STABILIZATION OF IMMUNOGLOBULINS THROUGH AQUEOUS FORMULATION WITH HISTIDINE AT WEAK ACIDIC TO NEUTRAL PH

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] The present application claims the benefit of U.S. Provisional Application No. 61/384,209, filed September 17, 2010, the content of which is expressly incorporated herein by reference in its entirety for all purposes.

BACKGROUND OF THE INVENTION

[0002] Biologics are medicinal products created by biological processes, including preparations isolated from natural sources (*e.g.*, human plasma) and recombinant DNA technologies. Within the healthcare and pharmaceutical industries, biologics are becoming increasingly important for patient treatment and overall revenue growth (Goodman M. Nat Rev Drug Discov. (2009) Nov;8(11):837). One important class of biologic drugs is therapeutic proteins, both isolated from natural sources and recombinantly produced. For example, plasma proteins are manufactured for therapeutic administration by isolation from pooled human plasma (*e.g.*, GAMMAGARD LIQUID® [IVIG, Immune Globulin Intravenous (Human) 10%]; Baxter International, Deerfield, IL) and recombinant means (*e.g.*, ADVATE® [Antihemophilic Factor (Recombinant), Plasma/Albumin-Free Method]; Baxter International, Deerfield, IL).

[0003] The administration of therapeutic proteins are primarily performed by intravenous (IV), subcutaneous (SQ), and intramuscular administration, although other routes of administration may be used depending upon the therapeutic protein and condition being treated. Most of the immunoglobulins are administered intravenously as larger volumes can be delivered rapidly by the intravenous route to provide the physiologic levels of IgG needed for the effective treatment of various diseases, such as primary immune deficiencies (PID), immune (idiopathic) thrombocytopenic purpura (ITP) and the Kawasaki syndrome. Due to the nature of IV administration, therapy via this route is a slow and timely process, leading to problems with patient compliance.

[0004] Subcutaneous (SQ) administration of therapeutic proteins is an alternative to intravenous administration. Compared to IV infusions, SQ administration has several advantages. For example, it can reduce the incidence of systemic reactions, it does not require sometimes-difficult IV access, and gives patients more independence.

[0005] In order to improve patient compliance, it would be convenient to provide the protein in a liquid ready to use formulation. However, many human or humanized therapeutic proteins are unstable when formulated at or near neutral pH. A variety of degradation pathways exist for proteins especially in liquid formulations, implicating both chemical and physical instability. Chemical instability includes deamination, aggregation, clipping of the peptide backbone, and oxidation of methionine residues. Physical instability encompasses many phenomena, including, for example, aggregation. Protein instability is particularly problematic for labile proteins that are unstable at mildly acidic to neutral pH. To combat these issues, intravenously administrable immunoglobulins have been formulated at acidic pH, effectively increasing their stability in the formulation (products that are formulated at acidic pH are, *e.g.*, Gamunex (Talecris), Gammagard Liquid (Baxter) or Privigen (CSL).

[0006] To combat these issues, therapeutic protein compositions are often formulated at acidic pH, effectively increasing their stability in the formulation. Unfortunately, scientific publications have reported that, for example, intramuscular administration of acidic aqueous preparations can cause pain, and potentially could result in tissue damage (Steen *et al.*, 2001; Sluka *et al.*, 2000, the disclosures of which are incorporated by reference herein in their entireties for all purposes). In other cases, where aqueous formulations have been found not to adequately stabilize the therapeutic proteins, lyophilized formulations are used which must be reconstituted prior to administration. In both cases, these factors can cause a less satisfactory drug administration experience and/or inconvenience for the patient, resulting in reduced patient compliance.

[0007] U.S. Patent No. 6,267,958 describes the formulation of lyophilized monoclonal antibodies with low concentrations of histidine buffer (*i.e.*, 5-10 mM) at pH 6.0 or 7.0 and a disaccharide (*i.e.*, sucrose or trehalose) at a molar concentration that is 100 to 1500 times greater than the molar concentration of the monoclonal antibody. However, the monoclonal antibody

formulations are unstable in the absence of the disaccharide, as evidenced by the high level of aggregate formation upon reconstitution when formulated with histidine alone.

[0008] U.S. Patent Application Publication No. 2010/0015157 describes the formulation of monoclonal antibodies with low concentrations of histidine acetate buffer (*i.e.*, 10-20 mM) at pH 5.5 to 6.5 with non-ionic surfactants and/or disaccharides (*i.e.*, sucrose or trehalose). However, the monoclonal antibody formulations are unstable in the absence of a non-ionic surfactants and/or disaccharides, as evidenced by the high turbidity and level of antibody aggregation seen in compositions formulated with histidine alone.

[0009] As such, there is a need in the art for formulations and methods of formulation that stabilize these labile therapeutic proteins in aqueous compositions at mildly acidic to neutral pH. The present invention satisfies these and other needs by, among other aspects, providing immunoglobulin compositions formulated with histidine at mild acidic to neutral pH that stabilize labile therapeutic proteins.

BRIEF SUMMARY OF INVENTION

[0010] [0008] The present invention is based in part by the surprising finding that the inclusion of histidine in an immunoglobulin composition formulated at mildly acidic to neutral pH significantly stabilizes the formulation.

[0011] Advantageously, the storage-stable aqueous immunoglobulin compositions provided herein remain stable for long periods at temperatures (*e.g.*, for a year or longer) without the inclusion of additional excipients such as non-ionic surfactants and saccharides.

[0012] In contrast to previously described monoclonal antibody compositions, that are formulated using low concentrations of histidine (*i.e.*, from 5 mM to 20 mM) at mildly acidic to neutral pH, the aqueous immunoglobulin compositions provided herein, which are formulated with moderate to high concentrations of histidine (*i.e.*, from 50 mM to 500 mM), are stable at mildly acidic to neutral pH in the absence of surfactants (*e.g.*, non-ionic surfactants such as polysorbate 80) and saccharides (*e.g.*, disaccharides such as sucrose and trehalose). The use of fewer components for the formulation of immunoglobulins may be beneficial, as acute renal failure or insufficiency has been linked to the use of IVIG formulated with sucrose, maltose, and

glucose (MMWR Morb Mortal Wkly Rep. 1999 Jun 25;48(24):518-21; Kwan *et al.* Hong Kong Med J. 2005 Feb;11(1):45-9). Similarly, sever hypersensitivity reactions may occur in patients administered IVIG formulated with polysorbate 80. In fact, Hizentra® (Immune Globulin Subcutaneous (Human), 20% Liquid; CSL Behring AG, Bern, Switzerland) is contraindicated in patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin or to components of Hizentra, such as polysorbate 80 (Hizentra Prescribing Information). Furthermore, the ability to stably formulate immunoglobulins at mildly acidic to neutral pH allows for the manufacture of pharmaceutical compositions that may be administered subcutaneously (SQ) or intramuscularly (IM) without the pain and potential for tissue damage that is associated with the SQ and IM administration of compositions formulated at acidic pH.

[0013] In one aspect, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: (a) an immunoglobulin; (b) from 50 mM to 500 mM histidine; (c) from 0 mM to 10 mM of an alkali metal cation; and (d) a pH from 5.5 to 7.0.

[0014] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition contains from 150 mM to 350 mM histidine.

[0015] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition contains from 225 mM to 275 mM histidine.

[0016] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition contains from 0 mM to 1 mM of an alkali metal cation.

[0017] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition contains from 10 mM to 400 mM chloride ions.

[0018] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition contains from 100 mM to 200 mM chloride ions.

[0019] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the pH of the composition is from 5.5 to 6.5.

[0020] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the pH of the composition is 6.1±0.2.

[0021] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition further comprises an antioxidant.

[0022] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition does not contain a surfactant or sugar.

[0023] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition is stored under an inert gas.

[0024] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition is stored under an inert gas selected from the group consisting of nitrogen, argon, carbon dioxide, helium, krypton, and xenon.

[0025] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition is stored under nitrogen.

[0026] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition is stored under argon.

[0027] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the immunoglobulin is a polyclonal immunoglobulin.

[0028] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the immunoglobulin is a monoclonal immunoglobulin.

[0029] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the immunoglobulin is an IgG immunoglobulin.

[0030] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the immunoglobulin is enriched from pooled human plasma.

[0031] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the immunoglobulin is a recombinant immunoglobulin.

[0032] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the concentration of the immunoglobulin is 50±5 g/L.

[0033] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the concentration of the immunoglobulin is less than 50 g/L.

[0034] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the concentration of the immunoglobulin is at least 50 g/L.

[0035] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the concentration of the immunoglobulin is from 50 g/L to 150 g/L.

[0036] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the concentration of the immunoglobulin is 100±10 g/L.

[0037] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the concentration of the immunoglobulin is at least 100 g/L.

[0038] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the concentration of the immunoglobulin is 150±15 g/L.

[0039] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the concentration of the immunoglobulin is from 150 g/L to 250 g/L.

[0040] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the concentration of the immunoglobulin is 200±20 g/L.

[0041] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the concentration of the immunoglobulin is at least 200 g/L.

[0042] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition is stable for at least 1 month when stored at from 38°C to 42°C.

[0043] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition is stable for at least 3 months when stored at from 38°C to 42°C.

[0044] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition is stable for at least 6 months when stored at from 38°C to 42°C.

[0045] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition is stable for at least 6 months when stored at from 28°C to 32°C.

[0046] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition is stable for at least 1 year when stored at from 28°C to 32°C.

[0047] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition is stable for at least 2 years when stored at from 28°C to 32°C.

[0048] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state remains below 2%.

[0049] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state is from 0% to 2% and the percentage of immunoglobulin in the monomeric state is from 85% to 100%.

[0050] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, a composition having the same components, but formulated at pH 4.8, is stable for less than 1 month when stored at from 38°C to 42°C.

[0051] In a specific embodiment of the storage stable, aqueous immunoglobulin compositions provided above, a composition having the same components, but formulated at pH 4.8, is stable for less than 6 months when stored at from 28°C to 32°C.

[0052] In one aspect, the present invention provides a method for stabilizing an immunoglobulin composition, the method comprising formulating the composition at a pH between 5.5 and 7.0, wherein the formulated composition comprises: (a) an immunoglobulin; (b) from 50 mM to 500 mM histidine; and (c) from 0 mM to 10 mM of an alkali metal cation.

[0053] In a specific embodiment of the methods provided above, the formulated composition contains from 150 mM to 350 mM histidine.

[0054] In a specific embodiment of the methods provided above, the formulated composition contains from 225 mM to 275 mM histidine.

[0055] In a specific embodiment of the methods provided above, the formulated composition contains from 0 mM to 1 mM of an alkali metal cation.

[0056] In a specific embodiment of the methods provided above, the formulated composition contains from 10 mM to 400 mM chloride ions.

[0057] In a specific embodiment of the methods provided above, the formulated composition contains from 100 mM to 200 mM chloride ions.

[0058] In a specific embodiment of the methods provided above, the pH of the formulated composition is from 5.5 to 6.5.

[0059] In a specific embodiment of the methods provided above, the pH of the formulated composition is 6.1±0.2.

[0060] In a specific embodiment of the methods provided above, the formulated composition further comprises an antioxidant.

[0061] In a specific embodiment of the methods provided above, the formulated composition does not contain a surfactant or sugar.

[0062] In a specific embodiment of the methods provided above, the formulated composition is stored under an inert gas.

[0063] In a specific embodiment of the methods provided above, the formulated composition is stored under an inert gas selected from the group consisting of nitrogen, argon, carbon dioxide, helium, krypton, and xenon.

[0064] In a specific embodiment of the methods provided above, the formulated composition is stored under nitrogen.

[0065] In a specific embodiment of the methods provided above, the formulated composition is stored under argon.

[0066] In a specific embodiment of the methods provided above, the immunoglobulin is a polyclonal immunoglobulin.

[0067] In a specific embodiment of the methods provided above, the immunoglobulin is a monoclonal immunoglobulin.

[0068] In a specific embodiment of the methods provided above, the immunoglobulin is an IgG immunoglobulin.

[0069] In a specific embodiment of the methods provided above, the immunoglobulin is enriched from pooled human plasma.

[0070] In a specific embodiment of the methods provided above, the immunoglobulin is a recombinant immunoglobulin.

[0071] In a specific embodiment of the methods provided above, the concentration of the immunoglobulin in the formulated composition is 50±5 g/L.

[0072] In a specific embodiment of the methods provided above, the concentration of the immunoglobulin in the formulated composition is less than 50 g/L.

[0073] In a specific embodiment of the methods provided above, the concentration of the immunoglobulin in the formulated composition is at least 50 g/L.

[0074] In a specific embodiment of the methods provided above, the concentration of the immunoglobulin in the formulated composition is from 50 g/L to 150 g/L.

[0075] In a specific embodiment of the methods provided above, the concentration of the immunoglobulin in the formulated composition is 100±10 g/L.

[0076] In a specific embodiment of the methods provided above, the concentration of the immunoglobulin in the formulated composition is at least 100 g/L.

[0077] In a specific embodiment of the methods provided above, the concentration of the immunoglobulin in the formulated composition is 150±15 g/L.

[0078] In a specific embodiment of the methods provided above, the concentration of the immunoglobulin in the formulated composition is from 150 g/L to 250 g/L.

[0079] In a specific embodiment of the methods provided above, the concentration of the immunoglobulin in the formulated composition is 200±20 g/L.

[0080] In a specific embodiment of the methods provided above, the concentration of the immunoglobulin in the formulated composition is at least 200 g/L.

[0081] In a specific embodiment of the methods provided above, the formulated composition is stable for at least 1 month when stored at from 38°C to 42°C.

[0082] In a specific embodiment of the methods provided above, the formulated composition is stable for at least 3 months when stored at from 38°C to 42°C.

[0083] In a specific embodiment of the methods provided above, the formulated composition is stable for at least 6 months when stored at from 38°C to 42°C.

[0084] In a specific embodiment of the methods provided above, the formulated composition is stable for at least 6 months when stored at from 28°C to 32°C.

[0085] In a specific embodiment of the methods provided above, the formulated composition is stable for at least 1 year when stored at from 28°C to 32°C.

[0086] In a specific embodiment of the methods provided above, the formulated composition is stable for at least 2 years when stored at from 28°C to 32°C.

[0087] In a specific embodiment of the methods provided above, the formulated composition is considered stable as long as the percentage of immunoglobulin in the aggregated state remains below 2%.

[0088] In a specific embodiment of the methods provided above, the formulated composition is considered stable as long as the percentage of immunoglobulin in the aggregated state is from 0% to 2% and the percentage of immunoglobulin in the monomeric state is from 85% to 100%.

[0089] In a specific embodiment of the methods provided above, an immunoglobulin composition having the same components as the formulated composition, but formulated at pH 4.8, is stable for less than 1 month when stored at from 38°C to 42°C.

[0090] In a specific embodiment of the methods provided above, an immunoglobulin composition having the same components as the formulated composition, but formulated at pH 4.8, is stable for less than 6 months when stored at from 28°C to 32°C.

BRIEF DESCRIPTION OF DRAWINGS

[0091] **Figure 1.** Aggregation of 20% IgG formulations after 6 months storage at 38°C to 42°C.

[0092] **Figure 2.** Discoloration of immunoglobulin compositions from study IGSC73 formulated with proline, histidine (pH 6.1), or glycine and stored at 28°C to 32°C under **(2A)** normal atmosphere, **(2B)** nitrogen, or **(2C)** argon for up to 12 months.

[0093] **Figure 3.** Discoloration of immunoglobulin compositions from study IGSC74 formulated with proline, histidine (pH 4.8), or glycine and stored at 28°C to 32°C under **(3A)** normal atmosphere, **(3B)** nitrogen, or **(3C)** argon for up to 12 months.

DETAILED DESCRIPTION OF INVENTION

I. Introduction

[0094] Therapeutic immunoglobulin preparations are often times formulated at acidic pH or as lyophilized compositions due to their labile nature in aqueous solution at or near neutral pH. As discussed above, these formulations are less convenient, may cause pain and/or tissue damage upon administration, and likely reduce patient compliance. Advantageously, the present invention provides means for stably formulating immunoglobulins in aqueous solution at or near neutral pH. In one aspect, the present invention provides immunoglobulin compositions stabilized by the addition of a moderate amount of histidine (*e.g.*, 50 mM to 500 mM histidine,

preferably 150 mM to 350 mM histidine) to formulations at mildly acidic to neutral pH (*e.g.*, 5.5 to 7.0).

[0095] The present invention is based in part on the discovery that immunoglobulin compositions can be stabilized by the addition of moderate levels of histidine to formulations at mildly acidic to neutral pH in the absence of an alkali metal cation (*e.g.*, Na^+ or K^+). Notably, the histidine formulations at mildly acidic to neutral pH provided herein are significantly more stable than similar compositions formulated at acidic pH, as well as immunoglobulin compositions formulated with proline or glycine at acidic pH. Advantageously, the ability to stably formulate immunoglobulins at mildly acidic to neutral pH provides for formulations that are not painful upon administration and do not have the same risks for tissue damage.

[0096] Our new studies provided herein demonstrate that purified plasma-derived immunoglobulin preparations formulated in 0.25 M glycine could be stabilized by the addition of sodium chloride in a pH dependent manner. Examples 1 and 2 shows that these immunoglobulin preparations, having a final concentration of between about 90 g/L and about 220 g/L, were stabilized for at least 24 months when stored at a temperature of 28°C to 32°C, and for at least 6 months when stored at a temperature of 38°C to 42°C. Maximum stability was observed with addition of 150 mM sodium chloride.

[0097] Under these conditions, the addition of sodium chloride to formulations at pH values at and above 7.0 resulted in considerably higher aggregation and fragmentation rates of the immunoglobulins, compared to samples formulated at a pH between 5.5 and 7.0 (**Table 3**). Similarly, it was previously observed that sodium chloride significantly destabilized immunoglobulin formulations with acidic pH values (under 5.5).

[0098] Advantageously, it is shown herein (*e.g.*, in Examples 3 to 17) that the use of histidine stabilizes immunoglobulin formulations at mildly acidic to neutral pH in the absence of sodium chloride. It should be noted that the formulations may contain chloride ions provided from hydrochloric acid used to pH histidine buffers and the final formulation itself.

II. Definitions

[0099] As used herein, a "storage stable" aqueous composition refers to a protein solution (*e.g.*, an immunoglobulin solution) that has been formulated with histidine to increase the stability of the protein in solution, for example by at least 20%, over a given storage time. In the context of the present invention, a labile protein solution (*e.g.*, immunoglobulin solution) formulated at a mildly acidic to neutral pH can be made "storage stable" by the addition of histidine as a stabilizing agent. The stability of the immunoglobulin formulation can be measured, for example, by monitoring the formation of aggregates, loss of bulk enzymatic activity, loss of antigenic titer or formation of degradation products, over a period of time.

[0100] As used herein, the term "time of stability" refers to the length of time a composition is considered stable. For example, the time of stability for a composition may refer to the length of time for which the level of protein aggregation and/or degradation in the composition remains below a certain threshold (*e.g.*, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, *etc.*), the length of time a composition maintains an enzymatic activity above a certain threshold (*e.g.*, 100%, 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, *etc.* of the amount of activity present in the composition at the start of the storage period), or the length of time a composition maintains an antigenic titer (*e.g.*, 100%, 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, *etc.* of the antigenic titer present in the composition at the start of the storage period).

[0101] In the context of the present invention, a storage stable aqueous composition of a therapeutic protein (*e.g.*, an immunoglobulin composition) formulated with histidine at mildly acidic to neutral pH will have a longer time of stability than a composition of the same therapeutic protein formulated at acidic pH with histidine or mildly acidic to neutral pH without histidine. A storage stable aqueous composition of a therapeutic protein (*e.g.*, an immunoglobulin composition), as provided herein, will have a time of stability that is, for example, at least 20% greater than the time of stability for the same composition formulated in the absence of a histidine or formulated at acid pH with histidine, or formulated at acidic pH with glycine or proline, or at least 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190% greater, or at least 2 times greater, or at least 2.5 times, 3.0 times, 3.5 times, 4.0 times, 4.5 times,

5.0 times, 5.5 times, 6.0 times, 6.5 times, 7.0 times, 7.5 times, 8.0 times, 8.5 times, 9.0 times, 9.5 times, 10 times, or more times greater than the time of stability for the same composition formulated in the absence of a histidine or formulated at acid pH with histidine, or formulated at acidic pH with glycine or proline. In one embodiment, the immunoglobulin composition may be stable under storage conditions for from 25% to 1000% longer when formulated with histidine at mildly acidic to neutral pH, as provided herein, as compared to the stability of the same immunoglobulin under formulated in the absence of a histidine or formulated at acid pH with histidine, or formulated at acidic pH with glycine or proline. In other embodiments, the composition may be stable for from 50% to 1000%, 100% to 1000%, 200% to 1000%, 300% to 1000%, 400% to 1000%, 500% to 1000%, 600% to 1000%, or 700% to 1000%, when formulated according to the present invention.

[0102] As used herein, the term "stable" refers to a state of a protein composition (*e.g.*, an immunoglobulin solution) suitable for pharmaceutical administration. In the context of the present invention, an immunoglobulin solution is generally considered to be stable when the level of immunoglobulin aggregation and/or degradation in the composition remains below a certain threshold (*e.g.*, below 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, *etc.*) or the when the antigenic titer remains above a certain threshold (*e.g.*, above 100%, 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, *etc.* of the antigenic titer present in the composition at the start of a storage period).

[0103] The European Pharmacopoeia (Ph. Eur.) standard for normal human immunoglobulins is that the composition have: (i) a monomer and dimer content equal to or greater than 85% of the total area of a standard chromatogram; and (ii) a polymer and aggregate sum content of not more than 10% of the total area of the chromatogram. For IGIV the sum of the peak areas of the monomer and dimer represents not less than 95 per cent and the maximum amount of polymers and aggregates is no more than 2%. Accordingly, in one embodiment, a composition provided herein is considered to be stable when at least 85% of the immunoglobulin content is monomeric and no more than 2% of the immunoglobulin content is aggregated.

[0104] As used herein, "storage" means that a formulation is not immediately administered to a subject once prepared, but is kept for a period of time under particular conditions (*e.g.*, at a

particular temperature, under a particular atmosphere, protected from light, *etc.*) prior to use. For example, a liquid formulation can be kept for days, weeks, months or years, prior to administration to a subject under varied temperatures such as refrigerated (0° to 10°C) or room temperature (e.g., temperature between 20 and 25° C).

[0105] For the purposes of the present invention, when referring to a concentration of an individual component of a composition, the phrases "no more than X" and "from 0 to X" are equivalent and refer to any concentration between and including 0 and X. For example, the phrases "a concentration of no more than 2%" and "a concentration of from 0% to 2%" are equivalent and include 0%, 1%, and 2%.

[0106] For the purposes of the present invention, when referring to a concentration of an individual component of a composition, the phrases "no less than X" refers to any concentration X or higher. For example, the phrase "a concentration of no less than 98%" includes 98%, 99%, and 100%.

[0107] For the purposes of the present invention, when referring to a concentration of an individual component of a composition, the phrases "between X and Y" and "from X to X" are equivalent and refer to any concentration between and including X and Y. For example, the phrases "a concentration of between 49% and 51%" and "a concentration of from 49% to 51%" are equivalent and include 49%, 50%, and 51%.

[0108] As used herein, an "alkali metal chloride salt" refers to an inorganic salt of an alkali metal and chlorine. For the purposes of the present invention, the alkali metal chloride salt will be a pharmaceutically acceptable salt, most commonly sodium or potassium chloride. In a preferred embodiment, the salt is sodium chloride.

[0109] Likewise, an "alkali metal cation" will most commonly refer to a sodium cation (Na^+) or potassium cation (K^+) and can be contributed by an alkali metal chloride salt or other source. In the context of the present invention, a hydrogen ion is not considered an alkali metal cation, and thus the inclusion of hydrochloric acid will not contribute to the alkali metal cation content of the formulation.

[0110] As used herein, an "antibody" refers to a polypeptide substantially encoded by an immunoglobulin gene or immunoglobulin genes, or fragments thereof, which specifically bind and recognize an analyte (antigen). The recognized immunoglobulin genes include the kappa, lambda, alpha, gamma, delta, epsilon and mu constant region genes, as well as the myriad immunoglobulin variable region genes. Light chains are classified as either kappa or lambda. Heavy chains are classified as gamma, mu, alpha, delta, or epsilon, which in turn define the immunoglobulin classes, IgG, IgM, IgA, IgD, and IgE, respectively.

[0111] An exemplary immunoglobulin (antibody) structural unit is composed of two pairs of polypeptide chains, each pair having one "light" (about 25 kD) and one "heavy" chain (about 50-70 kD). The N-terminus of each chain defines a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The terms variable light chain (VL) and variable heavy chain (VH) refer to these light and heavy chains respectively. In a particular exemplary embodiment, the immunoglobulin will consist of an immunoglobulin preparation isolated from pooled plasma (preferably human plasma) comprising IgG immunoglobulins.

[0112] As used herein, the term "about" denotes an approximate range of plus or minus 10% from a specified value. For instance, the language "about 20%" encompasses a range of 18-22%. As used herein, about also includes the exact amount. Hence "about 20%" means "about 20%" and also "20%."

[0113] By "therapeutically effective amount or dose" or "sufficient/effective amount or dose," it is meant a dose that produces effects for which it is administered. The exact dose will depend on the purpose of the treatment, and will be ascertainable by one skilled in the art using known techniques (*see, e.g.*, Lieberman, Pharmaceutical Dosage Forms (vols. 1-3, 1992); Lloyd, The Art, Science and Technology of Pharmaceutical Compounding (1999); Pickar, Dosage Calculations (1999); and Remington: The Science and Practice of Pharmacy, 20th Edition, 2003, Gennaro, Ed., Lippincott, Williams & Wilkins).

[0114] As used herein, a "stabilizing agent" refers to a chemical, other than an alkali metal chloride salt, which aids in the stabilization of a therapeutic agent in an aqueous formulation under mildly acid to neutral pH. Examples of suitable stabilizing agents for the formulations and methods provided herein include, without limitation, buffering agents (e.g., TRIS, HEPES,

potassium or sodium phosphate, amino acids, etc.), osmolytes (e.g., sugars, sugar alcohols, etc.), bulking agents (e.g., amino acids, etc.), divalent salts, surfactants, and the like.

[0115] As used herein, "amino acids" refers to any natural or non-natural pharmaceutically acceptable amino acid. Non-limiting examples of amino acids include, isoleucine, alanine, leucine, asparagine, lysine, aspartic acid, methionine, cysteine, phenylalanine, glutamic acid, threonine, glutamine, tryptophan, glycine, valine, proline, selenocysteine, serine, tyrosine, arginine, histidine, ornithine, taurine, and the like.

[0116] Any sugar such as mono-, di-, or polysaccharides, or water-soluble glucans, including for example fructose, glucose, mannose, sorbose, xylose, maltose, lactose, sucrose, dextran, trehalose, pullulan, dextrin, cyclodextrin, soluble starch, hydroxyethyl starch, and carboxymethylcellulose may be used.

[0117] As used herein, a "sugar alcohol" refers to a hydrocarbon having between about 4 and about 8 carbon atoms and at least one hydroxyl group. Non-limiting examples of sugar alcohols that may be used in formulations provided herein include, mannitol, sorbitol, inositol, galactitol, dulcitol, xylitol, and arabitol.

[0118] As used herein, the term "activity" refers to a functional activity or activities of a polypeptide or portion thereof associated with a full-length (complete) protein. Functional activities include, but are not limited to, biological activity, catalytic or enzymatic activity, antigenicity (*i.e.*, the ability to bind or compete with a polypeptide for binding to an anti-polypeptide antibody), immunogenicity, ability to form multimers, and the ability to specifically bind to a receptor or ligand for the polypeptide.

III. Formulations

[0119] Among other aspects, the present invention provides stabilized formulations of immunoglobulins for therapeutic administration. The following embodiments are based in part on the unexpected discovery that the formulation of immunoglobulins with histidine at mildly acidic to neutral pH stabilizes the immunoglobulins that are otherwise labile at these pH values, and/or labile when formulated with histidine at an acidic pH, and/or labile when formulated in the presence of alkali metal cations.

[0120] As will be recognized by one of skill in the art, immunoglobulin compositions formulated at a particular pH may contain residual counter ions contributed from one or more pH modifying agents. For example, the storage stable compositions provided herein may contain chloride anions contributed from hydrochloric acid, acetate anions contributed from glacial acetic acid, sodium cations contributed from sodium hydroxide, and the like. In the context of the present invention, a storage stable immunoglobulin composition consisting of or consisting essentially of: an immunoglobulin and histidine may further comprise one or more counter ion, as necessitated by the formulation process at a particular pH.

[0121] Any immunoglobulin may be stabilized by the formulations provided herein. Non-limiting examples of immunoglobulin preparations that may be stabilized include, plasma-derived immunoglobulin preparations, recombinant polyclonal or monoclonal preparations, minibodies, diabodies, triabodies, antibody fragments such as Fv, Fab and F(ab)2 or fragmented antibodies such as monovalent or multivalent single chain Fvs (scFv, sc(Fv)2, minibodies, diabodies, and triabodies such as scFv dimers) in which the variable regions of an antibody are joined together via a linker such as a peptide linker, and the like. Recombinant antibodies include murine antibodies, rodent antibodies, human antibodies, chimeric human antibodies (e.g., human / murine chimeras), humanized antibodies (e.g., humanized murine antibodies), and the like. In preferred embodiments, the recombinant antibody is a human, chimeric human, or humanized antibody suitable for administration to a human. In a preferred embodiment, the immunoglobulin in a full length, or near full length immunoglobulin, which will generally be more labile then engineered fragments thereof.

[0122] Generally, storage stable immunoglobulin formulations provided herein will be stabilized at room temperature (*i.e.*, between 20°C and 25°C) for an extended period of time. For example, in one embodiment, a storage stable, aqueous immunoglobulin composition will be stable when stored at room temperature for at least about 2 months. In another embodiment, the composition will be stable for at least about 3 months. In yet other embodiment, the composition will be stable for at least 1 about month, or at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, or more months. In a preferred embodiment, the composition will be stable for at least about 6 months. In a more preferred embodiment, the composition will be

stable for at least about 1 year. In a more preferred embodiment, the composition will be stable for at least about 2 years.

[0123] In one embodiment, the storage stable, aqueous immunoglobulin composition will be stable for at least six months at a temperature between about 28°C and about 32°C. In a specific embodiment, the storage stable, aqueous immunoglobulin composition will be stable for at least one year at a temperature between about 28°C and about 32°C. In a more specific embodiment, the storage stable, aqueous immunoglobulin composition will be stable for at least two years at a temperature between about 28°C and about 32°C. In another embodiment, the storage stable, aqueous immunoglobulin composition will be stable for at least one month at a temperature between about 38°C and about 42°C. In a specific embodiment, the storage stable, aqueous immunoglobulin composition will be stable for at least three months at a temperature between about 38°C and about 42°C. In a more specific embodiment, the storage stable, aqueous immunoglobulin composition will be stable for at least one year at a temperature between about 38°C and about 42°C.

[0124] In one embodiment, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state no more than 10%. In a preferred embodiment, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state no more than 9%. In a more preferred embodiment, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state no more than 8%. In a more preferred embodiment, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state no more than 7%. In a more preferred embodiment, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state no more than 6%. In a more preferred embodiment, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state no more than 5%. In a more preferred embodiment, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state no more than 4%. In a more preferred embodiment, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state no more than 3%. In a most preferred embodiment, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state no more than 2%.

[0125] In one embodiment, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state no more than 10% and the percentage of immunoglobulin in the monomeric state is no less than 85%. In a preferred embodiment, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state no more than 9% and the percentage of immunoglobulin in the monomeric state is no less than 85%. In a preferred embodiment, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state no more than 8% and the percentage of immunoglobulin in the monomeric state is no less than 85%. In a preferred embodiment, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state no more than 7% and the percentage of immunoglobulin in the monomeric state is no less than 85%. In a preferred embodiment, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state no more than 6% and the percentage of immunoglobulin in the monomeric state is no less than 85%. In a preferred embodiment, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state no more than 5% and the percentage of immunoglobulin in the monomeric state is no less than 85%. In a preferred embodiment, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state no more than 4% and the percentage of immunoglobulin in the monomeric state is no less than 85%. In a preferred embodiment, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state no more than 3% and the percentage of immunoglobulin in the monomeric state is no less than 85%. In a most preferred embodiment, the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state no more than 2% and the percentage of immunoglobulin in the monomeric state is no less than 85%.

[0126] After formulation, the storage stable, aqueous immunoglobulin compositions provided herein are typically sterile filtered and dispensed into a sterile containment vessel, which is sealed air-tight, for example, using a rubber stopper. Immunoglobulin compositions in the air-tight vessels are preferably protected from ambient light by storage in a dark place, the use of a tinted vessel material (typically glass or plastic), and/or covering the surface of the vessel with an opaque substance.

[0127] In certain embodiments, the headspace air in the containment vessel is replaced with an inert gas. The inert gas helps to maintain an inert atmosphere above the liquid composition. In one embodiment, the liquid is overlaid with inert gas. In another embodiment the liquid is degassed before overlaying it with inert gas, meaning that residual oxygen in the atmosphere may vary. In the context of the present invention, when an immunoglobulin composition is stored in a vessel in which the headspace air has been replaced with an inert gas, the composition has been overlaid with inert gas, or the composition is degassed prior to overlaying with inert gas, the composition is said to be "stored under inert gas." Non-limiting examples of inert gasses than may be used in conjunction with the present invention include, nitrogen, argon, carbon dioxide, helium, krypton, and xenon. In one particular embodiment, the inert gas is nitrogen. In another particular embodiment, the inert gas is argon. .

A. General Immunoglobulin Formulations

[0128] In one embodiment, the present invention provides storage stable, aqueous immunoglobulin composition comprising: an immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0129] In a particular embodiment, the storage stable, aqueous immunoglobulin composition comprises: an immunoglobulin; between 50 mM and 500 mM histidine; no more than 1 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0130] Advantageously, it has been found that the formulation of immunoglobulins with moderate concentrations of histidine (*e.g.*, 50 mM to 500 mM) at mildly acidic to neutral pH stabilizes the immunoglobulin composition in the absence of traditional stabilizing and bulking agents, such as surfactants (*e.g.*, non-ionic surfactants), sugars, and sugar alcohols.

[0131] Accordingly, in a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising an immunoglobulin; between 50 mM and 500 mM histidine; no more than 1 mM of an alkali metal cation; no more than 0.01% of a surfactant; no more than 1 mM of a sugar; no more than 1 mM of a sugar alcohol; and a pH between 5.5 and 7.0. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0132] In another specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: an immunoglobulin; between 50 mM and 500 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0133] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of an immunoglobulin; between 50 mM and 500 mM histidine; no more than 1 mM of an alkali metal cation; no more than 0.01% of a surfactant; no more than 1 mM of a sugar; no more than 1 mM of a sugar alcohol; and a pH between 5.5 and 7.0. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under

nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0134] The histidine formulations provided by the present invention may be used to stabilize any immunoglobulin composition, including but not limited to: immunoglobulin compositions isolated from pooled plasma (*e.g.*, human pooled plasma); immunoglobulin compositions isolated from mammary secretions; immunoglobulin compositions isolated from avian sources (*e.g.*, IgY containing compositions isolated from the yolk of chicken eggs); and recombinant immunoglobulins (*e.g.*, monoclonal or polyclonal antibodies). In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0135] In a preferred embodiment, the present invention provides a storage stable composition of immunoglobulins isolated from pooled plasma (*e.g.*, human pooled plasma). In a particular embodiment, the immunoglobulin composition isolated from pooled plasma comprises at least 90% IgG immunoglobulins. In a specific embodiment, the immunoglobulin composition isolated from pooled plasma comprises at least 95% IgG immunoglobulins. In a more specific embodiment, the immunoglobulin composition isolated from pooled plasma comprises at least 98% IgG immunoglobulins. In certain embodiments, the immunoglobulin composition isolated from pooled plasma comprises IgA and/or IgM immunoglobulins. In a specific embodiment, the final composition does not contain a surfactant or sugar.

1. Histidine

[0136] In one embodiment, the concentration of histidine in a storage stable immunoglobulin composition provided herein is between 50 mM and 500 mM. In another embodiment, the concentration of histidine in the formulation will be between 100 mM and 400 mM. In another embodiment, the concentration of histidine in the formulation will be between 200 mM and 300 mM. In another embodiment, the concentration of histidine in the formulation will be between 225 mM and 275 mM. In another embodiment, the concentration of histidine in the formulation will be between 240 mM and 260 mM. In a particular embodiment, the concentration of histidine will be 250 mM. In certain other embodiments, the concentration of histidine in the formulation will be 5±0.5 mM, 10±1 mM, 15±1.5 mM, 20±2 mM, 25±2.5 mM, 50±5 mM,

75±7.5 mM, 100±10 mM, 125±12.5 mM, 150±15 mM, 175±17.5 mM, 200±20 mM, 225±22.5 mM, 250±25 mM, 275±27.5 mM, 300±30 mM, 325±32.5 mM, 350±35 mM, 375±37.5 mM, 400±40 mM, 425±42.5 mM, 450±45 mM, 475±47.5 mM, 500±50 mM or higher. In yet other embodiments, the concentration of histidine in the formulation will be 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 50 mM, 75 mM, 100 mM, 125 mM, 150 mM, 175 mM, 200 mM, 225 mM, 250 mM, 275 mM , 300 mM, 325 mM, 350 mM, 375 mM, 400 mM, 425 mM, 450 mM, 475 mM, 500 mM or higher.

[0137] Accordingly, in one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: an immunoglobulin; between 100 mM and 400 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0138] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: an immunoglobulin; between 100 mM and 400 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0139] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: an immunoglobulin; between 100 mM and 400 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a

specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0140] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0141] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: an immunoglobulin; between 200 mM and 300 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0142] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In

one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0143] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: an immunoglobulin; between 225 mM and 275 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0144] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: an immunoglobulin; between 225 mM and 275 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0145] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: an immunoglobulin; between 225 mM and 275 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment

vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0146] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: an immunoglobulin; between 240 mM and 260 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0147] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: an immunoglobulin; between 240 mM and 260 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0148] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: an immunoglobulin; between 240 mM and 260 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In

another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0149] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: an immunoglobulin; 250 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0150] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: an immunoglobulin; 250 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0151] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: an immunoglobulin; 250 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is

stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

2. pH

[0152] The storage stable immunoglobulin compositions provided by the present invention are formulated at mildly acidic to neutral pH. Generally, this includes pH values between 5.5 and 7.0. In a preferred embodiment, the pH value is between 5.5 and 6.5. However, the range of pH values at which any individual immunoglobulin composition is stabilized by the inclusion of histidine in the formulation may vary, dependent upon the properties of the particular immunoglobulin.

[0153] For example, in one embodiment, a storage stable formulation will have a pH between 5.5 and 7.0. In another embodiment, a storage stable formulation will have a pH between 5.5 and 6.5. In other embodiments, the pH of the stabilizing formulation will be between 6.0 and 7.0. In another embodiment, the pH of the stabilizing formulation will be between 5.5 and 6.0. In one embodiment, the pH of the stabilizing formulation will be between 6.0 and 6.5. In another embodiment, the pH of the stabilizing formulation will be between 6.5 and 7.0. In another embodiment, the stabilizing formulation will have a pH of 6.0±0.4. In another embodiment, the stabilizing formulation will have a pH of 6.0±0.3. In another embodiment, the stabilizing formulation will have a pH of 6.0±0.2. In another embodiment, the stabilizing formulation will have a pH of 6.0±0.1. In another embodiment, the stabilizing formulation will have a pH of 6.1±0.5. In another embodiment, the stabilizing formulation will have a pH of 6.1±0.4. In another embodiment, the stabilizing formulation will have a pH of 6.1±0.3. In another embodiment, the stabilizing formulation will have a pH of 6.1±0.2. In another embodiment, the stabilizing formulation will have a pH of 6.1±0.1. In other embodiments, the pH of the stabilizing formulation may be 5.5±0.2, or 5.6±0.2, 5.7±0.2, 5.8±0.2, 5.9±0.2, 6.0±0.2, 6.1±0.2, 6.2±0.2, 6.3±0.2, 6.4±0.2, 6.5±0.2, 6.6±0.2, 6.7±0.2, 6.8±0.2, 6.9±0.2, or 7.0±0.2. In other embodiments, the pH of the stabilizing formulation may be 5.5±0.1, or 5.6±0.1, 5.7±0.1, 5.8±0.1, 5.9±0.1, 6.0±0.1, 6.1±0.1, 6.2±0.1, 6.3±0.1, 6.4±0.1, 6.5±0.1, 6.6±0.1, 6.7±0.1, 6.8±0.1, 6.9±0.1, or 7.0±0.1. In yet other embodiments, the pH of the stabilizing formulation may be 5.5, or 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, or 7.0.

[0154] Accordingly, in one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: an immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 6.5. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0155] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: an immunoglobulin; between 50 mM and 500 mM histidine; and a pH between 5.5 and 6.5. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0156] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: an immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 6.5. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0157] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 6.5. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0158] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: an immunoglobulin; between 200 mM and 300 mM histidine; and a pH between 5.5 and 6.5. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0159] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 6.5. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0160] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.4. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0161] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: an immunoglobulin; between 200 mM and 300 mM histidine; and a pH of 6.1±0.4. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0162] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.4. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0163] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.3. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0164] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: an immunoglobulin; between 200 mM and 300 mM histidine; and a pH of 6.1±0.3. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0165] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.3. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0166] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.2. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0167] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: an immunoglobulin; between 200 mM and 300 mM histidine; and a pH of 6.1±0.2. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0168] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.2. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0169] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.1. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0170] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: an immunoglobulin; between 200 mM and 300 mM histidine; and a pH of 6.1±0.1. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0171] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.1. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0172] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0173] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: an immunoglobulin; between 200 mM and 300 mM histidine; and a pH of 6.1. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0174] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0175] In certain embodiments, the combination of histidine concentration and pH of the formulation will be selected from any one of variations (Var.) 1 to 952, as provided in **Table 1** and **Table 2**.

[0176] Accordingly, in one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: an immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0177] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: an immunoglobulin and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0178] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: an immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a

specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

Table 1. Particular combinations of histidine concentration and pH useful for the formulation of immunoglobulins.

	Histidine (mM)							
pH	5-500	100-400	200-300	225-275	250±10	250	50±5	100±10
5.5-7.0	Var. 1	Var. 57	Var. 113	Var. 169	Var. 225	Var. 281	Var. 337	Var. 393
5.5-6.5	Var. 2	Var. 58	Var. 114	Var. 170	Var. 226	Var. 282	Var. 338	Var. 394
5.5-6.0	Var. 3	Var. 59	Var. 115	Var. 171	Var. 227	Var. 283	Var. 339	Var. 395
6.0-7.0	Var. 4	Var. 60	Var. 116	Var. 172	Var. 228	Var. 284	Var. 340	Var. 396
6.0-6.5	Var. 5	Var. 61	Var. 117	Var. 173	Var. 229	Var. 285	Var. 341	Var. 397
6.1±0.5	Var. 6	Var. 62	Var. 118	Var. 174	Var. 230	Var. 286	Var. 342	Var. 398
6.1±0.4	Var. 7	Var. 63	Var. 119	Var. 175	Var. 231	Var. 287	Var. 343	Var. 399
6.1±0.3	Var. 8	Var. 64	Var. 120	Var. 176	Var. 232	Var. 288	Var. 344	Var. 400
6.1±0.2	Var. 9	Var. 65	Var. 121	Var. 177	Var. 233	Var. 289	Var. 345	Var. 401
6.1±0.1	Var. 10	Var. 66	Var. 122	Var. 178	Var. 234	Var. 290	Var. 346	Var. 402
6.1	Var. 11	Var. 67	Var. 123	Var. 179	Var. 235	Var. 291	Var. 347	Var. 403
5.5±0.2	Var. 12	Var. 68	Var. 124	Var. 180	Var. 236	Var. 292	Var. 348	Var. 404
5.6±0.2	Var. 13	Var. 69	Var. 125	Var. 181	Var. 237	Var. 293	Var. 349	Var. 405
5.7±0.2	Var. 14	Var. 70	Var. 126	Var. 182	Var. 238	Var. 294	Var. 350	Var. 406
5.8±0.2	Var. 15	Var. 71	Var. 127	Var. 183	Var. 239	Var. 295	Var. 351	Var. 407
5.9±0.2	Var. 16	Var. 72	Var. 128	Var. 184	Var. 240	Var. 296	Var. 352	Var. 408
6.0±0.2	Var. 17	Var. 73	Var. 129	Var. 185	Var. 241	Var. 297	Var. 353	Var. 409
6.2±0.2	Var. 18	Var. 74	Var. 130	Var. 186	Var. 242	Var. 298	Var. 354	Var. 410
6.3±0.2	Var. 19	Var. 75	Var. 131	Var. 187	Var. 243	Var. 299	Var. 355	Var. 411
6.4±0.2	Var. 20	Var. 76	Var. 132	Var. 188	Var. 244	Var. 300	Var. 356	Var. 412
6.5±0.2	Var. 21	Var. 77	Var. 133	Var. 189	Var. 245	Var. 301	Var. 357	Var. 413
6.6±0.2	Var. 22	Var. 78	Var. 134	Var. 190	Var. 246	Var. 302	Var. 358	Var. 414
6.7±0.2	Var. 23	Var. 79	Var. 135	Var. 191	Var. 247	Var. 303	Var. 359	Var. 415
6.8±0.2	Var. 24	Var. 80	Var. 136	Var. 192	Var. 248	Var. 304	Var. 360	Var. 416
6.9±0.2	Var. 25	Var. 81	Var. 137	Var. 193	Var. 249	Var. 305	Var. 361	Var. 417
7.0±0.2	Var. 26	Var. 82	Var. 138	Var. 194	Var. 250	Var. 306	Var. 362	Var. 418
5.5±0.1	Var. 27	Var. 83	Var. 139	Var. 195	Var. 251	Var. 307	Var. 363	Var. 419
5.6±0.1	Var. 28	Var. 84	Var. 140	Var. 196	Var. 252	Var. 308	Var. 364	Var. 420
5.7±0.1	Var. 29	Var. 85	Var. 141	Var. 197	Var. 253	Var. 309	Var. 365	Var. 421
5.8±0.1	Var. 30	Var. 86	Var. 142	Var. 198	Var. 254	Var. 310	Var. 366	Var. 422
5.9±0.1	Var. 31	Var. 87	Var. 143	Var. 199	Var. 255	Var. 311	Var. 367	Var. 423
6.0±0.1	Var. 32	Var. 88	Var. 144	Var. 200	Var. 256	Var. 312	Var. 368	Var. 424
6.2±0.1	Var. 33	Var. 89	Var. 145	Var. 201	Var. 257	Var. 313	Var. 369	Var. 425
6.3±0.1	Var. 34	Var. 90	Var. 146	Var. 202	Var. 258	Var. 314	Var. 370	Var. 426
6.4±0.1	Var. 35	Var. 91	Var. 147	Var. 203	Var. 259	Var. 315	Var. 371	Var. 427
6.5±0.1	Var. 36	Var. 92	Var. 148	Var. 204	Var. 260	Var. 316	Var. 372	Var. 428

6.6±0.1	Var. 37	Var. 93	Var. 149	Var. 205	Var. 261	Var. 317	Var. 373	Var. 429
6.7±0.1	Var. 38	Var. 94	Var. 150	Var. 206	Var. 262	Var. 318	Var. 374	Var. 430
6.8±0.1	Var. 39	Var. 95	Var. 151	Var. 207	Var. 263	Var. 319	Var. 375	Var. 431
6.9±0.1	Var. 40	Var. 96	Var. 152	Var. 208	Var. 264	Var. 320	Var. 376	Var. 432
7.0±0.1	Var. 41	Var. 97	Var. 153	Var. 209	Var. 265	Var. 321	Var. 377	Var. 433
5.5	Var. 42	Var. 98	Var. 154	Var. 210	Var. 266	Var. 322	Var. 378	Var. 434
5.6	Var. 43	Var. 99	Var. 155	Var. 211	Var. 267	Var. 323	Var. 379	Var. 435
5.7	Var. 44	Var. 100	Var. 156	Var. 212	Var. 268	Var. 324	Var. 380	Var. 436
5.8	Var. 45	Var. 101	Var. 157	Var. 213	Var. 269	Var. 325	Var. 381	Var. 437
5.9	Var. 46	Var. 102	Var. 158	Var. 214	Var. 270	Var. 326	Var. 382	Var. 438
6	Var. 47	Var. 103	Var. 159	Var. 215	Var. 271	Var. 327	Var. 383	Var. 439
6.2	Var. 48	Var. 104	Var. 160	Var. 216	Var. 272	Var. 328	Var. 384	Var. 440
6.3	Var. 49	Var. 105	Var. 161	Var. 217	Var. 273	Var. 329	Var. 385	Var. 441
6.4	Var. 50	Var. 106	Var. 162	Var. 218	Var. 274	Var. 330	Var. 386	Var. 442
6.5	Var. 51	Var. 107	Var. 163	Var. 219	Var. 275	Var. 331	Var. 387	Var. 443
6.6	Var. 52	Var. 108	Var. 164	Var. 220	Var. 276	Var. 332	Var. 388	Var. 444
6.7	Var. 53	Var. 109	Var. 165	Var. 221	Var. 277	Var. 333	Var. 389	Var. 445
6.8	Var. 54	Var. 110	Var. 166	Var. 222	Var. 278	Var. 334	Var. 390	Var. 446
6.9	Var. 55	Var. 111	Var. 167	Var. 223	Var. 279	Var. 335	Var. 391	Var. 447
7	Var. 56	Var. 112	Var. 168	Var. 224	Var. 280	Var. 336	Var. 392	Var. 448

Table 2. Particular combinations of histidine concentration and pH useful for the formulation of immunoglobulins.

	Histidine [mM]								
pH	150±15	175±17.5	200±20	225±22.5	275±27.5	300±30	350±35	400±40	500±50
5.5-7.0	Var. 449	Var. 505	Var. 561	Var. 617	Var. 673	Var. 729	Var. 785	Var. 841	Var. 897
5.5-6.5	Var. 450	Var. 506	Var. 562	Var. 618	Var. 674	Var. 730	Var. 786	Var. 842	Var. 898
5.5-6.0	Var. 451	Var. 507	Var. 563	Var. 619	Var. 675	Var. 731	Var. 787	Var. 843	Var. 899
6.0-7.0	Var. 452	Var. 508	Var. 564	Var. 620	Var. 676	Var. 732	Var. 788	Var. 844	Var. 900
6.0-6.5	Var. 453	Var. 509	Var. 565	Var. 621	Var. 677	Var. 733	Var. 789	Var. 845	Var. 901
6.1±0.5	Var. 454	Var. 510	Var. 566	Var. 622	Var. 678	Var. 734	Var. 790	Var. 846	Var. 902
6.1±0.4	Var. 455	Var. 511	Var. 567	Var. 623	Var. 679	Var. 735	Var. 791	Var. 847	Var. 903
6.1±0.3	Var. 456	Var. 512	Var. 568	Var. 624	Var. 680	Var. 736	Var. 792	Var. 848	Var. 904
6.1±0.2	Var. 457	Var. 513	Var. 569	Var. 625	Var. 681	Var. 737	Var. 793	Var. 849	Var. 905
6.1±0.1	Var. 458	Var. 514	Var. 570	Var. 626	Var. 682	Var. 738	Var. 794	Var. 850	Var. 906
6.1	Var. 459	Var. 515	Var. 571	Var. 627	Var. 683	Var. 739	Var. 795	Var. 851	Var. 907
5.5±0.2	Var. 460	Var. 516	Var. 572	Var. 628	Var. 684	Var. 740	Var. 796	Var. 852	Var. 908
5.6±0.2	Var.	Var. 517	Var.	Var. 629	Var. 685	Var.	Var.	Var.	Var.

	461		573			741	797	853	909
5.7±0.2	Var. 462	Var. 518	Var. 574	Var. 630	Var. 686	Var. 742	Var. 798	Var. 854	Var. 910
5.8±0.2	Var. 463	Var. 519	Var. 575	Var. 631	Var. 687	Var. 743	Var. 799	Var. 855	Var. 911
5.9±0.2	Var. 464	Var. 520	Var. 576	Var. 632	Var. 688	Var. 744	Var. 800	Var. 856	Var. 912
6.0±0.2	Var. 465	Var. 521	Var. 577	Var. 633	Var. 689	Var. 745	Var. 801	Var. 857	Var. 913
6.2±0.2	Var. 466	Var. 522	Var. 578	Var. 634	Var. 690	Var. 746	Var. 802	Var. 858	Var. 914
6.3±0.2	Var. 467	Var. 523	Var. 579	Var. 635	Var. 691	Var. 747	Var. 803	Var. 859	Var. 915
6.4±0.2	Var. 468	Var. 524	Var. 580	Var. 636	Var. 692	Var. 748	Var. 804	Var. 860	Var. 916
6.5±0.2	Var. 469	Var. 525	Var. 581	Var. 637	Var. 693	Var. 749	Var. 805	Var. 861	Var. 917
6.6±0.2	Var. 470	Var. 526	Var. 582	Var. 638	Var. 694	Var. 750	Var. 806	Var. 862	Var. 918
6.7±0.2	Var. 471	Var. 527	Var. 583	Var. 639	Var. 695	Var. 751	Var. 807	Var. 863	Var. 919
6.8±0.2	Var. 472	Var. 528	Var. 584	Var. 640	Var. 696	Var. 752	Var. 808	Var. 864	Var. 920
6.9±0.2	Var. 473	Var. 529	Var. 585	Var. 641	Var. 697	Var. 753	Var. 809	Var. 865	Var. 921
7.0±0.2	Var. 474	Var. 530	Var. 586	Var. 642	Var. 698	Var. 754	Var. 810	Var. 866	Var. 922
5.5±0.1	Var. 475	Var. 531	Var. 587	Var. 643	Var. 699	Var. 755	Var. 811	Var. 867	Var. 923
5.6±0.1	Var. 476	Var. 532	Var. 588	Var. 644	Var. 700	Var. 756	Var. 812	Var. 868	Var. 924
5.7±0.1	Var. 477	Var. 533	Var. 589	Var. 645	Var. 701	Var. 757	Var. 813	Var. 869	Var. 925
5.8±0.1	Var. 478	Var. 534	Var. 590	Var. 646	Var. 702	Var. 758	Var. 814	Var. 870	Var. 926
5.9±0.1	Var. 479	Var. 535	Var. 591	Var. 647	Var. 703	Var. 759	Var. 815	Var. 871	Var. 927
6.0±0.1	Var. 480	Var. 536	Var. 592	Var. 648	Var. 704	Var. 760	Var. 816	Var. 872	Var. 928
6.2±0.1	Var. 481	Var. 537	Var. 593	Var. 649	Var. 705	Var. 761	Var. 817	Var. 873	Var. 929
6.3±0.1	Var. 482	Var. 538	Var. 594	Var. 650	Var. 706	Var. 762	Var. 818	Var. 874	Var. 930
6.4±0.1	Var. 483	Var. 539	Var. 595	Var. 651	Var. 707	Var. 763	Var. 819	Var. 875	Var. 931
6.5±0.1	Var. 484	Var. 540	Var. 596	Var. 652	Var. 708	Var. 764	Var. 820	Var. 876	Var. 932
6.6±0.1	Var. 485	Var. 541	Var. 597	Var. 653	Var. 709	Var. 765	Var. 821	Var. 877	Var. 933
6.7±0.1	Var. 486	Var. 542	Var. 598	Var. 654	Var. 710	Var. 766	Var. 822	Var. 878	Var. 934
6.8±0.1	Var. 487	Var. 543	Var. 599	Var. 655	Var. 711	Var. 767	Var. 823	Var. 879	Var. 935

6.9±0.1	Var. 488	Var. 544	Var. 600	Var. 656	Var. 712	Var. 768	Var. 824	Var. 880	Var. 936
7.0±0.1	Var. 489	Var. 545	Var. 601	Var. 657	Var. 713	Var. 769	Var. 825	Var. 881	Var. 937
5.5	Var. 490	Var. 546	Var. 602	Var. 658	Var. 714	Var. 770	Var. 826	Var. 882	Var. 938
5.6	Var. 491	Var. 547	Var. 603	Var. 659	Var. 715	Var. 771	Var. 827	Var. 883	Var. 939
5.7	Var. 492	Var. 548	Var. 604	Var. 660	Var. 716	Var. 772	Var. 828	Var. 884	Var. 940
5.8	Var. 493	Var. 549	Var. 605	Var. 661	Var. 717	Var. 773	Var. 829	Var. 885	Var. 941
5.9	Var. 494	Var. 550	Var. 606	Var. 662	Var. 718	Var. 774	Var. 830	Var. 886	Var. 942
6	Var. 495	Var. 551	Var. 607	Var. 663	Var. 719	Var. 775	Var. 831	Var. 887	Var. 943
6.2	Var. 496	Var. 552	Var. 608	Var. 664	Var. 720	Var. 776	Var. 832	Var. 888	Var. 944
6.3	Var. 497	Var. 553	Var. 609	Var. 665	Var. 721	Var. 777	Var. 833	Var. 889	Var. 945
6.4	Var. 498	Var. 554	Var. 610	Var. 666	Var. 722	Var. 778	Var. 834	Var. 890	Var. 946
6.5	Var. 499	Var. 555	Var. 611	Var. 667	Var. 723	Var. 779	Var. 835	Var. 891	Var. 947
6.6	Var. 500	Var. 556	Var. 612	Var. 668	Var. 724	Var. 780	Var. 836	Var. 892	Var. 948
6.7	Var. 501	Var. 557	Var. 613	Var. 669	Var. 725	Var. 781	Var. 837	Var. 893	Var. 949
6.8	Var. 502	Var. 558	Var. 614	Var. 670	Var. 726	Var. 782	Var. 838	Var. 894	Var. 950
6.9	Var. 503	Var. 559	Var. 615	Var. 671	Var. 727	Var. 783	Var. 839	Var. 895	Var. 951
7	Var. 504	Var. 560	Var. 616	Var. 672	Var. 728	Var. 784	Var. 840	Var. 896	Var. 952

3. Counter Ions

[0179] Generally, the storage stable immunoglobulin compositions provided herein will also contain counter ions, both anions and cations, contributed from pH modifying reagents such as hydrochloric acid, glacial acetic acid, and sodium hydroxide. Accordingly, in certain embodiments, the storage stable immunoglobulin compositions provided herein will further comprise chloride or acetate anions contributed from their respective acids used to pH the solution. In one embodiment, the immunoglobulin composition with comprise between 10 mM and 400 mM chloride ions.

[0180] The amount of counter ions present in a storage stable immunoglobulin composition provided herein will depend on the amount of pH modifying agent (*e*.g., hydrochloric acid (HCl), acetic acid, sodium hydroxide, *etc.*) used to formulate the immunoglobulin composition at a desired pH. Factors that may contribute to variability in the amount of a pH modifying agent used for this purpose include the identity and concentration of the immunoglobulins being formulated, the desired pH (*i.e.*, the lower the desired pH, the more acid will be needed for formulation), and the concentration of histidine in the formulation. For instance, it was found that the amount of HCl needed to formulate the 20% IgG immunoglobulin compositions described in the Examples below with 250 mM histidine at pH 6.1 resulted in a final immunoglobulin composition containing about 155 mM chloride ions. In certain instances where the pH of the composition is being adjusted with an acid, the use of sodium hydroxide may be necessary if the pH drops below the desired pH (*i.e.*, back titration of pH using sodium hydroxide).

[0181] Accordingly, in one embodiment, the storage stable immunoglobulin composition will contain no more than 500 mM chloride ions. In another embodiment, the composition will contain no more than 400 mM chloride ions. In another embodiment, the composition will contain no more than 300 mM chloride ions. In another embodiment, the composition will contain no more than 200 mM chloride ions. In yet another embodiment, the composition will contain no more than 100 mM chloride ions. In one embodiment, the concentration of chloride ions in a storage stable aqueous immunoglobulin composition provided herein is between 1 mM and 400 mM. In another embodiment, the concentration of chloride ions is between 10 mM and 400 mM. In another embodiment, the concentration of chloride ions is between 10 mM and 300 mM. In another embodiment, the concentration of chloride ions is between 10 mM and 200 mM. In another embodiment, the concentration of chloride ions is between 10 mM and 100 mM. In one embodiment, the concentration of chloride ions is between 50 mM and 400 mM. In another embodiment, the concentration of chloride ions is between 50 mM and 300 mM. In another embodiment, the concentration of chloride ions is between 50 mM and 200 mM. In one embodiment, the concentration of chloride ions is between 100 mM and 400 mM. In another embodiment, the concentration of chloride ions is between 100 mM and 300 mM. In another embodiment, the concentration of chloride ions is between 100 mM and 200 mM. In yet other

embodiments, the concentration of chloride ions is 10±1 mM, 20±2 mM, 30±3 mM, 40±4 mM, 50±5 mM, 60±6 mM, 70±7 mM, 80±8 mM, 90±9 mM, 100±10 mM, 125±12.5 mM, 150±15 mM, 175±17.5 mM, 200±20 mM, 225±22.5 mM, 250±25 mM, 300±30 mM, 350±35 mM, 400±40 mM, 450±45 mM, or 500±50 mM.

[0182] In one embodiment, the present invention provides a storage stable immunoglobulin composition comprising: an immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; between 10 mM and 400 mM chloride ions; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0183] In a specific embodiment, the present invention provides a storage stable immunoglobulin composition consisting essentially of: an immunoglobulin; between 50 mM and 500 mM histidine; between 10 mM and 400 mM chloride ions; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0184] In a more specific embodiment, the present invention provides a storage stable immunoglobulin composition consisting of: an immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; between 10 mM and 400 mM chloride ions; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the

composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0185] In one embodiment, the present invention provides a storage stable immunoglobulin composition comprising: an immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; between 100 mM and 200 mM chloride ions; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0186] In a specific embodiment, the present invention provides a storage stable immunoglobulin composition consisting essentially of: an immunoglobulin; between 50 mM and 500 mM histidine; between 100 mM and 200 mM chloride ions; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0187] In a more specific embodiment, the present invention provides a storage stable immunoglobulin composition consisting of: an immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; between 100 mM and 200 mM chloride ions; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored

under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0188] In one embodiment, the present invention provides a storage stable immunoglobulin composition comprising: an immunoglobulin; no more than 10 mM of an alkali metal cation; a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**; and between 10 mM and 400 mM chloride ions. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0189] In a specific embodiment, the present invention provides a storage stable immunoglobulin composition consisting essentially of: an immunoglobulin; a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**; and between 10 mM and 400 mM chloride ions. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0190] In a more specific embodiment, the present invention provides a storage stable immunoglobulin composition consisting of: an immunoglobulin; no more than 10 mM of an alkali metal cation; a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**; and between 10 mM and 400 mM chloride ions. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment

vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0191] In one embodiment, the present invention provides a storage stable immunoglobulin composition comprising: an immunoglobulin; no more than 10 mM of an alkali metal cation; a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**; and between 100 mM and 200 mM chloride ions. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0192] In a specific embodiment, the present invention provides a storage stable immunoglobulin composition consisting essentially of: an immunoglobulin; a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**; and between 100 mM and 200 mM chloride ions. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0193] In a more specific embodiment, the present invention provides a storage stable immunoglobulin composition consisting of: an immunoglobulin; no more than 10 mM of an alkali metal cation; a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**; and between 100 mM and 200 mM chloride ions. In

a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

4. Immunoglobulin Concentration

[0194] Generally, the histidine formulations provided herein are useful for stabilizing immunoglobulin compositions having a wide range of protein concentrations. For example, the histidine formulations provided herein are well suited to stabilize: low immunoglobulin concentrations that are used in the pharmaceutical formulation of monoclonal antibodies (*e.g.*, 10-40 g/L or lower); moderate immunoglobulin concentrations that are used in the pharmaceutical formulation of intravenous immunoglobulins (*e.g.*, 40-150 g/L); and high immunoglobulin concentration that are used in the pharmaceutical formulation of immunoglobulins administered subcutaneously or intramuscularly (*e.g.*, 150-250 g/L or higher). Generally, the upper limit of immunoglobulin concentrations that may be stabilized by the methods and formulations provided herein is only limited by the solubility limit of the immunoglobulins being formulated or the maximum concentration that can be achieved by the particular manufacturing process being employed. Accordingly, in one embodiment, the immunoglobulin concentration of a storage stable aqueous solution provided herein is between 1 g/L and 250 g/L.

a. Low Immunoglobulin Concentration

[0195] In one embodiment, the present invention provides a storage stable, low concentration immunoglobulin aqueous composition comprising: less than 40 g/L of an immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin

composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0196] In a particular embodiment, the present invention provides a storage stable, low concentration immunoglobulin aqueous composition comprising: less than 40 g/L of an immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0197] In a specific embodiment, the present invention provides a storage stable, low concentration immunoglobulin aqueous composition consisting essentially of: less than 40 g/L of an immunoglobulin and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In one embodiment, the composition contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0198] In a more specific embodiment, the present invention provides a storage stable, low concentration immunoglobulin aqueous composition consisting of: less than 40 g/L of an immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0199] In a specific embodiment, the concentration of the immunoglobulin in the storage stable, low concentration immunoglobulin aqueous composition is between 10 g/L and 40 g/L. In another embodiment, the concentration of the immunoglobulin is between 20 g/L and 30 g/L. In one embodiment, the concentration of the immunoglobulin is less than 40 g/L. In one embodiment, the concentration of the immunoglobulin is no more than 40 g/L. In another embodiment, the concentration of the immunoglobulin is no more than 30 g/L. In another embodiment, the concentration of the immunoglobulin is no more than 20 g/L. In another embodiment, the concentration of the immunoglobulin is no more than 10 g/L. In a specific embodiment, the concentration of the immunoglobulin is 10±1 g/L, 15±1.5 g/L, 20±2 g/L, 25±2.5 g/L, 30±3 g/L, 35±3.5 g/L, or 40±4 g/L. In yet other embodiments, the concentration of the immunoglobulin is 1 g/L, 2 g/L, 3 g/L, 4 g/L, 5 g/L, 6 g/L, 7 g/L, 8 g/L, 9 g/L, 10 g/L. 11 g/L. 12 g/L. 13 g/L. 14 g/L. 15 g/L. 16 g/L. 17 g/L. 18 g/L. 19 g/L. 20 g/L. 21 g/L. 22 g/L. 23 g/L. 24 g/L. 25 g/L. 26 g/L. 27 g/L. 28 g/L. 29 g/L. 30 g/L, 31 g/L, 32 g/L, 33 g/L, 34 g/L, 35 g/L, 36 g/L, 37 g/L, 38 g/L, 39 g/L, or 40 g/L.

b. Moderate Immunoglobulin Concentration

[0200] In another embodiment, the present invention provides a storage stable immunoglobulin aqueous composition comprising: between 40 g/L and 150 g/L of an immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between

5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0201] In a particular embodiment, the present invention provides a storage stable immunoglobulin aqueous composition comprising: between 40 g/L and 150 g/L of an immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0202] In a specific embodiment, the present invention provides a storage stable immunoglobulin aqueous composition consisting essentially of: between 40 g/L and 150 g/L of an immunoglobulin and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In one embodiment, the composition contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0203] In a more specific embodiment, the present invention provides a storage stable immunoglobulin aqueous composition consisting of: between 40 g/L and 150 g/L of an immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0204] In a specific embodiment the concentration of the immunoglobulin in the storage stable immunoglobulin aqueous composition is between 40 g/L and 60 g/L. In another specific embodiment, the concentration of the immunoglobulin is between 90 g/L and 110 g/L. In certain embodiments, the concentration of the immunoglobulin is 45±4.5 g/L, 50±5 g/L, 55±5.5 g/L, 60±6 g/L, 65±6.5 g/L, 70±7 g/L, 75±7.5 g/L, 80±8 g/L, 85±8.5 g/L, 90±9 g/L, 95±9.5 g/L, 100±10 g/L, 110±11 g/L, 120±12 g/L, 130±13 g/L, 140±14 g/L, or 150±15 g/L. In yet other embodiments, the concentration of the immunoglobulin is 40 g/L, 45 g/L, 50 g/L, 55 g/L, 60 g/L, 65 g/L, 70 g/L, 75 g/L, 80 g/L, 85 g/L, 90 g/L, 95 g/L, 100 g/L, 105 g/L, 110 g/L, 115 g/L, 120 g/L, 125 g/L, 130 g/L, 135 g/L, 140 g/L, 145 g/L, or 150 g/L.

c. High Immunoglobulin Concentration

[0205] In one embodiment, the present invention provides a storage stable, high concentration immunoglobulin aqueous composition comprising: more than 150 g/L of an immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the

composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0206] In a particular embodiment, the present invention provides a storage stable, high concentration immunoglobulin aqueous composition comprising: more than 150 g/L of an immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0207] In a specific embodiment, the present invention provides a storage stable, high concentration immunoglobulin aqueous composition consisting essentially of: more than 150 g/L of an immunoglobulin and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In one embodiment, the composition contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0208] In a more specific embodiment, the present invention provides a storage stable, high concentration immunoglobulin aqueous composition consisting of: more than 150 g/L of an immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination

selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0209] In one embodiment, the concentration of the immunoglobulin in the storage stable, high concentration immunoglobulin aqueous composition is at least 150 g/L. In a specific embodiment, the concentration of immunoglobulin is at least 175 g/L. In another specific embodiment, the concentration of immunoglobulin is at least 200 g/L. In another specific embodiment, the concentration of immunoglobulin is at least 225 g/L. In one embodiment, the concentration of the immunoglobulin is between 150 g/L and 250 g/L. In another embodiment, the concentration of the immunoglobulin is between 175 g/L and 225 g/L In certain embodiments, the concentration of the immunoglobulin is 150±15 g/L, 160±16 g/L, 170±17 g/L, 180±18 g/L, 190±19 g/L, 200±20 g/L, 210±21 g/L, 220±22 g/L, 230±23 g/L, 240±24 g/L, or 250±25 g/L. In yet other embodiments, the concentration of the immunoglobulin is 150 g/L, 160 g/L, 170 g/L, 180 g/L, 190 g/L, 200 g/L, 210 g/L, 220 g/L, 230 g/L, 240 g/L, 250 g/L, or higher.

5. Administration

[0210] In certain embodiments, the storage stable compositions provided herein will be formulated for parenteral administration including, but not limited to, intradermal, subcutaneous, transdermal implant, intracavernous, intravitreal, transscleral, intracerebral, intrathecal, epidural, intravenous, intracardiac, intramuscular, intraosseous, intraperitoneal, and nanocell injection administration. In one preferred embodiment, the compositions provided herein will be formulated for intravenous administration. In another preferred embodiment, the compositions provided herein will be formulated for subcutaneous administration. In yet another preferred embodiment, the compositions provided herein will be formulated for intramuscular

administration. In yet another embodiment, the formulation is suitable for intravenous administration as well as either or both subcutaneous and intramuscular administration.

6. Excipients

[0211] In certain embodiments, the storage stable immunoglobulin aqueous compositions provided herein further comprise one or more excipients. Non-limiting examples of excipients that can be included in the formulations provided herein include non-ionic surfactants, bulking agents (*e.g.*, sugars and sugar alcohols), antioxidants, polysaccharides, and pharmaceutically acceptable water-soluble polymers (*e.g.*, poly(acrylic acid), poly(ethylene oxide), poly(ethylene glycol), poly(vinyl pyrrolidone), hydroxyethyl cellulose, hydroxypropyl cellulose, and starch).

[0212] In one embodiment, the excipient is an agent for adjusting the osmolarity of the composition. Non-limiting examples of osmolarity agents include mannitol, sorbitol, glycerol, sucrose, glucose, dextrose, levulose, fructose, lactose, polyethylene glycols, phosphates, calcium chloride, calcium gluconoglucoheptonate, dimethyl sulfone, and the like.

[0213] In one embodiment, the present invention provides a storage stable immunoglobulin aqueous composition comprising: an immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; an antioxidant; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0214] In a particular embodiment, the present invention provides a storage stable immunoglobulin aqueous composition comprising: an immunoglobulin; no more than 10 mM of an alkali metal cation; an antioxidant; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific

embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0215] In a specific embodiment, the present invention provides a storage stable, low concentration immunoglobulin aqueous composition consisting essentially of: an immunoglobulin; an antioxidant; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0216] In a more specific embodiment, the present invention provides a storage stable immunoglobulin aqueous composition consisting of: an immunoglobulin; no more than 10 mM of an alkali metal cation; an antioxidant; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0217] In one embodiment, the present invention provides a storage stable immunoglobulin aqueous composition comprising: an immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; a sugar and/or sugar alcohol, and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide.

[0218] In a particular embodiment, the present invention provides a storage stable immunoglobulin aqueous composition comprising: an immunoglobulin; no more than 10 mM of an alkali metal cation; a sugar and/or sugar alcohol; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide.

[0219] In a specific embodiment, the present invention provides a storage stable, low concentration immunoglobulin aqueous composition consisting essentially of: an immunoglobulin; a sugar and/or sugar alcohol; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under

nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide.

[0220] In a more specific embodiment, the present invention provides a storage stable immunoglobulin aqueous composition consisting of: an immunoglobulin; no more than 10 mM of an alkali metal cation; a sugar and/or sugar alcohol; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide.

B. Plasma-Derived Immunoglobulins

[0221] Preparations of concentrated immunoglobulins (especially IgG) isolated from pooled human plasma are used for treating a variety of medical conditions, including immune deficiencies, inflammatory and autoimmune diseases, and acute infections. One IgG product, intravenous immunoglobulin or IVIG, is formulated for intravenous administration, for example, at a concentration of at or about 10% IgG. Concentrated immunoglobulins may also be formulated for subcutaneous or intramuscular administration, for example, at a concentration at or about 20% IgG.

[0222] Generally, plasma-derived immunoglobulin preparations formulated according to the present invention can be prepared from any suitable starting materials, for example, recovered plasma or source plasma. In a typical example, blood or plasma is collected from healthy donors. Immunoglobulins are isolated from the blood or plasma by suitable procedures, such as, for example, precipitation (alcohol fractionation or polyethylene glycol fractionation), chromatographic methods (ion exchange chromatography, affinity chromatography, immunoaffinity chromatography, etc.) ultracentrifugation, and electrophoretic preparation, and the like. (See, e.g., Cohn et al., J. Am. Chem. Soc. 68:459-75 (1946); Oncley et al., J. Am. Chem. Soc. 71:541-50 (1949); Barandun et al., Vox Sang. 7:157-74 (1962); Koblet et al., Vox

Sang. 13:93-102 (1967); U.S. Patent Nos. 5,122,373 and 5,177,194; PCT/US10/36470; and WO 2010/138736 the disclosures of which are hereby incorporated by reference in their entireties for all purposes).

[0223] In many cases, immunoglobulins are prepared from gamma globulin-containing compositions produced by alcohol fractionation and/or ion exchange and affinity chromatography methods well known to those skilled in the art. For example, purified Cohn Fraction II is commonly used as a starting point for the further purification of immunoglobulins. The starting Cohn Fraction II paste is typically about 95 percent IgG and is comprised of the four IgG subtypes. The different subtypes are present in Fraction II in approximately the same ratio as they are found in the pooled human plasma from which they are obtained. The Fraction II is further purified before formulation into an administrable product. For example, the Fraction II paste can be dissolved in a cold purified aqueous alcohol solution and impurities removed via precipitation and filtration. Following the final filtration, the immunoglobulin suspension can be dialyzed or diafiltered (e.g., using ultrafiltration membranes having a nominal molecular weight limit of less than or equal to 100,000 daltons) to remove the alcohol. The solution can be concentrated or diluted to obtain the desired protein concentration and can be further purified by techniques well known to those skilled in the art.

[0224] Furthermore, additional preparative steps can be used to enrich a particular isotype or subtype of immunoglobulin. For example, protein A, protein G or protein H sepharose chromatography can be used to enrich a mixture of immunoglobulins for IgG, or for specific IgG subtypes. *See* generally, Harlow and Lane, *Using Antibodies*, Cold Spring Harbor Laboratory Press (1999); Harlow and Lane, *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory Press (1988); and U.S. Patent No. 5,180,810, the disclosures of which are hereby incorporated by reference in their entireties for all purposes.

[0225] As will be recognized by one of skill in the art, immunoglobulin compositions isolated from pooled plasma contain impurities carried over from the starting plasma. Typically, pharmaceutically acceptable plasma-derived immunoglobulin compositions will contain at least 90% immunoglobulins, preferably at least 95% immunoglobulins, more preferably at least 98% immunoglobulins; most preferably at least 99% immunoglobulins, expressed as a function of

total protein content. For example, GAMMAGARD® LIQUID (Baxter International; Deerfield, IL) is a plasma-derived immunoglobulin composition formulated at 100 g/L protein. According to the specifications, at least 98% of the protein is immune globulin, the average immunoglobulin A (IgA) concentration is 37 μg/mL, and immunoglobulin M is present in trace amounts (GAMMAGARD® LIQUID Prescribing Information). Accordingly, unless otherwise specified, an immunoglobulin composition provided herein comprising; consisting essentially of; or consisting of "a plasma-derived immunoglobulin" may contain up to 10% plasma protein impurities carried through during the manufacturing process.

[0226] In a particular embodiment, the immunoglobulin composition isolated from pooled plasma comprises at least 90% IgG immunoglobulins. In a specific embodiment, the immunoglobulin composition isolated from pooled plasma comprises at least 95% IgG immunoglobulins. In a more specific embodiment, the immunoglobulin composition isolated from pooled plasma comprises at least 98% IgG immunoglobulins. In a yet more specific embodiment, the immunoglobulin composition isolated from pooled plasma comprises at least 99% IgG immunoglobulins. In certain embodiments, the IgG immunoglobulin composition isolated from pooled plasma further comprises IgA and/or IgM immunoglobulins.

[0227] In another embodiment, the immunoglobulin composition isolated from pooled plasma comprises at least 10% IgA. In a specific embodiment, the immunoglobulin composition isolated from pooled plasma comprises at least 25% IgA. In a more specific embodiment, immunoglobulin composition isolated from pooled plasma comprises at least 50% IgA. In yet other embodiments, the immunoglobulin composition isolated from pooled plasma comprises at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more IgA. In certain embodiments, the IgA immunoglobulin composition isolated from pooled plasma further comprises IgG and/or IgM immunoglobulins.

[0228] In another embodiment, the immunoglobulin composition isolated from pooled plasma comprises at least 10% IgM. In a specific embodiment, the immunoglobulin composition isolated from pooled plasma comprises at least 25% IgM. In a more specific embodiment, immunoglobulin composition isolated from pooled plasma comprises at least 50% IgM. In yet

other embodiments, the immunoglobulin composition isolated from pooled plasma comprises at least 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or more IgM. In certain embodiments, the IgM immunoglobulin composition isolated from pooled plasma further comprises IgG and/or IgA immunoglobulins.

[0229] In another embodiment, the storage stable, plasma derived immunoglobulin composition is a hyper-immune immunoglobulin preparation. For example, in certain embodiments, the hyper-immune preparation may be an anti-tetanus, anti-D, anti-varicella, anti-rabies, anti-CMV, anti-hepatitis A, or anti-hepatitis B immunoglobulin preparation.

[0230] Accordingly, in one embodiment, the present invention provides storage stable, aqueous immunoglobulin composition comprising: a plasma-derived immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition.

[0231] In a particular embodiment, the storage stable, aqueous immunoglobulin composition comprises: a plasma-derived immunoglobulin; between 50 mM and 500 mM histidine; no more than 1 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0232] Advantageously, it has been found that the formulation of plasma-derived immunoglobulins with moderate concentrations of histidine (*e.g.*, 50 mM to 500 mM) at mildly

acidic to neutral pH stabilizes the immunoglobulin composition in the absence of traditional stabilizing and bulking agents, such as surfactants (*e.g.*, non-ionic surfactants), sugars, and sugar alcohols.

[0233] Accordingly, in a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising a plasma-derived immunoglobulin; between 50 mM and 500 mM histidine; no more than 1 mM of an alkali metal cation; no more than 0.01% of a surfactant; no more than 1 mM of a sugar; no more than 1 mM of a sugar alcohol; and a pH between 5.5 and 7.0. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0234] In another specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: a plasma-derived immunoglobulin; between 50 mM and 500 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0235] The storage stable plasma derived IgG aqueous compositions provided herein are stable at room temperature (*i.e.*, 20°C to 25°C) for an extended period of time. For example, in one embodiment, the storage stable, aqueous IgG composition is stable for at least about 2 months. In another embodiment, the composition will be stable for at least about 3 months. In yet other

embodiment, the composition will be stable for at least 1 about month, or at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, or more months. In a preferred embodiment ,the composition will be stable for at least about 6 months. In a more preferred embodiment, the composition will be stable for at least about 1 year. In a more preferred embodiment, the composition will be stable for at least about 2 years.

1. Histidine

[0236] In one embodiment, the concentration of histidine in a storage stable plasma-derived immunoglobulin composition provided herein is between 50 mM and 500 mM. In another embodiment, the concentration of histidine in the formulation will be between 100 mM and 400 mM. In another embodiment, the concentration of histidine in the formulation will be between 200 mM and 300 mM. In another embodiment, the concentration of histidine in the formulation will be between 225 mM and 275 mM. In another embodiment, the concentration of histidine in the formulation will be between 240 mM and 260 mM. In a particular embodiment, the concentration of histidine will be 250 mM. In certain other embodiments, the concentration of histidine in the formulation will be 50±5 mM, 75±7.5 mM, 100±10 mM, 125±12.5 mM, 150±15 mM, 175±17.5 mM, 200±20 mM, 225±22.5 mM, 250±25 mM, 275±27.5 mM, 300±30 mM, 325±32.5 mM, 350±35 mM, 375±37.5 mM, 400±40 mM, 425±42.5 mM, 450±45 mM, 475±47.5 mM, 500±50 mM or higher. In yet other embodiments, the concentration of histidine in the formulation will be 50 mM, 75 mM, 100 mM, 125 mM, 150 mM, 175 mM, 200 mM, 225 mM, 250 mM, 275 mM , 300 mM, 325 mM, 350 mM, 375 mM, 400 mM, 425 mM, 450 mM, 475 mM, 500 mM or higher.

[0237] Accordingly, in one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: a plasma-derived immunoglobulin; between 100 mM and 400 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another

specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0238] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: a plasma-derived immunoglobulin; between 100 mM and 400 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0239] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: a plasma-derived immunoglobulin; between 100 mM and 400 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0240] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: a plasma derived immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and

7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0241] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0242] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0243] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: a plasma-derived immunoglobulin; between 225 mM and 275 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0244] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: a plasma-derived immunoglobulin; between 225 mM and 275 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0245] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: a plasma-derived immunoglobulin; between 225 mM and 275 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular

embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0246] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: a plasma-derived immunoglobulin; between 240 mM and 260 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0247] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: a plasma-derived immunoglobulin; between 240 mM and 260 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0248] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: a plasma-derived immunoglobulin; between 240 mM and 260 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali

metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0249] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: a plasma-derived immunoglobulin; 250 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0250] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: a plasma-derived immunoglobulin; 250 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0251] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: a plasma-derived immunoglobulin; 250 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

2. pH

[0252] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: a plasma-derived immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 6.5. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0253] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: a plasma-derived immunoglobulin; between 50 mM and 500 mM histidine; and a pH between 5.5 and 6.5. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In

another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0254] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: a plasma-derived immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 6.5. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0255] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 6.5. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0256] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; and a pH between 5.5 and 6.5. In a particular

embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0257] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 6.5. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0258] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.4. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0259] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; and a pH of 6.1±0.4. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0260] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.4. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0261] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.3. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the

plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0262] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; and a pH of 6.1±0.3. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0263] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.3. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0264] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.2. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In

another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0265] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; and a pH of 6.1±0.2. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0266] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.2. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0267] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.1. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In

one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0268] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; and a pH of 6.1±0.1. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0269] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.1. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0270] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: a plasma-derived immunoglobulin; between 200 mM

and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0271] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; and a pH of 6.1. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0272] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: a plasma-derived immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0273] In one embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising: a plasma-derived immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0274] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: a plasma-derived immunoglobulin and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0275] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of: a plasma-derived immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment,

the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

3. Counter Anions

[0276] In one embodiment, the present invention provides a storage stable immunoglobulin composition comprising: a plasma-derived immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; between 10 mM and 400 mM chloride ions; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0277] In a specific embodiment, the present invention provides a storage stable immunoglobulin composition consisting essentially of: a plasma-derived immunoglobulin; between 50 mM and 500 mM histidine; between 10 mM and 400 mM chloride ions; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0278] In a more specific embodiment, the present invention provides a storage stable immunoglobulin composition consisting of: a plasma-derived immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; between 10 mM and 400 mM chloride ions; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0279] In one embodiment, the present invention provides a storage stable immunoglobulin composition comprising: a plasma-derived immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; between 100 mM and 200 mM chloride ions; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0280] In a specific embodiment, the present invention provides a storage stable immunoglobulin composition consisting essentially of: a plasma-derived immunoglobulin; between 50 mM and 500 mM histidine; between 100 mM and 200 mM chloride ions; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon.

In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0281] In a more specific embodiment, the present invention provides a storage stable immunoglobulin composition consisting of: a plasma-derived immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; between 100 mM and 200 mM chloride ions; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0282] In one embodiment, the present invention provides a storage stable immunoglobulin composition comprising: a plasma-derived immunoglobulin; no more than 10 mM of an alkali metal cation; a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**; and between 10 mM and 400 mM chloride ions. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0283] In a specific embodiment, the present invention provides a storage stable immunoglobulin composition consisting essentially of: a plasma-derived immunoglobulin; a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided

in **Table 1** and **Table 2**; and between 10 mM and 400 mM chloride ions. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0284] In a more specific embodiment, the present invention provides a storage stable immunoglobulin composition consisting of: a plasma-derived immunoglobulin; no more than 10 mM of an alkali metal cation; a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**; and between 10 mM and 400 mM chloride ions. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0285] In one embodiment, the present invention provides a storage stable immunoglobulin composition comprising: a plasma-derived immunoglobulin; no more than 10 mM of an alkali metal cation; a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**; and between 100 mM and 200 mM chloride ions. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the

plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0286] In a specific embodiment, the present invention provides a storage stable immunoglobulin composition consisting essentially of: a plasma-derived immunoglobulin; a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**; and between 100 mM and 200 mM chloride ions. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0287] In a more specific embodiment, the present invention provides a storage stable immunoglobulin composition consisting of: a plasma-derived immunoglobulin; no more than 10 mM of an alkali metal cation; a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**; and between 100 mM and 200 mM chloride ions. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

4. Immunoglobulin Concentration

[0288] Generally, the histidine formulations provided herein are useful for stabilizing plasma-derived immunoglobulin compositions having a wide range of protein concentrations. For

example, the histidine formulations provided herein are well suited to stabilize: low immunoglobulin concentrations *e.g.*, 10-40 g/L or lower); moderate immunoglobulin concentrations that are used in the pharmaceutical formulation of intravenous immunoglobulins (*e.g.*, 40-150 g/L); and high immunoglobulin concentration that are used in the pharmaceutical formulation of immunoglobulins administered subcutaneously or intramuscularly (*e.g.*, 150-250 g/L or higher). Generally, the upper limit of immunoglobulin concentrations that may be stabilized by the methods and formulations provided herein is only limited by the solubility limit of the immunoglobulins being formulated or the maximum concentration that can be achieved by the particular manufacturing process being employed. Accordingly, in one embodiment, the immunoglobulin concentration of a storage stable aqueous solution provided herein is between 1 g/L and 250 g/L. Immunoglobulin concentrations may be referred to in terms of g/L or percentage, with an immunoglobulin concentration of 10 g/L corresponding to a protein concentration of 1%.

a. Low Immunoglobulin Concentration

[0289] In one embodiment, the present invention provides a storage stable, low concentration immunoglobulin aqueous composition comprising: less than 40 g/L of a plasma-derived immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0290] In a particular embodiment, the present invention provides a storage stable, low concentration immunoglobulin aqueous composition comprising: less than 40 g/L of a plasma-derived immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH

combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0291] In a specific embodiment, the present invention provides a storage stable, low concentration immunoglobulin aqueous composition consisting essentially of: less than 40 g/L of a plasma-derived immunoglobulin and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In one embodiment, the composition contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0292] In a more specific embodiment, the present invention provides a storage stable, low concentration immunoglobulin aqueous composition consisting of: less than 40 g/L of a plasma-derived immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is

contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

b. Moderate Immunoglobulin Concentration

[0293] In another embodiment, the present invention provides a storage stable immunoglobulin aqueous composition comprising: between 40 g/L and 150 g/L of a plasma-derived immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0294] In a particular embodiment, the present invention provides a storage stable immunoglobulin aqueous composition comprising: between 40 g/L and 150 g/L of a plasma-derived immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon

dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0295] In a specific embodiment, the present invention provides a storage stable immunoglobulin aqueous composition consisting essentially of: between 40 g/L and 150 g/L of a plasma-derived immunoglobulin and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In one embodiment, the composition contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0296] In a more specific embodiment, the present invention provides a storage stable immunoglobulin aqueous composition consisting of: between 40 g/L and 150 g/L of a plasma-derived immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

c. High Immunoglobulin Concentration

[0297] In one embodiment, the present invention provides a storage stable, high concentration immunoglobulin aqueous composition comprising: more than 150 g/L of a plasma-derived immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0298] In a particular embodiment, the present invention provides a storage stable, high concentration immunoglobulin aqueous composition comprising: more than 150 g/L of a plasma-derived immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0299] In a specific embodiment, the present invention provides a storage stable, high concentration immunoglobulin aqueous composition consisting essentially of: more than 150 g/L of a plasma-derived immunoglobulin and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In one embodiment, the

composition contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0300] In a more specific embodiment, the present invention provides a storage stable, high concentration immunoglobulin aqueous composition consisting of: more than 150 g/L of a plasma-derived immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the plasma-derived immunoglobulin is an IgG-containing immunoglobulin composition. In a specific embodiment, the final composition does not contain a surfactant or sugar.

C. Recombinant Immunoglobulins

[0301] In one aspect, the present invention provides storage stable, recombinant immunoglobulin preparations. Methods for obtaining recombinant antibodies, such as recombinant human antibodies are well known in the art. For example, a desired human antibody having a binding activity for a desired antigen can be obtained by in vitro immunizing human lymphocytes with the desired antigen or a cell expressing the desired antigen and fusing the immunized lymphocytes to human myeloma cells. A desired human antibody can also be obtained by

immunizing a transgenic animal having all human antibody gene repertoires with an antigen (see, International Publications Nos. WO 93/12227, WO 92/03918, WO 94/02602, WO 94/25585, WO 96/34096, WO 96/33735). Methods for obtaining a human antibody by panning using a human antibody library are also known. For example, phages binding to an antigen can be selected by expressing the variable regions of a human antibody as single chain antibody fragments (scFv) on phage surfaces by a phage display method. The DNA sequences encoding the variable regions of the human antibody binding to the antigen can be determined by analyzing the genes of the selected phages. A whole human antibody can be obtained by preparing a suitable expression vector containing the determined DNA sequences of the scFv fragments binding to the antigen. These methods have already been well known from WO 92/01047, WO 92/20791, WO 93/06213, WO 93/11236, WO 93/19172, WO 95/01438, and WO 95/15388.

[0302] Methods for the expression of recombinant immunoglobulins are also well known in the art. For example, recombinant antibodies can be expressed in tissue or cell culture after transforming a recombinant gene for the construct into a suitable host. Suitable eukaryotic cells for use as hosts include animal, plant and fungal cells. Known animal cells include (1) mammalian cells such as CHO, COS, myeloma, BHK (baby hamster kidney), HeLa and Vero cells; (2) amphibian cells such as *Xenopus oocytes*; or (3) insect sells such as sf9, sf21 and Tn5. Known plant cells include cells of *Nicotiana* such as *Nicotiana tabacum*, which can be used as callus cultures. Known fungi include yeasts such as *Saccharomyces spp.*, e.g. *Saccharomyces serevisiae* and filamentous fungi such as *Aspergillus spp.*, e.g. *Aspergillus niger*. Prokaryotic cells can be used as producing systems using bacterial cells. Known bacterial cells include *E. coli* and *Bacillus subtilis*. Antibodies can be obtained by transforming these cells with an antibody gene of interest and culturing the transformed cells in vitro.

[0303] In one embodiment of the present invention, the media used to express a recombinant protein can be animal protein-free and chemically defined. Methods of preparing animal protein-free and chemically defined culture mediums are known in the art, for example in US 2008/0009040 and US 2007/0212770, which are both incorporated herein for all purposes. "Protein free" and related terms refers to protein that is from a source exogenous to or other than the cells in the culture, which naturally shed proteins during growth. In another embodiment, the

culture medium is polypeptide free. In another embodiment, the culture medium is serum free. In another embodiment the culture medium is animal protein free. In another embodiment the culture medium is animal component free. In another embodiment, the culture medium contains protein, e.g., animal protein from serum such as fetal calf serum. In another embodiment, the culture has recombinant proteins exogenously added. In another embodiment, the proteins are from a certified pathogen free animal. The term "chemically defined" as used herein shall mean, that the medium does not comprise any undefined supplements, such as, for example, extracts of animal components, organs, glands, plants, or yeast. Accordingly, each component of a chemically defined medium is accurately defined. In a preferred embodiment, the media are animal-component free and protein free.

[0304] Typically a recombinant antibody formulated as provided herein is specific for a polypeptide associated with a disease or disorder. Non-limiting examples of such polypeptides include macrophage migration inhibitory factor (MIF), tissue factor pathway inhibitor (TFPI); alpha-1-antitrypsin; insulin A-chain; insulin B-chain; proinsulin; follicle stimulating hormone; calcitonin; luteinizing hormone; glucagon; clotting factors such as Factor II (prothrombin), Factor III (platelet tissue factor), Factor V, Factor VII, Factor VIII, Factor IX, Factor X, Factor XI, Factor XII, Factor XIII, and von Willebrand factor; anti-clotting factors such as Antithrombin III (ATIII), Protein C; atrial natriuretic factor; lung surfactant; a plasminogen activator, such as urokinase or human urine or tissue-type plasminogen activator (t-PA); bombesin; thrombin; hemopoietic growth factor; tumor necrosis factor-alpha and -beta; enkephalinase; RANTES (regulated on activation normally T-cell expressed and secreted); human macrophage inflammatory protein (MIP-1-alpha); a serum albumin such as human serum albumin; Muellerian-inhibiting substance; relaxin A-chain; relaxin B-chain; prorelaxin; mouse gonadotropin-associated peptide; a microbial protein, such as beta-lactamase; DNase; IgE; a cytotoxic T-lymphocyte associated antigen (CTLA), such as CTLA-4; inhibin; activin; vascular endothelial growth factor (VEGF); receptors for hormones or growth factors; protein A or D; rheumatoid factors; a neurotrophic factor such as bone-derived neurotrophic factor (BDNF), neurotrophin-3,-4, -5, or -6 (NT-3, NT-4, NT-5, or NT-6), or a nerve growth factor such as NGF-b; platelet-derived growth factor (PDGF); fibroblast growth factor such as aFGF and bFGF; epidermal growth factor (EGF); transforming growth factor (TGF) such as TGF-alpha and TGF-

beta, including TGF-b1, TGF-b2, TGF-b3, TGF-b4, or TGF-b5; a tumor necrosis factor (TNF) such as TNF-alpha or TNF-beta; insulin-like growth factor-I and -II (IGF-I and IGF-II); des(1-3)-IGF-I (brain IGF-I), insulin-like growth factor binding proteins; CD proteins such as CD3, CD4, CD8, CD19, CD20, CD22 and CD40; erythropoietin; osteoinductive factors; immunotoxins; a bone morphogenetic protein (BMP); an interferon such as interferon-alpha, -beta, and -gamma; colony stimulating factors (CSFs), e.g., M-CSF, GM-CSF, and G-CSF; interleukins (ILs), e.g., IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9 and IL-10; superoxide dismutase; T-cell receptors; surface membrane proteins; decay accelerating factor; viral antigen such as, for example, a portion of the AIDS envelope; transport proteins; homing receptors; addressins; regulatory proteins; integrins such as CD11a, CD11b, CD11c, CD18, an ICAM, VLA-4 and VCAM; a tumor associated antigen such as HER2, HER3 or HER4 receptor; and fragments of any of the above-listed polypeptides.

[0305] In one embodiment, the present invention provides storage stable, aqueous immunoglobulin composition comprising: a recombinant immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the antibody is a recombinant anti-MIF antibody. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0306] In a particular embodiment, the storage stable, aqueous immunoglobulin composition comprises: a recombinant immunoglobulin; between 50 mM and 500 mM histidine; no more than 1 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the antibody is a recombinant anti-MIF antibody. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0307] In a specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition comprising a recombinant immunoglobulin; between 50 mM and 500 mM histidine; no more than 1 mM of an alkali metal cation; no more than 0.01% of a surfactant; no more than 1 mM of a sugar; no more than 1 mM of a sugar alcohol; and a pH between 5.5 and 7.0. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the antibody is a recombinant anti-MIF antibody. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0308] In another specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting essentially of: a recombinant immunoglobulin; between 50 mM and 500 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the composition contains no more than 1 mM of an alkali metal cation. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the antibody is a recombinant anti-MIF antibody. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0309] In a more specific embodiment, the present invention provides a storage stable, aqueous immunoglobulin composition consisting of a recombinant immunoglobulin; between 50 mM and 500 mM histidine; no more than 1 mM of an alkali metal cation; no more than 0.01% of a surfactant; no more than 1 mM of a sugar; no more than 1 mM of a sugar alcohol; and a pH between 5.5 and 7.0. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular

embodiment, the antibody is a recombinant anti-MIF antibody. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0310] In a particular embodiment, the present invention provides a storage stable immunoglobulin aqueous composition comprising: a recombinant immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the antibody is a recombinant anti-MIF antibody. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0311] In a specific embodiment, the present invention provides a storage stable immunoglobulin aqueous composition consisting essentially of: a recombinant immunoglobulin and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In one embodiment, the composition contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the antibody is a recombinant anti-MIF antibody. In a specific embodiment, the final composition does not contain a surfactant or sugar.

[0312] In a more specific embodiment, the present invention provides a storage stable immunoglobulin aqueous composition consisting of: a recombinant immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group

consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the composition contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the composition further comprises between 10 mM and 400 mM chloride ions. In one embodiment, the immunoglobulin composition is contained in an air-tight containment vessel under inert gas. In a specific embodiment, the composition is stored under nitrogen. In another specific embodiment, the composition is stored under argon. In yet another specific embodiment, the composition is stored under carbon dioxide. In a particular embodiment, the antibody is a recombinant anti-MIF antibody. In a specific embodiment, the final composition does not contain a surfactant or sugar.

IV. Methods for Stabilizing Immunoglobulin Compositions

[0313] Among other aspects, the present invention provides methods for stabilizing immunoglobulin compositions for therapeutic administration. The following embodiments are based in part on the unexpected discovery that the formulation of immunoglobulins with histidine at mildly acidic to neutral pH stabilizes the immunoglobulins that are otherwise labile at these pH values, and/or labile when formulated with histidine at an acidic pH, and/or labile when formulated in the presence of alkali metal cations.

[0314] Any immunoglobulin may be stabilized by the methods provided herein. Non-limiting examples of immunoglobulin preparations that may be stabilized include, plasma-derived immunoglobulin preparations, recombinant polyclonal or monoclonal preparations, minibodies, diabodies, triabodies, antibody fragments such as Fv, Fab and F(ab)2 or fragmented antibodies such as monovalent or multivalent single chain Fvs (scFv, sc(Fv)2, minibodies, diabodies, and triabodies such as scFv dimers) in which the variable regions of an antibody are joined together via a linker such as a peptide linker, and the like. Recombinant antibodies include murine antibodies, rodent antibodies, human antibodies, chimeric human antibodies (e.g., human / murine chimeras), humanized antibodies (e.g., humanized murine antibodies), and the like. In preferred embodiments, the recombinant antibody is a human, chimeric human, or humanized antibody suitable for administration to a human. In a preferred embodiment, the immunoglobulin in a full length, or near full length immunoglobulin, which will generally be more labile then engineered fragments thereof.

[0315] Generally, the methods provided herein stabilize immunoglobulin formulations at room temperature (*i.e.*, between 20°C and 25°C) for an extended period of time. For example, in one embodiment, the methods stabilize an immunoglobulin composition stored at room temperature for at least about 2 months. In another embodiment, the methods stabilize an immunoglobulin composition stored at room temperature for at least about 3 months. In yet other embodiment, the methods stabilize an immunoglobulin composition stored at room temperature for at least 1 about month, or at least about 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, or more months. In a preferred embodiment, the methods stabilize an immunoglobulin composition stored at room temperature for at least about 6 months. In a more preferred embodiment, methods stabilize an immunoglobulin composition stored at room temperature for at least about 1 year. In a more preferred embodiment, methods stabilize an immunoglobulin composition stored at room temperature for at least about 2 years.

[0316] In one embodiment, the methods stabilize an immunoglobulin composition for at least six months when stored at a temperature between about 28°C and about 32°C. In a specific embodiment, the methods stabilize an immunoglobulin composition for at least one year when stored at a temperature between about 28°C and about 32°C. In a more specific embodiment, the methods stabilize an immunoglobulin composition for at least two years when stored at a temperature between about 28°C and about 32°C. In another embodiment, the methods stabilize an immunoglobulin composition for at least six months when stored at a temperature between about 38°C and about 42°C. In a specific embodiment, the methods stabilize an immunoglobulin composition for at least one year when stored at a temperature between about 38°C and about 42°C. In a more specific embodiment, the methods stabilize an immunoglobulin composition for at least two years when stored at a temperature between about 38°C and about 42°C.

[0317] In certain embodiments, the methods provided herein further comprise dispensing the composition into a sterile containment vessel and sealing the vessel air-tight, for example, using a rubber stopper. Immunoglobulin compositions in the air-tight vessels are preferably protected from ambient light by storage in a dark place, the use of a tinted vessel material (typically glass or plastic), and/or covering the surface of the vessel with an opaque substance.

[0318] In certain embodiments, the methods further comprise filling the headspace in the containment vessel with an inert gas (*i.e.*, replacing the headspace air in the containment vessel with an inert gas). The inert gas helps to maintain an inert atmosphere above the liquid composition. When an immunoglobulin composition is stored in a vessel in which the headspace air has been replaced with an inert gas, the composition is said to be "stored under inert gas." Accordingly, in one embodiment, the methods provided herein comprise a step of storing the storage stable immunoglobulin composition under inert gas. Non-limiting examples of inert gasses than may be used in conjunction with the methods of the present invention include, nitrogen, argon, and carbon dioxide. In one particular embodiment, the inert gas is nitrogen. In another particular embodiment, the inert gas is argon. In yet another particular embodiment, the inert gas is carbon dioxide.

A. General Immunoglobulin Formulations

[0319] In one embodiment, the present invention provides a method for stabilizing an aqueous immunoglobulin composition, the method comprising formulating an immunoglobulin composition with between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In one embodiment, method further comprises storing the immunoglobulin composition in an air-tight containment vessel under an inert gas. In a specific embodiment, the inert gas is nitrogen. In another specific embodiment, the inert gas is argon. In yet another specific embodiment, the inert gas is carbon dioxide. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0320] In a particular embodiment, the present invention provides a method for stabilizing an aqueous immunoglobulin composition, the method comprising formulating an immunoglobulin composition with: between 50 mM and 500 mM histidine; no more than 1 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In one embodiment, method further comprises storing the immunoglobulin composition in an air-tight containment vessel under inert gas. In a specific embodiment, the inert gas is nitrogen. In another specific embodiment, the inert gas is argon. In yet another specific embodiment, the inert gas is carbon dioxide. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0321] In a specific embodiment, the final formulation comprises: an immunoglobulin; between 50 mM and 500 mM histidine; no more than 1 mM of an alkali metal cation; no more than 0.01% of a surfactant; no more than 1 mM of a sugar; no more than 1 mM of a sugar alcohol; and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0322] In another specific embodiment, the final formulation consists essentially of: an immunoglobulin; between 50 mM and 500 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0323] In a more specific embodiment, the present invention provides a method for stabilizing an aqueous immunoglobulin composition, the method comprising formulating an immunoglobulin composition with: between 50 mM and 500 mM histidine; no more than 1 mM of an alkali metal cation; no more than 0.01% of a surfactant; no more than 1 mM of a sugar; no more than 1 mM of a sugar alcohol; and a pH between 5.5 and 7.0. In one embodiment, method further comprises storing the immunoglobulin composition in an air-tight containment vessel under inert gas. In a specific embodiment, the inert gas is nitrogen. In another specific embodiment, the inert gas is argon. In yet another specific embodiment, the inert gas is carbon dioxide. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0324] The methods provided by the present invention may be used to stabilize any immunoglobulin composition, including but not limited to: immunoglobulin compositions isolated from pooled plasma (*e.g.*, human pooled plasma); immunoglobulin compositions isolated from mammary secretions; immunoglobulin compositions isolated from avian sources (*e.g.*, IgY containing compositions isolated from the yolk of chicken eggs); and recombinant immunoglobulins (*e.g.*, monoclonal or polyclonal antibodies).

1. Histidine

[0325] Accordingly, in one embodiment, the present invention provides a method for stabilizing an aqueous immunoglobulin composition, the method comprising formulating an immunoglobulin composition with: between 100 mM and 400 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In one embodiment, method further comprises storing the immunoglobulin composition in an air-tight containment vessel under inert gas. In a specific embodiment, the inert gas is nitrogen. In another specific embodiment, the inert gas is argon. In yet another specific embodiment, the inert gas is carbon dioxide. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0326] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin; between 100 mM and 400 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0327] In a more specific embodiment, the final formulation consists of: an immunoglobulin; between 100 mM and 400 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0328] In one embodiment, the final formulation comprises: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0329] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin; between 200 mM and 300 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the final formulation contains no more than 10 mM of an alkali metal

cation. In another particular embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0330] In a more specific embodiment, the final formulation consists of: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0331] In one embodiment, the final formulation comprises: an immunoglobulin; between 225 mM and 275 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0332] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin; between 225 mM and 275 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0333] In a more specific embodiment, the final formulation consists of: an immunoglobulin; between 225 mM and 275 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0334] In one embodiment, the final formulation comprises: an immunoglobulin; between 240 mM and 260 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation.

[0335] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin; between 240 mM and 260 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0336] In a more specific embodiment, the final formulation consists of: an immunoglobulin; between 240 mM and 260 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0337] In one embodiment, the final formulation comprises: an immunoglobulin; 250 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0338] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin; 250 mM histidine; and a pH between 5.5 and 7.0. In a particular embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0339] In a more specific embodiment, the final formulation consists of: an immunoglobulin; 250 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

2. pH

[0340] The storage stable immunoglobulin compositions provided by the present invention are formulated at mildly acidic to neutral pH. Generally, this includes pH values between 5.5 and 7.0. In a preferred embodiment, the pH value is between 5.5 and 6.5. However, the range of pH

values at which any individual immunoglobulin composition is stabilized by the inclusion of histidine in the formulation may vary, dependent upon the properties of the particular immunoglobulin.

[0341] For example, in one embodiment, the methods comprise formulating immunoglobulins at a pH between 5.5 and 7.0. In another embodiment, the methods comprise formulating immunoglobulins at a pH between 5.5 and 6.5. In other embodiments, the methods comprise formulating immunoglobulins at a pH between 6.0 and 7.0. In another embodiment, the methods comprise formulating immunoglobulins at a pH between 5.5 and 6.0. In one embodiment, the methods comprise formulating immunoglobulins at a pH between 6.0 and 6.5. In another embodiment, the methods comprise formulating immunoglobulins at a pH between 6.5 and 7.0. In another embodiment, the methods comprise formulating immunoglobulins at a pH of 6.0±4. In another embodiment, the methods comprise formulating immunoglobulins at a pH of 6.0±3. In another embodiment, the methods comprise formulating immunoglobulins at a pH of 6.0±2. In another embodiment, the methods comprise formulating immunoglobulins at a pH of 6.0±1. In another embodiment, the methods comprise formulating immunoglobulins at a pH of 6.1±5. In another embodiment, the methods comprise formulating immunoglobulins at a pH of 6.1±4. In another embodiment, the methods comprise formulating immunoglobulins at a pH of 6.1±3. In another embodiment, the methods comprise formulating immunoglobulins at a pH of 6.1±2. In another embodiment, the methods comprise formulating immunoglobulins at a pH of 6.1±1. In other embodiments, the methods comprise formulating immunoglobulins at a pH of 5.5±0.2, 5.6±0.2, 5.7±0.2, 5.8±0.2, 5.9±0.2, 6.0±0.2, 6.1±0.2, 6.2±0.2, 6.3±0.2, 6.4±0.2, 6.5±0.2, 6.6±0.2, 6.7±0.2, 6.8±0.2, 6.9±0.2, or 7.0±0.2. In other embodiments, the methods comprise formulating immunoglobulins at a pH of 5.5±0.1, or 5.6±0.1, 5.7±0.1, 5.8±0.1, 5.9±0.1, 6.0±0.1, 6.1±0.1, 6.2±0.1, 6.3±0.1, 6.4±0.1, 6.5±0.1, 6.6±0.1, 6.7±0.1, 6.8±0.1, 6.9±0.1, or 7.0±0.1. In yet other embodiments, the methods comprise formulating immunoglobulins at a pH of 5.5, or 5.6, 5.7, 5.8, 5.9, 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, or 7.0.

[0342] Accordingly, in one embodiment, the present invention provides a method for stabilizing an aqueous immunoglobulin composition, the method comprising formulating an immunoglobulin composition with: between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 6.5. In a specific embodiment, the final

formulation contains no more than 1 mM of an alkali metal cation. In one embodiment, method further comprises storing the immunoglobulin composition in an air-tight containment vessel under inert gas. In a specific embodiment, the inert gas is nitrogen. In another specific embodiment, the inert gas is argon. In yet another specific embodiment, the inert gas is carbon dioxide. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0343] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin; between 50 mM and 500 mM histidine; and a pH between 5.5 and 6.5. In a particular embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0344] In a more specific embodiment, the final formulation consists of: an immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 6.5. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0345] In one embodiment, the final formulation comprises: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 6.5. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0346] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin; between 200 mM and 300 mM histidine; and a pH between 5.5 and 6.5. In a particular embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0347] In a more specific embodiment, the final formulation consists of: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 6.5. In a specific embodiment, the final formulation contains no more than

1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0348] In one embodiment, the final formulation comprises: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.4. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0349] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin; between 200 mM and 300 mM histidine; and a pH of 6.1±0.4. In a particular embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0350] In a more specific embodiment, the final formulation consists of: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.4. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0351] In one embodiment, the final formulation comprises: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.3. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0352] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin; between 200 mM and 300 mM histidine; and a pH of 6.1±0.3. In a particular embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0353] In a more specific embodiment, the final formulation consists of: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.3. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0354] In one embodiment, the final formulation comprises: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.2. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0355] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin; between 200 mM and 300 mM histidine; and a pH of 6.1±0.2. In a particular embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0356] In a more specific embodiment, the final formulation consists of: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.2. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0357] In one embodiment, the final formulation comprises: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.1. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0358] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin; between 200 mM and 300 mM histidine; and a pH of 6.1±0.1. In a particular embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the final formulation contains no more than 1 mM of an alkali

metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0359] In a more specific embodiment, the final formulation consists of: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1±0.1. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0360] In one embodiment, the final formulation comprises: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0361] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin; between 200 mM and 300 mM histidine; and a pH of 6.1. In a particular embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0362] In a more specific embodiment, the final formulation consists of: an immunoglobulin; between 200 mM and 300 mM histidine; no more than 10 mM of an alkali metal cation; and a pH of 6.1. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0363] In certain embodiments, the method comprises formulating an immunoglobulin composition with a combination of histidine concentration and pH selected from any one of variations (Var.) 1 to 952, as provided in **Table 1** and **Table 2**.

[0364] Accordingly, in one embodiment, the present invention provides a method for stabilizing an aqueous immunoglobulin composition, the method comprising formulating an immunoglobulin composition with: no more than 10 mM of an alkali metal cation; and a

histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In one embodiment, method further comprises storing the immunoglobulin composition in an air-tight containment vessel under inert gas. In a specific embodiment, the inert gas is nitrogen. In another specific embodiment, the inert gas is argon. In yet another specific embodiment, the inert gas is carbon dioxide. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0365] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a particular embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In another particular embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0366] In a more specific embodiment, the final formulation consists of: an immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a particular embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

3. Counter Anions

[0367] In one embodiment, the present invention provides a method for stabilizing an aqueous immunoglobulin composition, the method comprising formulating an immunoglobulin composition with: between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; between 10 mM and 400 mM chloride ions; and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In one embodiment, method further comprises storing the immunoglobulin composition in an air-tight containment vessel under inert gas. In a specific embodiment, the inert gas is nitrogen. In another specific embodiment, the inert gas is argon. In yet another specific embodiment, the inert gas is carbon dioxide. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0368] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin; between 50 mM and 500 mM histidine; between 10 mM and 400 mM chloride ions; and a pH between 5.5 and 7.0. In a particular embodiment, the composition contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0369] In a more specific embodiment, the final formulation consists of: an immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; between 10 mM and 400 mM chloride ions; and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0370] In one embodiment, the final formulation comprises: an immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; between 100 mM and 200 mM chloride ions; and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0371] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin; between 50 mM and 500 mM histidine; between 100 mM and 200 mM chloride ions; and a pH between 5.5 and 7.0. In a particular embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0372] In a more specific embodiment, the final formulation consists of: an immunoglobulin; between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; between 100 mM and 200 mM chloride ions; and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0373] In one embodiment, the final formulation comprises: an immunoglobulin; no more than 10 mM of an alkali metal cation; a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**; and between 10 mM and 400 mM chloride ions. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0374] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin; a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**; and between 10 mM and 400 mM chloride ions. In a particular embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0375] In a more specific embodiment, the final formulation consists of: an immunoglobulin; no more than 10 mM of an alkali metal cation; a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**; and between 10 mM and 400 mM chloride ions. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0376] In one embodiment, the final formulation comprises: an immunoglobulin; no more than 10 mM of an alkali metal cation; a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**; and between 100 mM and 200 mM chloride ions. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0377] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin; a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**; and between 100 mM and 200 mM chloride ions. In a particular embodiment, the final formulation contains no more than 10 mM of an alkali metal

cation. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0378] In a more specific embodiment, the final formulation consists of: an immunoglobulin; no more than 10 mM of an alkali metal cation; a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**; and between 100 mM and 200 mM chloride ions. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

4. Immunoglobulin Concentration

[0379] Generally, the methods provided herein are useful for stabilizing immunoglobulin compositions having a wide range of protein concentrations. For example, the methods provided herein are well suited to stabilize: low immunoglobulin concentrations that are used in the pharmaceutical formulation of monoclonal antibodies (*e.g.*, 10-40 g/L or lower); moderate immunoglobulin concentrations that are used in the pharmaceutical formulation of intravenous immunoglobulins (*e.g.*, 40-150 g/L); and high immunoglobulin concentration that are used in the pharmaceutical formulation of immunoglobulins administered subcutaneously or intramuscularly (*e.g.*, 150-250 g/L or higher). Generally, the upper limit of immunoglobulin concentrations that may be stabilized by the methods and formulations provided herein is only limited by the solubility limit of the immunoglobulins being formulated or the maximum concentration that can be achieved by the particular manufacturing process being employed. Accordingly, in one embodiment, the immunoglobulin concentration of a storage stable aqueous solution provided herein is between 1 g/L and 250 g/L.

a. Low Immunoglobulin Concentration

[0380] In one embodiment, the present invention provides a method for stabilizing an aqueous immunoglobulin composition, the method comprising formulating a composition comprising less than 40 g/L immunoglobulin with: between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the final

formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM and 400 mM chloride ions. In one embodiment, method further comprises storing the immunoglobulin composition in an air-tight containment vessel under inert gas. In a specific embodiment, the inert gas is nitrogen. In another specific embodiment, the inert gas is argon. In yet another specific embodiment, the inert gas is carbon dioxide. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0381] In a particular embodiment, the final formulation comprises: less than 40 g/L of an immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM and 400 mM chloride ions. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0382] In a specific embodiment, the final formulation consists essentially of: less than 40 g/L of an immunoglobulin and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In one embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM and 400 mM chloride ions.

[0383] In a more specific embodiment, the final formulation consists of: less than 40 g/L of an immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM and 400 mM chloride ions. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0384] In a specific embodiment, the method comprises formulating the immunoglobulin at a concentration between 10 g/L and 40 g/L. In another embodiment, the concentration of the

immunoglobulin is between 20 g/L and 30 g/L. In one embodiment, the concentration of the immunoglobulin is less than 40 g/L. In one embodiment, the concentration of the immunoglobulin is no more than 40 g/L. In another embodiment, the concentration of the immunoglobulin is no more than 30 g/L. In another embodiment, the concentration of the immunoglobulin is no more than 20 g/L. In another embodiment, the concentration of the immunoglobulin is no more than 10 g/L. In a specific embodiment, the concentration of the immunoglobulin is 10±1 g/L, 15±1.5 g/L, 20±2 g/L, 25±2.5 g/L, 30±3 g/L, 35±3.5 g/L, or 40±4 g/L. In yet other embodiments, the concentration of the immunoglobulin is 1 g/L, 2 g/L, 3 g/L, 4 g/L, 5 g/L, 6 g/L, 7 g/L, 8 g/L, 9 g/L, 10 g/L. 11 g/L. 12 g/L. 13 g/L. 14 g/L. 15 g/L. 16 g/L. 17 g/L. 18 g/L. 19 g/L. 20 g/L. 21 g/L. 22 g/L. 23 g/L. 24 g/L. 25 g/L. 26 g/L. 27 g/L. 28 g/L. 29 g/L. 30 g/L, 31 g/L, 32 g/L, 33 g/L, 34 g/L, 35 g/L, 36 g/L, 37 g/L, 38 g/L, 39 g/L, or 40 g/L.

b. Moderate Immunoglobulin Concentration

[0385] In another embodiment, the present invention provides a method for stabilizing an aqueous immunoglobulin composition, the method comprising formulating a composition comprising between 40 g/L and 150 g/L immunoglobulin with: between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM and 400 mM chloride ions. In one embodiment, method further comprises storing the immunoglobulin composition in an air-tight containment vessel under inert gas. In a specific embodiment, the inert gas is nitrogen. In another specific embodiment, the inert gas is argon. In yet another specific embodiment, the inert gas is carbon dioxide. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0386] In a particular embodiment, the final formulation comprises: between 40 g/L and 150 g/L of an immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises

between 10 mM and 400 mM chloride ions. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0387] In a specific embodiment, the final formulation consists essentially of: between 40 g/L and 150 g/L of an immunoglobulin and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In one embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM and 400 mM chloride ions. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0388] In a more specific embodiment, the final formulation consists of: between 40 g/L and 150 g/L of an immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM and 400 mM chloride ions. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0389] In a specific embodiment, the method comprises formulating the immunoglobulin at a concentration between 40 g/L and 60 g/L. In another specific embodiment, the concentration of the immunoglobulin is between 90 g/L and 110 g/L. In certain embodiments, the concentration of the immunoglobulin is 45±4.5 g/L, 50±5 g/L, 55±5.5 g/L, 60±6 g/L, 65±6.5 g/L, 70±7 g/L, 75±7.5 g/L, 80±8 g/L, 85±8.5 g/L, 90±9 g/L, 95±9.5 g/L, 100±10 g/L, 110±11 g/L, 120±12 g/L, 130±13 g/L, 140±14 g/L, or 150±15 g/L. In yet other embodiments, the concentration of the immunoglobulin is 40 g/L, 45 g/L, 50 g/L, 55 g/L, 60 g/L, 65 g/L, 70 g/L, 75 g/L, 80 g/L, 85 g/L, 90 g/L, 95 g/L, 100 g/L, 105 g/L, 110 g/L, 115 g/L, 120 g/L, 125 g/L, 130 g/L, 135 g/L, 140 g/L, 145 g/L, or 150 g/L.

c. High Immunoglobulin Concentration

[0390] In one embodiment, present invention provides a method for stabilizing an aqueous immunoglobulin composition, the method comprising formulating a composition comprising more than 150 g/L of an immunoglobulin with: between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM and 400 mM chloride ions. In one embodiment, method further comprises storing the immunoglobulin composition in an air-tight containment vessel under inert gas. In a specific embodiment, the inert gas is nitrogen. In another specific embodiment, the inert gas is argon. In yet another specific embodiment, the inert gas is carbon dioxide. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0391] In a particular embodiment, the final formulation comprises: more than 150 g/L of an immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM and 400 mM chloride ions. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0392] In a specific embodiment, the final formulation consists essentially of: more than 150 g/L of an immunoglobulin and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In one embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM and 400 mM chloride ions. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0393] In a more specific embodiment, the final formulation consists of: more than 150 g/L of an immunoglobulin; no more than 10 mM of an alkali metal cation; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In

a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM and 400 mM chloride ions. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0394] In a specific embodiment, the method comprises formulating the immunoglobulin at a concentration of at least 150 g/L. In a specific embodiment, the concentration of immunoglobulin is at least 175 g/L. In another specific embodiment, the concentration of immunoglobulin is at least 200 g/L. In another specific embodiment, the concentration of immunoglobulin is at least 225 g/L. In one embodiment, the concentration of the immunoglobulin is between 150 g/L and 250 g/L. In another embodiment, the concentration of the immunoglobulin is between 175 g/L and 225 g/L In certain embodiments, the concentration of the immunoglobulin is 150±15 g/L, 160±16 g/L, 170±17 g/L, 180±18 g/L, 190±19 g/L, 200±20 g/L, 210±21 g/L, 220±22 g/L, 230±23 g/L, 240±24 g/L, or 250±25 g/L. In yet other embodiments, the concentration of the immunoglobulin is 150 g/L, 160 g/L, 170 g/L, 180 g/L, 190 g/L, 200 g/L, 210 g/L, 220 g/L, 230 g/L, 240 g/L, 250 g/L, or higher.

5. Administration

[0395] In certain embodiments, the storage stable compositions provided herein will be formulated for parenteral administration including, but not limited to, intradermal, subcutaneous, transdermal implant, intracavernous, intravitreal, transscleral, intracerebral, intrathecal, epidural, intravenous, intracardiac, intramuscular, intraosseous, intraperitoneal, and nanocell injection administration. In one preferred embodiment, the compositions provided herein will be formulated for intravenous administration. In another preferred embodiment, the compositions provided herein will be formulated for subcutaneous administration. In yet another preferred embodiment, the compositions provided herein will be formulated for intramuscular administration. In yet another embodiment, the formulation is suitable for intravenous administration as well as either or both subcutaneous and intramuscular administration.

6. Excipients

[0396] In certain embodiments, the methods provided herein further comprise a formulation step of adding one or more excipients to the immunoglobulin composition. Non-limiting examples of excipients that can be included in the formulations provided herein include non-ionic surfactants, bulking agents (*e.g.*, sugars and sugar alcohols), antioxidants, polysaccharides, and pharmaceutically acceptable water-soluble polymers (*e.g.*, poly(acrylic acid), poly(ethylene oxide), poly(ethylene glycol), poly(vinyl pyrrolidone), hydroxyethyl cellulose, hydroxypropyl cellulose, and starch).

[0397] In one embodiment, the excipient is an agent for adjusting the osmolarity of the composition. Non-limiting examples of osmolarity agents include mannitol, sorbitol, glycerol, sucrose, glucose, dextrose, levulose, fructose, lactose, polyethylene glycols, phosphates, calcium chloride, calcium gluconoglucoheptonate, dimethyl sulfone, and the like.

[0398] In one embodiment, the present invention provides a method for stabilizing an aqueous immunoglobulin composition, the method comprising formulating an immunoglobulin composition with: between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; an antioxidant; and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM and 400 mM chloride ions. In one embodiment, method further comprises storing the immunoglobulin composition in an air-tight containment vessel under inert gas. In a specific embodiment, the inert gas is nitrogen. In another specific embodiment, the inert gas is argon. In yet another specific embodiment, the inert gas is carbon dioxide. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0399] In a particular embodiment, the final formulation comprises: an immunoglobulin; no more than 10 mM of an alkali metal cation; an antioxidant; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM

and 400 mM chloride ions. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0400] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin; an antioxidant; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM and 400 mM chloride ions. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0401] In a more specific embodiment, the final formulation consists of: an immunoglobulin; no more than 10 mM of an alkali metal cation; an antioxidant; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM and 400 mM chloride ions. In a specific embodiment, the final formulation does not contain a surfactant or sugar.

[0402] In one embodiment, the present invention provides a method for stabilizing an aqueous immunoglobulin composition, the method comprising formulating an immunoglobulin composition with: between 50 mM and 500 mM histidine; no more than 10 mM of an alkali metal cation; a sugar and/or sugar alcohol, and a pH between 5.5 and 7.0. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM and 400 mM chloride ions. In one embodiment, method further comprises storing the immunoglobulin composition in an air-tight containment vessel under inert gas. In a specific embodiment, the inert gas is nitrogen. In another specific embodiment, the inert gas is argon. In yet another specific embodiment, the inert gas is carbon dioxide.

[0403] In a particular embodiment, the final formulation comprises: an immunoglobulin; no more than 10 mM of an alkali metal cation; a sugar and/or sugar alcohol; and a histidine/pH

combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM and 400 mM chloride ions.

[0404] In a specific embodiment, the final formulation consists essentially of: an immunoglobulin; a sugar and/or sugar alcohol; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the final formulation contains no more than 10 mM of an alkali metal cation. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM and 400 mM chloride ions.

[0405] In a more specific embodiment, the final formulation consists of: an immunoglobulin; no more than 10 mM of an alkali metal cation; a sugar and/or sugar alcohol; and a histidine/pH combination selected from the group consisting of variations 1 to 952, as provided in **Table 1** and **Table 2**. In a specific embodiment, the final formulation contains no more than 1 mM of an alkali metal cation. In another specific embodiment, the final formulation further comprises between 10 mM and 400 mM chloride ions.

V. Examples

Example 1

[0406] To determine the role.pH and salt concentration have on a plasma-derived 20% IgG composition, a two year stability study was conducted. This study revealed that the inclusion of sodium chloride and/or the formulation at neutral to mildly acid pH imparted a stabilizing effect on the 20% IgG composition.

[0407] Briefly, two IgG compositions prepared from pooled plasma according to the Gammagard Liquid process outlined in Teschner *et al.* (Vox Sang. 2007 Jan;92(1):42-55) were concentrated to a final protein concentration of 20%. These preparations were then divided into several samples which were differentially formulated at a pH of 6.5, 7.0, or 7.5 with and without approximately 50 mM sodium chloride. The aqueous formulations were then stored at between

28°C and 32°C for 24 months. After the two year incubation period, the molecular size distribution of the IgG in the various formulations were investigated by high performance size exclusion chromatography (HP-SEC), the results of which are provided in **Table 3**.

Table 3. Molecular size distribution of 20% IgG (IGSC61 and IGSC63) formulations after two years storage at 28°C to 32°C.

Sample		T (℃)	Polymers	Oligo/Dimers	Monomers	Fragments
IGSC61						
pH 6.5	24 months	28-32	3.57	20.68	68.92	6.83
pH 7.0	24 months	28-32	10.32	19.78	60.96	8.94
pH 7.5	24 months	28-32	11.76	20.01	57.70	10.53
pH 6.5 3g/L NaCl	24 months	28-32	3.16	20.52	69.75	6.57
pH 7.0 3g/L NaCl	24 months	28-32	9.53	19.68	61.69	9.11
pH 7.5 3g/L NaCl	24 months	28-32	10.26	20.25	58.97	10.53
IGSC63						
pH 6.5	24 months	28-32	2.34	20.99	68.84	7.83
pH 7.0	24 months	28-32	3.48	20.95	64.37	11.20
pH 7.5	24 months	28-32	6.00	23.23	58.39	12.39
pH 6.5 3g/L NaCl	24 months	28-32	1.92	19.33	70.36	8.40
pH 7.0 3g/L NaCl	24 months	28-32	2.63	21.10	64.98	11.29
pH 7.5 3g/L NaCl	24 months	28-32	5.51	23.13	59.24	12.12

[0408] The results shown in **Table 3** indicate that, within the pH range of 6.5 to 7.5, increases in pH result in increased aggregation of the IgG preparation, as shown by the increasing percentage of IgG polymers in the formulations at pH 7.0 and 7.5 compared to the formulations at pH 6.5. Inclusion of 50 mM sodium chloride in each formulation stabilizes the lower molecular weight IgG species, resulting in a nearly 14% reduction in the level of IgG polymers in the samples. This is in contrast to IgG compositions formulated as low pH (4.4 to 4.9), which are destabilized by the addition of sodium chloride.

Example 2

[0409] To further characterize the stabilizing effect that sodium chloride has on IgG compositions formulated at mildly acid to neutral pH, an accelerated stability study was performed. For the accelerated study, elevated temperatures (38°C to 42°C) were used to simulate longer time periods at room temperature (20°C to 25°C). Briefly, a 20% IgG composition, prepared as in Example 1, was divided into samples that were formulated with increasing salt concentrations (0 mM, 50 mM, 100 mM, and 150 mM) at mildly acid to neutral

pHs (pH 5.5, 6.0, 6.5, 7.0, and 7.5). The aqueous formulations were then stored at between 38°C and 42°C for 6 months. After the 6 month incubation period, the molecular size distribution of IgG in the various formulations were investigated by high performance size exclusion chromatography (HP-SEC). The percentage of IgG aggregates present in the various formulations is shown in Figure 1.

[0410] As seen in Figure 1, the stability of the immunoglobulin preparation is dependent upon both the pH and the salt concentration of the formulation. Addition of 100 mM or 150 mM sodium chloride in the formulation provided additional stability, as compared to the protective effects seen for 50 mM sodium chloride in Example 1, at pHs between 6.0 and 7.5. Significantly, inclusion of 150 mM sodium chloride in of IgG compositions formulates at pHs between 6.0 and 7.5 reduced IgG aggregation by more than 50% on average. Optimal stabilization was seen in formulations containing 150 mM sodium chloride at pH 6.5, in which aggregate formation was reduced more than 50% as compared to formulations with 50 mM sodium chloride and about 60% as compared to formulations with no sodium chloride. Consistent with previous observations, the addition of sodium chloride in IgG formulations at lower pH (5.5) results in a destabilizing effect.

Example 3 – Preparation of Samples for Study IGSC73

[0411] Hizentra® (20% Immune Globulin Subcutaneous (Human); CSL Behring) is a 20% immunoglobulin preparation for subcutaneous administration. This product is formulated at low pH (pH 4.8) employing proline as a stabilizer. Several reports have indicated that the use of proline as a stabilizer for immunoglobulin solutions is superior to the use of glycine or histidine (Maeder *et al.*, Biologicals. 2011 Jan;39(1):43-9; Bolli *et al.*, Biologicals. 2010 Jan;38(1):150-7).

[0412] The purpose of this study is to compare the stability of 20% immunoglobulin formulations using 0.25 M glycine, 0.25 M proline, or 0.25 M histidine. The liquid formulations were incubated at 28°C to 32°C and 38°C to 42°C for up to one year under air, nitrogen, or argon atmosphere.

[0413] In the first experiment (IGSC73) three Gammagard Liquid final containers (prepared from pooled plasma according to the Gammagard Liquid process outlined in Teschner *et al.*

(Vox Sang. 2007 Jan;92(1):42-55)) with lot numbers P00809NG, P00909NG, and P01009NG were pooled and the pH adjusted to 4.5 to 4.8. The composition of the starting material lots is provided in **Table 4**. The parameters of lot P00409NG are also shown in this table as this lot was used in other experiments described below.

Table 4. Compositions of starting IgG immunoglobulin lots.

		P00409NG FC	P00809NG FC	P00909NG FC	P01009NG FC
Protein (g/l)		10.6196	10.6431	11.8626	11.1902
IgA (%)		0.0029	0.0027	0.0032	0.003
MSD (HPLC) (% area)	Aggregates	0.0499	0.0938	0.0413	0.0385
	Oligo/Dimers	8.8804	7.9121	8.2818	8.4671
	Monomers	90.9821	91.9354	91.6040	91.4253
	Fragments	0.0876	0.1052	0.0730	0.0691
Amidolytic Activity (nmol/ml.min)		<10	<10	<10	<10

[0414] The pool was then split into three parts of 500 mL each to formulate the preparation at 20% protein in glycine, histidine, or proline. For the formulation containing glycine, the immunoglobulin pool was just concentrated to 20% using an ultra-/diafiltration device equipped with a 0.2 m^2 polyethersulfone membrane (Pellicon Mini 30K B-30V). To prepare the proline and histidine formulations, the pool aliquots were diafiltered ten times at a protein concentration of 5% against either 0.25 M proline (pH 4.8) or 0.25 M histidine (pH 6.0) prior to concentrating the samples to 20% protein using an ultra-/diafiltration device equipped with a 0.2 m^2 polyethersulfone membrane (Pellicon Mini 30K B-30V). The molecular size distribution (MSD) of the 20% formulations after ultra-/diafiltration is provided in **Table 5**. The data demonstrate that the ultra-/diafiltration steps do not drastically alter the molecular size distribution of the immunoglobulin preparations. Use of proline as a stabilizer appears to have an aggregation enhancing effect. All of the formulations were then sterile filtered using a Millipak 20 (Millipore), aliquoted into vials under and air atmosphere, and closed with stoppers suitable for lyophilization. A total of 18 vials were prepared as described in **Table 6** and **Table 7**.

Table 5. Molecular size distribution of the three amino acid formulations (IGSC73) after buffer exchange and concentration to 20%.

		Proline	Histidine	Glycine
MSD (HPLC) (% area)	Aggregates	0.48	0.11	0.15
	Oligo/Dimers	8.96	10.82	9.04
	Monomers	90.25	88.80	90.52
	Fragments	0.31	0.27	0.29

Table 6. Variation of amino acid and pH in each formulation.

Sample Identification	1F	2F	3F
Amino acid	Proline	Histidine	Glycine
pH	4.8	6.1	4.8
Tween 80 concentration (mg/L)	0	0	0
Atmosphere	Air	Air	Air

Table 7. Variation of atmosphere used for storage.

Sample Identification	4F	5F	6F	7F	8F	9F
Amino acid	Proline	Histidine	Glycine	Proline	Histidine	Glycine
pH	4.8	6.1	4.8	4.8	6.1	4.8
Tween 80 concentration (mg/L)	0	0	0	0	0	0
Atmosphere	N2	N2	N2	Argon	Argon	Argon

*Samples with the identification numbers 10F through 18F correspond to the formulations 1F to 9F, but are stored under light exposure at 38°C to 42°C.

Example 4 – Study IGSC73 – Normal Atmosphere; 28°C to 32°C

[0415] To determine the stabilizing effect of each amino acid formulation, samples 1F, 2F, and 3F, formulated without polysorbate 80 and stored under air, were stored between 28°C to 32°C protected from light for up to one year. The molecular size distribution of the samples were determined after 1, 3, 6, and 12 months. As seen in **Table 8**, the level of immunoglobulin aggregates in samples formulated with histidine at pH 6.1 was significantly depressed as compared to the proline and glycine formulations. Slightly lower levels of immunoglobulin fragmentation were observed in the histidine formulations as compared to the other two samples.

Table 8. Mass size distribution of formulations (IGSC73) stored under normal atmosphere at 28°C to 32°C.

		Sample Code		T (°C)	MSD (HPLC) Aggregates % area	Oligo/Dimers % area	Monomers % area	Fragments % area
Proline pH 4.8	Air	1 F	Start	2 - 8	0.48	8.96	90.25	0.31
		1 F	1 M	28 - 32	0.56	9.78	89.17	0.49
		1 F	3 M	28 - 32	0.62	9.83	88.85	0.70
		1 F	6 M	28 - 32	1.01	11.58	85.88	1.53
		1 F	12 M	28 - 32	1.45	11.62	84.84	2.10
Histidine pH 6.1		2 F	Start	2 - 8	0.11	10.82	88.8	0.27
		2 F	1 M	28 - 32	0.20	12.44	86.96	0.41
		2 F	3 M	28 - 32	0.26	12.58	86.44	0.72
		2 F	6 M	28 - 32	0.45	13.79	84.36	1.39
		2 F	12 M	28 - 32	0.96	13.10	83.99	1.95
Glycine pH 4.8		3 F	Start	2 - 8	0.15	9.04	90.51	0.29
		3 F	1 M	28 - 32	0.22	10.54	88.77	0.47
		3 F	3 M	28 - 32	0.39	10.61	88.19	0.81
		3 F	6 M	28 - 32	0.75	12.61	85.15	1.48
		3 F	12 M	28 - 32	1.41	12.58	83.88	2.14

Example 5 – Study IGSC73 – Nitrogen Atmosphere; 28°C to 32°C

[0416] To determine the stabilizing effect of each amino acid formulation, samples 4F, 5F, and 6F, formulated without polysorbate 80 and stored under nitrogen, were stored between 28°C to 32°C protected from light for up to one year. The molecular size distribution of the samples were determined after 1, 3, 6, and 12 months. As seen in **Table 9**, storage of the samples under nitrogen reduced the level of immunoglobulin aggregation in the proline and glycine formulated samples by 14% and 28%, respectively, as compared to samples 1F and 3F stored under normal atmosphere for 12 months. Notably, storage of the histidine formulation under nitrogen reduced the level of immunoglobulin aggregation by nearly 50% as compared to sample 2F stored under normal atmosphere for 12 months. Significantly, the level of immunoglobulin aggregation in the histidine-formulated sample stored under nitrogen (5F) was less than half of the levels of aggregation for the similarly stored proline and glycine formulations (4F and 6F, respectively) Even more interestingly, the level of immunoglobulin fragmentation in the histidine formulation stored under nitrogen was lowered as compared to the histidine formulated sample stored under air. The fragmentation levels of the proline and glycine formulations were not affected by storage under nitrogen.

Table 9. Mass size distribution of formulations (IGSC73) stored under nitrogen at 28°C to 32°C.

					MSD (HPLC)			
		Sample Code		T (°C)	Aggregates % area	Oligo/Dimers % area	Monomers % area	Fragments % area
Proline pH 4.8	Nitrogen	4F	Start	2 - 8	0.48	9.04	90.15	0.33
		4F	1 M	28 - 32	0.56	10.00	88.96	0.49
		4F	3 M	28 - 32	0.63	10.05	88.49	0.84
		4F	6 M	28 - 32	0.87	11.71	85.9	1.52
		4F	12 M	28 - 32	1.24	11.47	85.18	2.11
Histidine pH 6.1		5 F	Start	2 - 8	0.11	10.76	88.89	0.24
		5 F	1 M	28 - 32	0.20	12.40	87.06	0.35
		5 F	3 M	28 - 32	0.21	12.40	86.8	0.59
		5 F	6 M	28 - 32	0.33	14.10	84.38	1.19
		5 F	12 M	28 - 32	0.49	13.28	84.55	1.67
Glycine pH 4.8		6 F	Start	2 - 8	0.17	9.36	90.2	0.27
		6 F	1 M	28 - 32	0.27	10.32	88.95	0.46
		6 F	3 M	28 - 32	0.35	10.71	88.13	0.82
		6 F	6 M	28 - 32	0.60	12.47	85.46	1.46
		6 F	12 M	28 - 32	1.02	11.93	84.87	2.17

Example 6 – Study IGSC73 – Argon Atmosphere; 28°C to 32°C

[0417] To determine the stabilizing effect of each amino acid formulation, samples 7F, 8F, and 9F, formulated without polysorbate 80 and stored under argon, were stored between 28°C to 32°C protected from light for up to one year. The molecular size distribution of the samples were determined after 1, 3 ,6, and 12 months. As seen for the formulations stored under nitrogen, storage of the proline and glycine formulations under argon resulted in a less than 30% reduction in the level of immunoglobulin aggregates, as compared to samples 1F and 3F stored under normal atmosphere for 12 months (**Table 10**). Likewise, storage of the histidine formulation under argon reduced the level of immunoglobulin aggregation by 50% as compared to sample 2F stored under normal atmosphere for 12 months. Again, the level of immunoglobulin aggregation in the histidine-formulated sample stored under argon (8F) was less than half of the levels of aggregation for the similarly stored proline and glycine formulations (7F and 9F, respectively). Similarly, the level of immunoglobulin fragmentation in the histidine formulation stored under argon was again lowered as compared to the histidine formulated

sample stored under air. The fragmentation levels of the proline and glycine formulations were again not affected by storage under argon.

Table 10. Mass size distribution of formulations (IGSC73) stored under argon at 28°C to 32°C.

					MSD (HPLC)			
		Sample Code		T (°C)	Aggregates % area	Oligo/Dimers % area	Monomers % area	Fragments % area
Proline pH 4.8	Argon	7 F	Start	2 - 8	0.48	9.12	90.09	0.31
		7 F	1 M	28 - 32	0.56	10.00	88.95	0.50
		7 F	3 M	28 - 32	0.59	10.17	88.32	0.91
		7 F	6 M	28 - 32	0.90	11.96	85.60	1.54
		7 F	12 M	28 - 32	1.39	11.67	84.82	2.12
Histidine pH 6.1		8 F	Start	2 - 8	0.12	10.71	88.91	0.26
		8 F	1 M	28 - 32	0.20	12.43	87.04	0.33
		8 F	3 M	28 - 32	0.25	12.25	86.77	0.72
		8 F	6 M	28 - 32	0.34	13.97	84.44	1.25
		8 F	12 M	28 - 32	0.48	13.09	84.79	1.63
Glycine pH 4.8		9 F	Start	2 - 8	0.17	9.46	90.13	0.25
		9 F	1 M	28 - 32	0.26	10.45	88.83	0.46
		9 F	3 M	28 - 32	0.35	10.78	88.01	0.85
		9 F	6 M	28 - 32	0.59	12.35	85.60	1.47
		9 F	12 M	28 - 32	1.03	11.90	84.90	2.18

Example 7 – Study IGSC73 – Normal Atmosphere; 38°C to 42°C

[0418] To determine the stabilizing effect of each amino acid formulation under more stressful conditions, samples 10F, 11F, and 12F, formulated without polysorbate 80 and stored under air, were stored between 38°C to 42°C protected from light for up to five weeks. The molecular size distribution of the samples was determined after 1, 2, and 5 weeks. As seen in **Table 11**, the level of immunoglobulin aggregates in samples formulated with histidine at pH 6.1 was significantly depressed as compared to the proline and glycine formulations. Slightly lower levels of immunoglobulin fragmentation were observed in the histidine formulations as compared to the other two samples.

Table 11. Mass size distribution of formulations (IGSC73) stored under normal atmosphere at 38°C to 42°C. *MSD was measured after five weeks of incubation for these samples.

		Sample Code		T (°C)	MSD (HPLC) Aggregates % area	Oligo/Dimers % area	Monomers % area	Fragments % area
Proline pH 4.8	Air	10 F = 1 F	Start	2 - 8	0.48	8.96	90.25	0.31
		10 F	1 W	38 - 42	2.14	7.78	89.48	0.60
		10 F	2 W	38 - 42	3.14	7.35	88.79	0.71
		10 F	4 W	38 - 42	4.84	7.91	86.13	1.12
Histidine pH 6.1		11 F = 2 F	Start	2 - 8	0.11	10.82	88.8	0.27
		11 F	1 W	38 - 42	0.45	10.04	89.01	0.50
		11 F	2 W	38 - 42	0.70	8.39	90.41	0.49
		11 F	4 W*	38 - 42	1.42	10.18	87.41	0.99
Glycine pH 4.8		12 F = 3 F	Start	2 - 8	0.15	9.04	90.51	0.29
		12 F	1 W	38 - 42	1.64	8.35	89.48	0.53
		12 F	2 W	38 - 42	2.32	7.67	89.42	0.59
		12 F	4 W*	38 - 42	4.24	8.74	85.88	1.14

Example 8 – Study IGSC73 – Nitrogen Atmosphere; 38°C to 42°C

[0419] To determine the stabilizing effect of each amino acid formulation under more stressful conditions, samples 13F, 14F, and 15F, formulated without polysorbate 80 and stored under nitrogen, were stored between 38°C to 42°C protected from light for up to four weeks. The molecular size distributions of the samples were determined after 1, 2, and 4 weeks. As seen in **Table 12**, storage of the samples under nitrogen reduced the level of immunoglobulin aggregation in the proline and histidine, but not the glycine formulated samples, as compared to samples stored under normal atmosphere (compare **Table 11** and **Table 12** at 2 weeks). Significantly, the level of immunoglobulin aggregation in the histidine-formulated sample stored under nitrogen (14F) was less than a third of the levels of aggregation for the similarly stored proline and glycine formulations (13F and 15F, respectively) The fragmentation levels of the proline and histidine formulations were not affected by storage under nitrogen, while a slight increase in the amount of immunoglobulin fragmentation was seen in the glycine formulation.

Table 12. Mass size distribution of formulations (IGSC73) stored under nitrogen at 38°C to 42°C.

					MSD (HPLC)			
		Sample Code		T (°C)	Aggregates % area	Oligo/Dimers % area	Monomers % area	Fragments % area
Proline pH 4.8	Nitrogen	13 F = 4 F	Start	2 - 8	0.48	9.04	90.15	0.33
		13 F	1 W	38 - 42	2.09	7.96	89.37	0.58
		13 F	2 W	38 - 42	2.80	7.30	89.17	0.73
		13 F	4 W	38 - 42	4.49	7.83	86.56	1.12
Histidine pH 6.1		14 F = 5 F	Start	2 - 8	0.11	10.76	88.89	0.24
		14 F	1 W	38 - 42	0.45	10.07	88.99	0.50
		14 F	2 W	38 - 42	0.64	8.51	90.37	0.48
		14 F	4 W	38 - 42	1.20	10.27	87.81	0.72
Glycine pH 4.8		15 F = 6 F	Start	2 - 8	0.17	9.36	90.2	0.27
		15 F	1 W	38 - 42	1.53	8.35	89.65	0.47
		15 F	2 W	38 - 42	2.38	7.57	89.32	0.73
		15 F	4 W	38 - 42	3.87	8.37	86.62	1.14

Example 9 – Study IGSC73 – Argon Atmosphere; 38°C to 42°C

[0420] To determine the stabilizing effect of each amino acid formulation under more stressful conditions, samples 16F, 17F, and 18F, formulated without polysorbate 80 and stored under argon, were stored between 38°C to 42°C protected from light for up to four weeks. The molecular size distribution of the samples were determined after 1, 2, and 4 weeks. As seen in **Table 13**, storage of all three formulations under argon resulted in a slight reduction in the level of immunoglobulin aggregates, as compared to samples stored under normal atmosphere for 12 months. As seen for the samples stored under nitrogen, the level of immunoglobulin aggregation in the histidine-formulated sample stored under argon (17F) was less than a third of the levels of aggregation for the similarly stored proline and glycine formulations (16F and 18F, respectively). The level of immunoglobulin fragmentation in the histidine formulation stored under argon was again lowered as compared to the histidine formulated sample stored under air. The fragmentation levels of the proline and glycine formulations were slightly increased as compared to those stored under normal atmosphere.

Table 13. Mass size distribution of formulations (IGSC73) stored under argon at 38°C to 42°C.

					MSD (HPLC)			
		Sample Code		T (°C)	Aggregates % area	Oligo/Dimers % area	Monomers % area	Fragments % area
Proline pH 4.8	Argon	16 F = 7 F	Start	2 - 8	0.48	9.12	90.09	0.31
		16 F	1 W	38 - 42	2.09	8.04	89.28	0.6
		16 F	2 W	38 - 42	2.92	7.43	88.89	0.77
		16 F	4 W	38 - 42	4.64	7.96	86.26	1.14
Histidine pH 6.1		17 F = 8 F	Start	2 - 8	0.12	10.71	88.91	0.26
		17 F	1 W	38 - 42	0.45	10.31	88.86	0.38
		17 F	2 W	38 - 42	0.67	8.63	90.27	0.42
		17 F	4 W	38 - 42	1.24	10.24	87.77	0.74
Glycine pH 4.8		18 F = 9 F	Start	2 - 8	0.17	9.46	90.13	0.25
		18 F	1 W	38 - 42	1.68	8.57	89.26	0.49
		18 F	2 W	38 - 42	2.45	7.58	89.36	0.62
		18 F	4 W	38 - 42	4.06	8.44	86.38	1.12

Example 10 – Study IGSC73 – Optical Density; 38°C to 42°C

[0421] To determine the effect of each amino acid formulation on the discoloration of the immunoglobulin composition, the optical density (OD) of each sample was monitored at 350 nm for samples stored under normal atmosphere, nitrogen, and argon at 28°C to 32°C for up to 12 months. As disclosed in the literature, the OD values for all readings, except those taken at time 0, have been corrected by the OD at 500 nm to account for air trapped in the highly concentrated solution.

[0422] As evidenced in Figures 2A, 2B, and 2C, the histidine formulation at pH 6.1 (■) starts to develop a strong discoloration after three months under normal atmosphere. However, the use of inert gas significantly protects the histidine formulation from this discoloration.

Example 11 – Preparation of Samples for Study IGSC74

[0423] Sample formulation for study IGSC74 was performed as for study IGSC73, described in Example 3, except for the following changes: i.) four Gammagard Liquid final containers (prepared from pooled plasma according to the Gammagard Liquid process outlined in Teschner *et al.* (Vox Sang. 2007 Jan;92(1):42-55)) with lot numbers P00409NG, P00809NG, P00909NG, and P01009NG were pooled and the pH adjusted to 4.5 to 4.8; and ii.) the sample stabilized with histidine was formulated at pH 4.8, rather than 6.1. Samples were numbered as for study IGSC73 in Example 3 (1F to 18F).

[0424] The molecular size distribution (MSD) of the 20% formulations after ultra-/diafiltration is provided in **Table 14**The data again demonstrate that the ultra-/diafiltration steps did not drastically alter the molecular size distribution of the immunoglobulin preparations. Similarly, the use of proline as a stabilizer again appeared to have an aggregation enhancing effect.

Table 14. Molecular size distribution of the three amino acid formulations (IGSC74) after buffer exchange and concentration to 20%.

		Proline	Histidine	Glycine
MSD (HPLC) (% area)	Aggregates	0.46	0.10	0.11
	Oligo/Dimers	7.22	6.53	7.26
	Monomers	92.02	93.14	92.33
	Fragments	0.30	0.23	0.30

Example 12 – Study IGSC74 – Normal Atmosphere; 28°C to 32°C

[0425] To determine the stabilizing effect of each amino acid formulation, samples 1F, 2F, and 3F, formulated without polysorbate 80 and stored under air, were stored between 28°C to 32°C protected from light for up to one year. The molecular size distributions of the samples were determined after 1, 3, 6, and 12 months. As seen in **Table 15**, the histidine formulation at pH 4.8 had significantly higher levels of immunoglobulin aggregates and fragments after storage for 12 months, as compared to the proline and glycine formulations. This is in stark contrast to the immunoglobulin compositions formulated with histidine at pH 6.1, which displayed increased stability over time as compared to the proline and glycine formulations. Notably, the level of immunoglobulin aggregation and fragmentation of the proline and glycine formulations was nearly identical for study IGSC73 and IGSC74.

Table 15. Mass size distribution of formulations (IGSC74) stored under normal atmosphere at 28°C to 32°C.

					MSD (HPLC)			
		Sample Code		T (°C)	Aggregates % area	Oligo/Dimers % area	Monomers % area	Fragments % area
Proline pH 4.8	Air	1 F	Start	2 - 8	0.46	7.22	92.02	0.30
		1 F	1 M	28 - 32	0.54	10.63	88.39	0.45
		1 F	3 M	28 - 32	0.62	11.10	87.53	0.75
		1 F	6 M	28 - 32	0.88	11.82	85.77	1.53
		1 F	12 M	28 - 32	1.41	11.21	85.35	2.02
Histidine pH 4.8		2 F	Start	2 - 8	0.10	6.53	93.14	0.23
		2 F	1 M	28 - 32	0.79	9.15	89.56	0.51
		2 F	3 M	28 - 32	1.57	9.67	87.7	1.07
		2 F	6 M	28 - 32	2.68	10.09	85.42	1.81
		2 F	12 M	28 - 32	5.04	9.14	83.14	2.68
Glycine pH 4.8		3 F	Start	2 - 8	0.11	7.26	92.33	0.30
		3 F	1 M	28 - 32	0.24	10.96	88.33	0.46
		3 F	3 M	28 - 32	0.36	11.62	87.24	0.77
		3 F	6 M	28 - 32	0.71	12.61	85.14	1.54
		3 F	12 M	28 - 32	1.36	12.42	84.09	2.14

Example 13 – Study IGSC74 – Nitrogen Atmosphere; 28°C to 32°C

[0426] To determine the stabilizing effect of each amino acid formulation, samples 4F, 5F, and 6F, formulated without polysorbate 80 and stored under nitrogen, were stored between 28°C to 32°C protected from light for up to one year. The molecular size distributions of the samples were determined after 1, 3, 6, and 12 months. As for the formulations stored under normal atmosphere, the histidine formulation at pH 4.8 had significantly higher levels of immunoglobulin aggregates and fragments after storage for 12 months, as compared to the proline and glycine formulations (**Table 16**). The level of immunoglobulin aggregation and fragmentation of the proline and glycine formulations stored under nitrogen was very similar for study IGSC73 and IGSC74.

Table 16. Mass size distribution of formulations (IGSC74) stored under nitrogen at 28°C to 32°C.

		Sample Code		T (°C)	MSD (HPLC) Aggregates % area	Oligo/Dimers % area	Monomers % area	Fragments % area
Proline pH 4.8	Nitrogen	4 F	Start	2 - 8	0.45	7.26	91.96	0.33
		4 F	1 M	28 - 32	0.51	10.48	88.61	0.40
		4 F	3 M	28 - 32	0.58	10.76	87.83	0.84
		4 F	6 M	28 - 32	0.79	11.77	86.01	1.44
		4 F	12 M	28 - 32	1.10	11.11	85.77	2.02
Histidine pH 4.8		5 F	Start	2 - 8	0.10	6.59	93.07	0.24
		5 F	1 M	28 - 32	0.70	8.92	89.9	0.47
		5 F	3 M	28 - 32	1.41	9.43	88.07	1.09
		5 F	6 M	28 - 32	2.45	10.03	85.7	1.83
		5 F	12 M	28 - 32	4.44	9.19	83.62	2.74
Glycine pH 4.8		6 F	Start	2 - 8	0.12	7.28	92.33	0.27
		6 F	1 M	28 - 32	0.23	10.96	88.32	0.48
		6 F	3 M	28 - 32	0.35	11.56	87.38	0.72
		6 F	6 M	28 - 32	0.57	12.36	85.58	1.49
		6 F	12 M	28 - 32	0.98	11.83	85.07	2.12

Example 14 – Study IGSC74 – Argon Atmosphere; 28°C to 32°C

[0427] To determine the stabilizing effect of each amino acid formulation, samples 7F, 8F, and 9F, formulated without polysorbate 80 and stored under argon, were stored between 28°C to 32°C protected from light for up to one year. The molecular size distributions of the samples were determined after 1, 3, 6, and 12 months. As for the formulations stored under normal atmosphere and nitrogen, the histidine formulation at pH 4.8 had significantly higher levels of immunoglobulin aggregates and fragments after storage for 12 months, as compared to the proline and glycine formulations (**Table 17**). The level of immunoglobulin aggregation and fragmentation of the proline and glycine formulations stored under argon was similar for study IGSC73 and IGSC74.

Table 17. Mass size distribution of formulations (IGSC74) stored under argon at 28°C to 32°C.

		Sample Code		T (°C)	MSD (HPLC) Aggregates % area	Oligo/Dimers % area	Monomers % area	Fragments % area
Proline pH 4.8	Argon	7 F	Start	2 - 8	0.44	7.37	91.96	0.24
		7 F	1 M	28 - 32	0.51	10.48	88.59	0.42
		7 F	3 M	28 - 32	0.57	11.07	87.73	0.63
		7 F	6 M	28 - 32	0.84	12.00	85.7	1.47
		7 F	12 M	28 - 32	1.22	11.26	85.51	2.00
Histidine pH 4.8		8 F	Start	2 - 8	0.10	6.76	92.92	0.21
		8 F	1 M	28 - 32	0.79	8.93	89.75	0.53
		8 F	3 M	28 - 32	1.58	9.74	87.66	1.03
		8 F	6 M	28 - 32	2.57	10.13	85.49	1.82
		8 F	12 M	28 - 32	4.67	9.18	83.41	2.74
Glycine pH 4.8		9 F	Start	2 - 8	0.11	7.61	92.01	0.27
		9 F	1 M	28 - 32	0.25	10.86	88.41	0.47
		9 F	3 M	28 - 32	0.37	11.75	87.04	0.84
		9 F	6 M	28 - 32	0.71	12.7	85.03	1.55
		9 F	12 M	28 - 32	1.23	12.09	84.56	2.12

Example 15 – Study IGSC74 – Normal Atmosphere; 38°C to 42°C

[0428] To determine the stabilizing effect of each amino acid formulation under more stressful conditions, samples 10F, 11F, and 12F, formulated without polysorbate 80 and stored under air, were stored between 38°C to 42°C protected from light for up to four weeks. The molecular size distributions of the samples were determined after 1, 2, and 4 weeks. As seen in **Table 18**, histidine formulation at pH 4.8 is not stable at all and the analysis was discontinued after two weeks. In comparison with study IGSC73, the preparations stabilized with glycine and proline show less aggregation. Especially the formulation with proline has only 3.8% aggregates at the end of the study, while in IGSC73 the aggregate content rose to 4.8%. Nevertheless, the proline stabilized immunoglobulin tends more to aggregation than the glycine stabilized IgG. Oligo-/dimer contents are slightly lower in the proline formulation.

Table 18. Mass size distribution of formulations (IGSC73) stored under normal atmosphere at 38°C to 42°C.

					MSD (HPLC)			
		Probenbezeichnung		T (°C)	Aggregate % area	Oligo/Dim. % area	Monomer % area	Fragmente % area
Proline pH 4.8	Air	10 F = 1 F	Start	2 - 8	0.46	7.22	92.02	0.30
		10 F	1 W	38 - 42	1.73	7.52	90.39	0.36
		10 F	2 W	38 - 42	2.01	8.74	88.64	0.61
		10 F	4 W	38 - 42	3.82	8.28	86.99	0.91
Histidine pH 4.8		11 F = 2 F	Start	2 - 8	0.10	6.53	93.14	0.23
		11 F	1 W	38 - 42	14.68	5.57	79.14	0.61
		11 F	2 W	38 - 42	15.58	5.68	77.91	0.82
		11 F	4 W	38 - 42				
Glycine pH 4.8		12 F = 3 F	Start	2 - 8	0.11	7.26	92.33	0.30
		12 F	1 W	38 - 42	1.34	7.85	90.44	0.38
		12 F	2 W	38 - 42	1.84	9.27	88.22	0.67
		12 F	4 W	38 - 42	3.65	8.77	86.57	1.01

Example 16 – Study IGSC74 – Nitrogen Atmosphere; 38°C to 42°C

[0429] To determine the stabilizing effect of each amino acid formulation under more stressful conditions, samples 13F, 14F, and 15F, formulated without polysorbate 80 and stored under nitrogen, were stored between 38°C to 42°C protected from light for up to four weeks. The molecular size distributions of the samples were determined after 1, 2, and 4 weeks. As seen in **Table 19**, the histidine formulation shows instability at pH 4.8 even under inert gas. When nitrogen is used as inert gas, again glycine formulated IgG is the most stable. In comparison to proline stabilized IgG, it aggregates less. The oligo-/ dimer contents are almost at the same level.

Table 19. Mass size distribution of formulations (IGSC74) stored under nitrogen at 38°C to 42°C.

					MSD (HPLC)			
		Sample Code		T (°C)	Aggregates % area	Oligo/Dimers % area	Monomers % area	Fragments % area
Proline pH 4.8	Nitrogen	13 F = 4 F	Start	2 - 8	0.45	7.26	91.96	0.33
		13 F	1 W	38 - 42	1.70	7.69	90.20	0.41
		13 F	2 W	38 - 42	2.05	9.03	88.28	0.64
		13 F	4 W	38 - 42	3.56	8.24	87.29	0.91
Histidine pH 4.8		14 F = 5 F	Start	2 - 8	0.10	6.59	93.07	0.24
		14 F	1 W	38 - 42	14.15	5.51	79.70	0.64
		14 F	2 W	38 - 42	16.21	5.83	77.20	0.76
		14 F	4 W	38 - 42				
Glycine pH 4.8		15 F = 6 F	Start	2 - 8	0.12	7.28	92.33	0.27
		15 F	1 W	38 - 42	1.28	8.09	90.23	0.40
		15 F	2 W	38 - 42	1.76	9.46	88.11	0.67
		15 F	4 W	38 - 42	3.07	8.64	87.35	0.94

Example 17 – Study IGSC74 – Argon Atmosphere; 38°C to 42°C

[0430] To determine the stabilizing effect of each amino acid formulation under more stressful conditions, samples 16F, 17F, and 18F, formulated without polysorbate 80 and stored under argon, were stored between 38°C to 42°C protected from light for up to four weeks. The molecular size distributions of the samples were determined after 1, 2, and 4 weeks. As seen in **Table 20**, the histidine formulation shows instability at pH 4.8 even under inert gas. With an overlay of argon the formulations with glycine or proline give the same molecular size distribution results as under normal atmosphere.

Table 20. Mass size distribution of formulations (IGSC74) stored under argon at 38°C to 42°C.

					MSD (HPLC)		
	Sample Code		T (°C)	Aggregates % area	Oligo/Dimers % area	Monomers % area	Fragments % area
Proline pH 4.8	Argon	16 F = 7 F	Start	2 - 8	0.44	7.37	91.96	0.24
		16 F	1 W	38 - 42	1.68	7.69	90.25	0.38
		16 F	2 W	38 - 42	2.19	9.08	88.03	0.70
		16 F	4 W	38 - 42	3.53	8.31	87.23	0.93
Histidine pH 4.8		17 F = 8 F	Start	2 - 8	0.10	6.76	92.92	0.21
		17 F	1 W	38 - 42	14.81	5.56	79.11	0.51
		17 F	2 W	38 - 42	18.92	5.62	74.76	0.70
		17 F	4 W	38 - 42				
Glycine pH 4.8		18 F = 9 F	Start	2 - 8	0.11	7.61	92.01	0.27
		18 F	1 W	38 - 42	1.33	8.3	89.91	0.46
		18 F	2 W	38 - 42	2.07	9.52	87.77	0.65
		18 F	4 W	38 - 42	3.57	8.89	86.53	1.01

Example 18 – Study IGSC73 – Optical Density; 38°C to 42°C

[0431] To determine the effect of each amino acid formulation on the discoloration of the immunoglobulin composition, the optical density (OD) of each sample was monitored at 350 nm for samples stored under normal atmosphere, nitrogen, and argon at 28°C to 32°C for up to 12 months. As disclosed in the literature, the OD values for all readings, except those taken at time 0, have been corrected by the OD at 500 nm to account for air trapped in the highly concentrated solution.

[0432] As evidenced in Figures 3A, 3B, and 3C, the histidine formulation at pH 4.8 (■) starts to develop a much stronger discoloration after three months under normal atmosphere, but under

inert gas the color is only half as intensive. In comparison to the histidine formulation at pH 6.1 the discoloration is less pronounced under normal atmosphere and about the same under inert gas. This confirms the observation that the discoloration is not correlated to the aggregate level. Discoloration under inert gas, especially under nitrogen is also less pronounced for proline and glycine formulated solutions in this study compared to the same formulations under normal atmosphere.

[0433] It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims. All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

WHAT IS CLAIMED IS:

1. A storage stable, aqueous immunoglobulin composition comprising:
(a) an immunoglobulin
(b) from 50 mM to 500 mM histidine;
(c) from 0 mM to 10 mM of an alkali metal cation; and
(d) a pH from 5.5 to 7.0.

2. The composition according to claim 1, containing from 150 mM to 350 mM histidine.

3. The composition of claim 2, containing from 225 mM to 275 mM histidine.

4. The composition according to any one of claims 1 to 3, containing from 0 mM to 1 mM of an alkali metal cation.

5. The composition according to any one of claims 1 to 4, wherein the composition contains from 10 mM to 400 mM chloride ions.

6. The composition of claim 5, containing from 100 mM to 200 mM chloride ions.

7. The composition according to any one of claims 1 to 6, wherein the pH of the composition is from 5.5 to 6.5.

8. The composition of claim 7, wherein the pH of the composition is 6.1±0.2.

9. The composition according to any one of claims 1 to 8, wherein the composition further comprises an antioxidant.

10. The composition according to any one of claims 1 to 9, wherein the composition does not contain a surfactant or sugar.

11. The composition according to any one of claims 1 to 10, wherein the composition is stored under an inert gas.

12. The composition of claim 11, wherein the inert gas is selected from the group consisting of nitrogen, argon, carbon dioxide, helium, krypton, and xenon.

13. The composition of claim 11, wherein the inert gas is nitrogen.

14. The composition of claim 11, wherein the inert gas is argon.

15. The composition according to any one of claims 1 to 14, wherein the immunoglobulin is a polyclonal immunoglobulin.

16. The composition according to any one of claims 1 to 14, wherein the immunoglobulin is a monoclonal immunoglobulin.

17. The composition according to any one of claims 1 to 16, wherein the immunoglobulin is an IgG immunoglobulin.

18. The composition according to any one of claims 1 to 17, wherein the immunoglobulin is enriched from pooled human plasma.

19. The composition according to any one of claims 1 to 17, wherein the immunoglobulin is a recombinant immunoglobulin.

20. The composition according to any one of claims 1 to 19, wherein the concentration of the immunoglobulin is 50±5 g/L.

21. The composition according to any one of claims 1 to 19, wherein the concentration of the immunoglobulin is less than 50 g/L.

22. The composition according to any one of claims 1 to 19, wherein the concentration of the immunoglobulin is at least 50 g/L.

23. The composition of claim 22, wherein the concentration of the immunoglobulin is from 50 g/L to 150 g/L.

24. The composition of claim 23, wherein the concentration of the immunoglobulin is 100±10 g/L.

25. The composition of claim 22, wherein the concentration of the immunoglobulin is at least 100 g/L.

26. The composition of claim 25, wherein the concentration of the immunoglobulin is 150±15 g/L.

27. The composition of claim 25, wherein the concentration of the immunoglobulin is from 150 g/L to 250 g/L.

28. The composition of claim 27, wherein the concentration of the immunoglobulin is 200±20 g/L.

29. The composition of claim 22, wherein the concentration of the immunoglobulin is at least 200 g/L.

30. The composition according to any one of claims 1 to 29, wherein the composition is stable for at least 1 month when stored at from 38°C to 42°C.

31. The composition of claim 30, wherein the composition is stable for at least 3 months when stored at from 38°C to 42°C.

32. The composition of claim 31, wherein the composition is stable for at least 6 months when stored at from 38°C to 42°C.

33. The composition according to any one of claims 1 to 32, wherein the composition is stable for at least 6 months when stored at from 28°C to 32°C.

34. The composition of claim 33, wherein the composition is stable for at least 1 year when stored at from 28°C to 32°C.

35. The composition of claim 34, wherein the composition is stable for at least 2 years when stored at from 28°C to 32°C.

36. The composition according to any one of claims 1 to 35, wherein the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state remains below 2%.

37. The composition according to any one of claims 1 to 35, wherein the composition is considered stable as long as the percentage of immunoglobulin in the aggregated state is from 0% to 2% and the percentage of immunoglobulin in the monomeric state is from 85% to 100%.

38. The composition according to any one of claims 1 to 37, wherein a composition having the same components, but formulated at pH 4.8, is stable for less than 1 month when stored at from 38°C to 42°C.

39. The composition according to any one of claims 1 to 38, wherein a composition having the same components, but formulated at pH 4.8, is stable for less than 6 months when stored at from 28°C to 32°C.

40. A method for stabilizing an immunoglobulin composition, the method comprising formulating the composition at a pH between 5.5 and 7.0,

wherein the formulated composition comprises:

(a) an immunoglobulin

(b) from 50 mM to 500 mM histidine; and

(c) from 0 mM to 10 mM of an alkali metal cation.

41. The method according to claim 40, wherein the formulated composition contains from 150 mM to 350 mM histidine.

42. The method according to claim 41, wherein the formulated composition contains from 225 mM to 275 mM histidine.

43. The method according to any one of claims 40 to 42, wherein the formulated composition contains from 0 mM to 1 mM of an alkali metal cation.

44. The method according to any one of claims 40 to 43, wherein the formulated composition contains from 10 mM to 400 mM chloride ions.

45. The method according to claim 44, wherein the formulated composition contains from 100 mM to 200 mM chloride ions.

46. The method according to any one of claims 40 to 45, wherein the pH of the formulated composition is from 5.5 to 6.5.

47. The method according to claim 46, wherein the pH of the formulated composition is 6.1±0.2.

48. The method according to any one of claims 40 to 47, wherein the formulated composition further comprises an antioxidant.

49. The method according to any one of claims 40 to 48, wherein the formulated composition does not contain a surfactant or sugar.

50. The method according to any one of claims 40 to 49, wherein the formulated composition is stored under an inert gas.

51. The method according to claim 50, wherein the inert gas is selected from the group consisting of nitrogen, argon, carbon dioxide, helium, krypton, and xenon.

52. The method according to claim 50, wherein the inert gas is nitrogen.

53. The method according to claim 50, wherein the inert gas is argon.

54. The method according to any one of claims 40 to 53, wherein the immunoglobulin is a polyclonal immunoglobulin.

55. The method according to any one of claims 40 to 53, wherein the immunoglobulin is a monoclonal immunoglobulin.

56. The method according to any one of claims 40 to 55, wherein the immunoglobulin is an IgG immunoglobulin.

57. The method according to any one of claims 40 to 56, wherein the immunoglobulin is enriched from pooled human plasma.

58. The method according to any one of claims 40 to 56, wherein the immunoglobulin is a recombinant immunoglobulin.

59. The method according to any one of claims 40 to 58, wherein the concentration of the immunoglobulin in the formulated composition is 50±5 g/L.

60. The method according to any one of claims 40 to 58, wherein the concentration of the immunoglobulin in the formulated composition is less than 50 g/L.

61. The method according to any one of claims 40 to 58, wherein the concentration of the immunoglobulin in the formulated composition is at least 50 g/L.

62. The method according to claim 61, wherein the concentration of the immunoglobulin in the formulated composition is from 50 g/L to 150 g/L.

63. The method according to claim 62, wherein the concentration of the immunoglobulin in the formulated composition is 100±10 g/L.

64. The method according to claim 61, wherein the concentration of the immunoglobulin in the formulated composition is at least 100 g/L.

65. The method according to claim 64, wherein the concentration of the immunoglobulin in the formulated composition is 150±15 g/L.

66. The method according to claim 64, wherein the concentration of the immunoglobulin in the formulated composition is from 150 g/L to 250 g/L.

67. The method according to claim 64, wherein the concentration of the immunoglobulin in the formulated composition is 200±20 g/L.

68. The method according to claim 64, wherein the concentration of the immunoglobulin in the formulated composition is at least 200 g/L.

69. The method according to any one of claims 40 to 68, wherein the formulated composition is stable for at least 1 month when stored at from 38°C to 42°C.

70. The method according to claim 69, wherein the formulated composition is stable for at least 3 months when stored at from 38°C to 42°C.

71. The method according to claim 69, wherein the formulated composition is stable for at least 6 months when stored at from 38°C to 42°C.

72. The method according to any one of claims 40 to 71, wherein the formulated composition is stable for at least 6 months when stored at from 28°C to 32°C.

73. The method according to claim 72, wherein the formulated composition is stable for at least 1 year when stored at from 28°C to 32°C.

74. The method according to claim 72, wherein the formulated composition is stable for at least 2 years when stored at from 28°C to 32°C.

75. The method according to any one of claims 40 to 74, wherein the formulated composition is considered stable as long as the percentage of immunoglobulin in the aggregated state remains below 2%.

76. The method according to any one of claims 40 to 74, wherein the formulated composition is considered stable as long as the percentage of immunoglobulin in the aggregated state is from 0% to 2% and the percentage of immunoglobulin in the monomeric state is from 85% to 100%.

77. The method according to any one of claims 40 to 76, wherein an immunoglobulin composition having the same components as the formulated composition, but formulated at pH 4.8, is stable for less than 1 month when stored at from 38°C to 42°C.

78. The method according to any one of claims 40 to 77, wherein an immunoglobulin composition having the same components as the formulated composition, but formulated at pH 4.8, is stable for less than 6 months when stored at from 28°C to 32°C.