typically bulky polar organic compounds, such as many of the GRAS (US Food and Drug Administration's list of compounds generally regarded as safe), inactive injectable ingredients and FDA-approved therapeutics.

The concentration of proteins is between about 10 mg/mL and about 5,000 mg/mL, more preferably from about 100 mg/mL to about 2,000 mg/mL. In some examples, the concentration of proteins is between about 100 mg/mL to about 500 mg/mL, more preferably from about 300 mg/mL to about 500 mg/mL. Formulations containing proteins and viscosity-lowering agents are stable when stored at a temperature of 4° C, for a period of at least one month, preferably at least two months, and most preferably at least three months. The viscosity of the formulation is less than about 75 cP, preferably below 50 cP, and most preferably below 20 cP at about 25° C. In some examples, the viscosity is less than about 15 cP or even less than or about 10 cP at about 25° C. In certain examples, the viscosity of the formulation is about 10 cP. Formulations containing proteins and viscosity-lowering agents typically are measured at shear rates from about 0.6 s^{-1} to about 450 s^{-1}, and preferably from about 2 s^{-1} to about 400 s^{-1}, when measured using a cone and plate viscometer. Formulations containing proteins and viscosity-lowering agents typically are measured at shear rates from about 3 s^{-1} to about 55,000 s^{-1}, and preferably from about 20 s^{-1} to about 2,000s^{-1},when measured using a microfluidic viscometer.

The viscosity of the protein formulation is reduced by the presence of one or more viscosity-lowering agents. Unless specifically stated otherwise, the term "viscosity-lowering agent" includes both single compounds and mixtures of two or more compounds. It is preferred that the viscosity-lowering agent is present in the formulation at a concentration less than about 1.0 M, preferably less than about 0.50 M, more preferably less than about 0.30 M, and most preferably less than about 0.15 M. In some examples, the viscosity-lowering agent is present in the formulation in concentrations as low as 0.01 M. The formulations can have a viscosity that is at least about 30% less, preferably at least about 50% less, most preferably at least about 75% less, than the viscosity of the corresponding formulation under the same conditions except for replacement of the viscosity-lowering agent with an appropriate buffer or salt of about the same concentration. In

some examples, a low-viscosity formulation is provided where the viscosity of the corresponding formulation without the viscosity-lowering agent is greater than about 200 cP, greater than about 500 cP, or even above about 1,000 cP. In a preferred example, the shear rate of the formulation is at least about 0.5 s^{-1}, when measured using a cone and plate viscometer or at least about 1.0 s^{-1}, when measured using a microfluidic viscometer.

For examples in which the protein is a "high-molecular-weight protein", the high molecular weight protein may have a molecular weight between about 100 kDa and about 1,000 kDa, preferably between about 120 kDa and about 500 kDa, and most preferably between about 120 kDa and about 250 kDa. The high-molecular-weight protein can be an antibody, such as a mAb, or a PEGylated, or otherwise a derivatized form thereof. Preferred mAbs include natalizumab (TYSABRI®), cetuximab (ERBITUX®), bevacizumab (AVASTIN®), trastuzumab (HERCEPTIN®), infliximab (REMICADE®), rituximab (RITUXAN®), panitumumab (VECTIBIX®), ofatumumab (ARZERRA®), and biosimilars thereof. The high-molecular-weight protein, optionally PEGylated, can be an enzyme. Other proteins and mixtures of proteins may also be formulated to reduce their viscosity.

In some examples, the protein and viscosity-lowering agent are provided in a lyophilized dosage unit, sized for reconstitution with a sterile aqueous pharmaceutically acceptable vehicle, to yield the concentrated low-viscosity liquid formulations. The presence of the viscosity-lowering agent(s) facilitates and/or accelerates the reconstitution of the lyophilized dosage unit compared to a lyophilized dosage unit not containing a viscosity lowering agent.

Methods are provided herein for preparing concentrated, low-viscosity liquid formulations of high-molecular-weight proteins such as mAbs, as well as methods for storing the low-viscosity, high-concentration protein formulations, and for administration thereof to patients. In another example, the viscosity-lowering agent is added to facilitate processing (e.g., pumping, concentration, and/or filtration) by reducing the viscosity of the protein solutions.

In a first aspect, there is provided a liquid pharmaceutical formulation for injection comprising: (i) at least 100 mg/ml of an antibody; (ii) cimetidine or a

pharmaceutically acceptable salt thereof; and (iii) a pharmaceutically acceptable solvent; wherein the liquid pharmaceutical formulation, when in a volume suitable for injection, has an absolute viscosity from about 1 cP to about 100 cP at 25°C as measured using a cone and plate viscometer or a microfluidic viscometer; and the absolute viscosity of the liquid pharmaceutical formulation is less than the absolute viscosity of a control formulation comprising the antibody and the pharmaceutically acceptable solvent, but without the cimetidine or a pharmaceutically acceptable salt thereof;

wherein the absolute viscosity is an extrapolated zero-shear viscosity.

In a second aspect, there is provided a method of preparing any of the liquid pharmaceutical formulation disclosed herein, comprising the step of combining the antibody, the pharmaceutically acceptable solvent, and the cimetidine or pharmaceutically acceptable salt thereof.

In a third aspect, there is provided a lyophilized composition comprising: (i) an antibody; (ii) cimetidine or a pharmaceutically acceptable salt thereof; and (iii) a pharmaceutically acceptable excipient;
wherein the lyophilized composition is reconstitutable to have an antibody concentration of at least 100 mg/ml.

We claim:

[Claim 1]

A liquid pharmaceutical formulation for injection comprising:

(i) at least 100 mg/ml of an antibody;

(ii) cimetidine or a pharmaceutically acceptable salt thereof; and

(iii) a pharmaceutically acceptable solvent;

wherein the liquid pharmaceutical formulation, when in a volume suitable for injection, has an absolute viscosity from about 1 cP to about 100 cP at 25°C as measured using a cone and plate viscometer or a microfluidic viscometer; and the absolute viscosity of the liquid pharmaceutical formulation is less than the absolute viscosity of a control formulation comprising the antibody and the pharmaceutically acceptable solvent, but without the cimetidine or a pharmaceutically acceptable salt thereof;

wherein the absolute viscosity is an extrapolated zero-shear viscosity.

[Claim 2]

The liquid pharmaceutical formulation of claim 1, wherein the antibody is a monoclonal antibody.

[Claim 3]

The liquid pharmaceutical formulation of claim 1 or 2, wherein the antibody has a molecular weight of from about 120 kDa to about 250 kDa.

[Claim 4]

The liquid pharmaceutical formulation of any one of claims 1-3, comprising from about 100 mg/ml to about 300 mg/ml of the antibody.

[Claim 5]

The liquid pharmaceutical formulation of any one of claims 1-4, comprising from about 183 mg/ml to about 215 mg/ml of the antibody.

[Claim 6]

The liquid pharmaceutical formulation of any one of claims 1-5, wherein the pharmaceutically acceptable solvent is aqueous.

[Claim 7]

The liquid pharmaceutical formulation of any one of claims 1-6, wherein the cimetidine or a pharmaceutically acceptable salt thereof is present at a concentration of from about 0.01 M to about 1.0 M.

[Claim 8]

The liquid pharmaceutical formulation of any one of claims 1-7, wherein the cimetidine or a pharmaceutically acceptable salt thereof is present at a concentration of from about 0.15 M to about 0.25 M.

[Claim 9]

The liquid pharmaceutical formulation of any one of claims 1-8, further comprising one or more pharmaceutically acceptable excipients comprising a sugar, sugar alcohol, buffering agent, preservative, carrier, antioxidant, chelating agent, natural polymer, synthetic polymer, cryoprotectant, lyoprotectant, surfactant, bulking agent, stabilizing agent, or any combination thereof.

[Claim 10]

The liquid pharmaceutical formulation of claim 9, wherein the sugar alcohol is sorbitol or mannitol.

[Claim 11]

The liquid pharmaceutical formulation of claim 9, wherein the one or more pharmaceutically acceptable excipients comprise a polysorbate, poloxamer 188, sodium lauryl sulfate, a polyol, a poly(ethylene glycol), glycerol, a propylene glycol, or a poly(vinyl alcohol).

[Claim 12]

The liquid pharmaceutical formulation of any one of claims 1-11 in a unit-dose vial, multidose vial, cartridge, or pre-filled syringe.

[Claim 13]

The liquid pharmaceutical formulation of any one of claims 1-12, wherein the liquid pharmaceutical formulation is reconstituted from a lyophilized composition.

[Claim 14]

The liquid pharmaceutical formulation of any one of claims 1-13, wherein the liquid pharmaceutical formulation is isotonic to human blood serum.

[Claim 15]

The liquid pharmaceutical formulation of any one of claims 1-14, wherein the absolute viscosity is measured at a shear rate of at least about 0.5 s^{-1} when measured using a cone and plate viscometer, or a shear rate of at least about 1.0 s^{-1} when measured using a microfluidic viscometer.

[Claim 16]

The liquid pharmaceutical formulation of any one of claims 1-15, characterized in that the liquid pharmaceutical formulation is to be administered to a subject, wherein the administration comprises subcutaneous or intramuscular injection.

[Claim 17]

The liquid pharmaceutical formulation of claim 16, wherein the injection is to be performed with a syringe.

[Claim 18]

The liquid pharmaceutical formulation of claim 17, wherein the syringe is a heated syringe, a self-mixing syringe, an auto-injector, a pre-filled syringe, or combinations thereof.

[Claim 19]

The liquid pharmaceutical formulation of any one of claims 16-18, wherein the liquid pharmaceutical formulation has a volume of equal to or less than about 1.5 ml for the subcutaneous injection, or equal to or less than about 3 ml for the intramuscular injection.

[Claim 20]

The liquid pharmaceutical formulation of any one of claims 16-19, wherein the liquid pharmaceutical formulation produces a primary irritation index of less than 3 when evaluated using a Draize scoring system.

[Claim 21]

The liquid pharmaceutical formulation of any one of claims 16-20, wherein the liquid pharmaceutical formulation is to be injected by an injection force that is at least 10% less than an injection force for a liquid pharmaceutical formulation comprising the antibody and the pharmaceutically acceptable solvent, but without the cimetidine or a pharmaceutically acceptable salt thereof.

[Claim 22]

The liquid pharmaceutical formulation of any one of claims 16-20, wherein the liquid pharmaceutical formulation is to be injected by an injection force that is at least 20% less than an injection force for a liquid pharmaceutical formulation comprising the antibody and the pharmaceutically acceptable solvent, but without the cimetidine or a pharmaceutically acceptable salt thereof.

[Claim 23]

The liquid pharmaceutical formulation of any one of claims 16-22, wherein the injection is to be performed with a needle between 27 and 31 gauge in diameter and the injection force is less than 30 N with the 27 gauge needle.

[Claim 24]

A method of preparing the liquid pharmaceutical formulation of any one of claims 1-15, comprising the step of combining the antibody, the pharmaceutically acceptable solvent, and the cimetidine or a pharmaceutically acceptable salt thereof.

[Claim 25]

A lyophilized composition comprising:

(i) an antibody;

(ii) cimetidine or a pharmaceutically acceptable salt thereof; and

(iii) a pharmaceutically acceptable excipient;

wherein the lyophilized composition is reconstitutable to have an antibody concentration of at least 100 mg/ml.