3D, 3E and 3F.

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

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
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

Table 3B continued …:

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
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

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

STABILITY AND VISCOSITY OF THE PHARMACEUTICAL FORMULATIONS

The pharmaceutical formulations of the present invention 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."

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.

Other methods may be used to assess the stability of the formulations of the present invention 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 invention 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.

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 invention 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.

In the fluid form, the pharmaceutical formulations of the present invention 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.

As used herein, a low level of viscosity, in reference to a fluid formulation of the present invention, will exhibit an absolute viscosity of less than about 20 cPoise (cP). For example, a fluid formulation of the invention 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 invention, will exhibit an absolute viscosity of between about 30 cP and about 20 cP. For example, a fluid formulation of the invention will 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.

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

The pharmaceutical formulations of the present invention 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 invention including, *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 invention.

The pharmaceutical formulations of the present invention 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 invention, 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.

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 invention, 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 invention 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, the contents of which are incorporated by reference herein in their entireties. Particular exemplary coated rubber stoppers and plungers that can be used in the context of the present invention are commercially available under the tradename "FluroTec®," available from West Pharmaceutical Services, Inc. (Lionville, PA).

According to certain embodiments of the present invention, 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 invention.

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 of the present invention. 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 invention include, 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.

The use of a microinfusor to deliver the pharmaceutical formulations of the present invention 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

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.

Thus, the present invention includes 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 of the present invention 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 invention further 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

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

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".

As a preliminary experiment, the stability of mAb1 in liquid solution was determined following various amounts of time in frozen storage at -20ºC, -30ºC and -80ºC. 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 invention).

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

	Storage Temperature		
Time (months)	-80ºC	-30ºC	-20ºC
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)	-80ºC	-30ºC	-20ºC
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

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 -80ºC.

Example 2. Stability of mAb1 Formulations Containing Minimal Excipients

Eight different formulations containing mAb1 and minimal excipients as shown in Table 6 were prepared. The formulations were tested for stability by SE-HPLC after various amounts of time at -30ºC and -20ºC. The results, expressed in percent of native mAb1 remaining, are shown in Tables 7 (-30ºC storage) and 8 (-20ºC).

Table 6: mAb1 Minimal Excipient Formulations

Formulation	Excipient	mAb1 (mg/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		

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

	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 -20ºC

	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

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 -20ºC and -30ºC. These results indicate that the stability of mAb1 at -20ºC and -30ºC can be enhanced by the addition of at least 2% sucrose.

Example 3. Stabilized Formulation of mAb1

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 5ºC

Formulation A (see Example 3) containing 25, 50 or 100 mg/mL mAb1 was tested for stability after several months of storage at 5ºC 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 5ºC in Clear Vials

	Length of 5ºC Storage (months)						
Parameter	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 5ºC in Clear Vials (0 – 9 months)

	Length of 5ºC Storage (months)					
Parameter	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

Table 11A continued …:						
% 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 5ºC in Clear Vials (12 – 24 months)

Parameter	Length of 5ºC 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
% Acidic Species mAb1 Recovered	28.1	28.3	29.0

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

Parameter	Length of 5ºC 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 5ºC in Clear Vials (12 – 24 months)

Parameter	Length of 5ºC 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

Table 12B continued …:			
% 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

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 5ºC 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 5ºC. In addition, the percent acidic species remained at 29% or lower for all time points analyzed, thus confirming the stability of the formulations.

Similar stability studies were also carried out using Formulation A containing 75 mg/mL mAb1 following storage at 2–8ºC. No significant degradation was observed for any of the concentrations tested after 24 months of 2–8ºC 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 5ºC 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

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 5ºC, 25ºC or 45ºC 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 5ºC 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 5ºC 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 5ºC 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 5ºC 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	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 5ºC 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

Table 18 continued …:							
% Native mAb1 Recovered	96.2	96.2	96.0	96.0	95.8	95.4	95.5
% 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 25ºC and 45ºC in Clear Vials

		Storage at 45ºC (days)			Storage at 25ºC (months)			
Parameter	0	7	14	28	1	2	3	6
Visual Appearance	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Turbidity (OD 405 nm)	0.0	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 25ºC and 45ºC in 5 mL Amber Vials

	t=0	Storage at 45ºC (days)			Storage at 25ºC (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	0.00	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 25ºC and 45ºC in 20 mL Amber Vials

Parameter	t=0	Storage at 45ºC (days)			Storage at 25ºC (months)			
	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

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 5ºC 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

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 45ºC 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.

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

mAb1 (mg/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		

Table 22 continued …:

mAb1 (mg/mL)	[Histidine] (mM)	[Arginine] (mM)	[Sucrose] (%)	Viscosity (cPoise)	Osmolality (mOsm)	
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	
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)

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.

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

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 invention).

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
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

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

Example 8: Stability of mAb1 Formulations in Prefilled Syringes

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 45ºC, 25ºC and 5ºC for various amounts of time (ranging from 14 days to 12 months, depending on the conditions tested).

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.

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.

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
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
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
45°C	28 days	Pass	0.00	103	93.3	22.8	64.7

Table 26 continued …:

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

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.

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 of the invention 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
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

The present invention is not to be limited in scope by the specific embodiments describe herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

CLAIMS

1. A stable 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 25 mM to 100 mM;

(iii) arginine at a concentration of from 25 mM to 50 mM;

(iv) sucrose in an amount of from 2% to 10% w/v; and

(v) polysorbate in an amount of from 0.1% to 0.2% w/v.

2. The pharmaceutical formulation of claim 1, wherein the histidine is at a concentration of 25 mM.

3. The pharmaceutical formulation of claim 1 or 2, wherein the arginine is present at a concentration of 50 mM.

4. The pharmaceutical formulation of any one of claims 1 to 3, wherein the sucrose is present in an amount of 5% w/v.

5. The pharmaceutical formulation of any one of claims 1 to 4, wherein the polysorbate is present at a concentration of 0.2% w/v.

6. The pharmaceutical formulation of any one of claims 1 to 5, wherein the formulation has a pH of 6.

7 The pharmaceutical formulation of any one of the preceding claims comprising 25 to 200 mg/mL of said human antibody that specifically binds to hIL-6R.

8. The pharmaceutical formulation of claim 7 comprising from 50 mg/mL to 180 mg/mL of the human antibody that specifically binds to hIL-6R.

9. The pharmaceutical formulation of claim 8, comprising 150 mg/mL of said human antibody that specifically binds to hIL-6R.

10. The pharmaceutical formulation of claim 8, comprising 175 mg/mL of said human antibody that specifically binds to hIL-6R.

11. The pharmaceutical formulation of any one of the preceding claims, wherein at least 90% of the native form of said antibody is recoverable after nine months of storage at 5ºC, as determined by size exclusion-high performance liquid chromatography (SE-HPLC).

12. The pharmaceutical formulation of claim 11, wherein at least 95% of the native form of said antibody is recoverable after nine months of storage at 5ºC, as determined by size exclusion-high performance liquid chromatography (SE-HPLC).

13. The pharmaceutical formulation of claim 12, wherein at least 96% of the native form of said antibody is recoverable after nine months of storage at 5ºC, as determined by size exclusion-high performance liquid chromatography (SE-HPLC).

14. The pharmaceutical formulation of any one of the preceding claims, wherein the formulation exhibits a viscosity of less than about 15 cPoise.

15. The pharmaceutical formulation of any one of claims 1 to 13, wherein the formulation exhibits a viscosity of less than about 12 cPoise.

16. The pharmaceutical formulation of claim 15, wherein the formulation exhibits a viscosity of less than about 9 cPoise.

17. A stable pharmaceutical formulation comprising:

(i) 5 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) 25 mM histidine;

(iii) 5% w/v sucrose;

(iv) 0.2% w/v polysorbate 20; and

(v) 50 mM arginine.

18. A stable pharmaceutical formulation comprising:

(i) 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) 25 mM histidine;

(iii) 5% sucrose;

(iv) 0.2% polysorbate 20; and

(v) 50 mM arginine.

19. The pharmaceutical formulation of any one of claims 1 to 18, wherein the formulation is contained in a stacked needle prefilled syringe.

20. The pharmaceutical formulation of any one of claims 1 to 18, wherein the formulation is contained in a glass vial, a syringe, or microinfusor.

21. The pharmaceutical formulation of claim 20, wherein said syringe comprises a fluorocarbon-coated plunger.

22. The pharmaceutical formulation of claim 20, wherein said syringe is a low tungsten syringe.

23. The pharmaceutical formulation of claim 17 or 18, wherein at least 96% of the native form of said antibody is recoverable after two months of storage at 5°C, as determined by size exclusion-high performance liquid chromatography.

24. Use of the stable pharmaceutical formulation of any one of claims 1 to 18 or 23 in the manufacture of a medicament of the treatment, prevention and/or amelioration of a disease or disorder associated with IL-6 activity including diseases or disorders mediated by activation of the IL-6 receptor (IL-6R).

25. The use of claim 24, wherein the disease or disorder is selected from the group consisting of 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, cancer, cachexia, chronic rejection of transplanted organs and cells, cardiopathy, viral infection, plasmacytosis, hyperimmunoglobulinemia, anemia, nephritis, mesothelioma, hearing loss, and other inner ear disorders.