IL-17 Antibody Formulation

The present invention relates to the field of medicine. More particularly, the present invention relates to a pharmaceutical formulation of an anti-IL- 17 antibody. This anti-IL-17 antibody pharmaceutical formulation is expected to be useful in treating Rheumatoid Arthritis (RA), Psoriasis (Ps), Ankylosing Spondilitis (AS), Psoriatic Arthritis (PA) or Multiple Myeloma (MM).

Pharmaceutical formulations of anti-IL-17 antibodies are needed for the treatment of patients with RA, Ps, AS, PA or MM. Certain concentrations of anti-IL-17 antibodies are needed for pharmaceutical formulations so that the antibody can be delivered subcutaneously to the patient. This pharmaceutical formulation with a certain concentration of the anti-IL-17 antibody must maintain physical and chemical stability of the anti-IL-17 antibody, while also avoiding viscosity that can unacceptably increase delivery time and force needed from a needle or auto-injector device.

Anti-IL-17 antibodies are disclosed in WO 07/70750 that neutralize biological activity associated with human IL-17 (SEQ ID NO: 1). In addition, WO 07/70750 discloses pharmaceutical compositions of anti-IL-17 monoclonal antibodies. With certain formulations for mAb 126, an anti-IL-17 antibody disclosed in WO 07/70750, it was discovered by Applicant as part of the present invention that three stability problems exist at concentrations in solutions greater than or equal to 50 mg/mL: liquid-liquid phase separation; gel formation or solid phase change; and chemical instability. Thus, pharmaceutical formulations for certain concentrations of anti-IL-17 antibodies are needed that avoid these observed problems. A need exists for alternative anti-IL-17 antibody pharmaceutical formulations. Further, a need exists for alternative anti-IL-17 antibody pharmaceutical solution formulations.

Summary

In a first aspect of the present disclosure, there is provided a pharmaceutical formulation comprising an anti-IL-17 antibody at a concentration in the range of about 80 mg/mL to about 150 mg/mL, citrate buffer at a concentration of about 20 mM, sodium chloride at a concentration of about 200 mM, polysorbate-80 at a concentration in the range of about 0.02% (w/v) to about 0.03% (w/v), and pH at about 5.7, wherein the anti-IL-17 antibody comprises an antibody with a light chain (LC) and a heavy chain (HC), wherein said LC is the amino acid sequence of SEQ ID NO: 4 and said HC is the amino acid sequence of SEQ ID NO: 5.

In a second aspect of the present disclosure, there is provided a pharmaceutical formulation comprising an anti-IL-17 antibody at a concentration of about 80 mg/mL, citrate buffer at a concentration of about 20 mM, sodium chloride at a concentration of about 200 mM, polysorbate-80 at a concentration of about 0.03%, and pH at about 5.7, wherein the anti-IL-17 antibody comprises an antibody comprising two light chains (LCs) and two heavy chains (HCs), wherein each LC is the amino acid sequence of SEQ ID NO: 4 and each HC is the amino acid sequence of SEQ ID NO: 5.

In a third aspect of the present disclosure, there is provided a pharmaceutical solution formulation comprising an anti-IL-17 antibody at a concentration of about 80 mg/mL, citrate buffer at a concentration of about 20 mM, sodium chloride at a concentration of about 200 mM, polysorbate-80 at a concentration of about 0.03%, and pH at about 5.7, wherein the anti-IL-17 antibody comprises an antibody comprising two light chains (LCs) and two heavy chains (HCs), wherein each LC is the amino acid sequence of SEQ ID NO: 4 and each HC is the amino acid sequence of SEQ ID NO: 5.

In a fourth aspect of the present disclosure, there is provided a pharmaceutical formulation as described herein for use in therapy.

In a fifth aspect of the present disclosure, there is provided a pharmaceutical formulation as described herein for use in the treatment of rheumatoid arthritis, psoriasis, ankylosing spondilitis, psoriatic arthritis or multiple myeloma.

Description

Accordingly, the present invention provides a pharmaceutical formulation comprising an anti-IL-17 antibody at a concentration in the range of about 80 mg/mL to about 150 mg/mL, citrate buffer at a concentration of about 20 mM, sodium chloride at a concentration of about 200 mM, polysorbate-80 at a concentration in the range of about 0.02% (w/v) to about 0.03% (w/v), and a pH at about 5.7, wherein the anti-IL-17 antibody comprises an antibody with a light chain (LC) and a heavy chain (HC), wherein said LC is the amino acid sequence of SEQ ID NO: 4 and said HC is the amino acid sequence of SEQ ID NO: 5. The present invention also provides a pharmaceutical formulation

comprising an anti-IL-17 antibody at a concentration of about 80 mg/mL, citrate buffer at a concentration of about 20 mM, sodium chloride at a concentration of about 200 mM, polysorbate-80 at a concentration of about 0.03%, and pH at about 5.7, wherein the anti-IL-17 antibody comprises an antibody comprising two light chains (LCs) and two heavy chains (HCs), wherein each LC is the amino acid sequence of SEQ ID NO: 4 and each HC is the amino acid sequence of SEQ ID NO: 5.

In addition, the present invention provides a method of treating RA, Ps, AS, PA or MM comprising administering to a patient in need thereof an effective amount of a pharmaceutical formulation of the present invention. More particularly, the present invention provides a method of treating Ps comprising administering to a patient in need thereof an effective amount of a pharmaceutical formulation of the present invention. Also, the present invention provides a method of treating RA comprising administering to a patient in need thereof an effective amount of a pharmaceutical formulation of the present invention. Also, the present invention provides a method of treating PA comprising administering to a patient in need thereof an effective amount of a pharmaceutical formulation of the present invention. Also, the present invention provides a method of treating AS comprising administering to a patient in need thereof an effective amount of a pharmaceutical formulation of the present invention.

In addition, the present invention provides the pharmaceutical formulation of the present invention for use in therapy. In addition, the present invention provides the pharmaceutical formulation of the present invention for use in the treatment of RA, Ps, AS, PA or MM. More particularly, the present invention provides the pharmaceutical formulation of the present invention for use in the treatment of Ps. Also, the present invention provides the pharmaceutical formulation of the present invention for use in the treatment of RA. Also, the present invention provides the pharmaceutical formulation of the present invention for use in the treatment of PA. Also, the present invention provides the pharmaceutical formulation of the present invention for use in the treatment of AS.

In addition, the present invention provides the use of the pharmaceutical formulation of the present invention in the manufacture of a medicament for the treatment of RA, Ps, AS, PA or MM. More particularly, the present invention provides the use of the pharmaceutical formulation of the present invention in the manufacture of a medicament for the treatment of Ps. Also, the present invention provides the use of the

pharmaceutical formulation of the present invention in the manufacture of a medicament for the treatment of RA. Also, the present invention provides the use of the pharmaceutical formulation of the present invention in the manufacture of a medicament for the treatment of PA. Also, the present invention provides the use of the pharmaceutical formulation of the present invention in the manufacture of a medicament for the treatment of AS.

Certain pharmaceutical formulations are preferred. The following enumerated selections describe such preferred classes:

1.) the anti-IL-17 antibody comprises an antibody with an LCVR and an HCVR, wherein said LCVR is the amino acid sequence of SEQ ID NO: 2 and said HCVR is the amino acid sequence of SEQ ID NO: 3; comprises an antibody with a light chain (LC) and a heavy chain (HC), wherein said LC is the amino acid sequence of SEQ ID NO: 4 and said HC is the amino acid sequence of SEQ ID NO: 5; or comprises an antibody comprising two light chains (LCs) and two heavy chains (HCs), wherein each LC is the amino acid sequence of SEQ ID NO: 4 and each HC is the amino acid sequence of SEQ ID NO: 5;

2.) the anti-IL-17 antibody comprises an antibody with a light chain (LC) and a heavy chain (HC), wherein said LC is the amino acid sequence of SEQ ID NO: 4 and said HC is the amino acid sequence of SEQ ID NO: 5;

3.) the anti-IL-17 antibody comprises an antibody comprising two light chains (LCs) and two heavy chains (HCs), wherein each LC is the amino acid sequence of SEQ ID NO: 4 and each HC is the amino acid sequence of SEQ ID NO: 5;

4.) the anti-IL-17 antibody at a concentration in the range of about 80 mg/mL to about 150 mg/mL;

5.) the anti-IL-17 antibody at a concentration of about 80 mg/mL;

6.) the polysorbate-80 at a concentration in the range of about 0.02% (w/v) to about 0.03% (w/v);

7.) the polysorbate-80 at a concentration of about 0.03% (w/v).

Certain pharmaceutical solution formulations are preferred. The following enumerated selections describe such preferred classes:

1.) the anti-IL-17 antibody comprises an antibody with an LCVR and an HCVR, wherein said LCVR is the amino acid sequence of SEQ ID NO: 2 and said HCVR is the amino acid sequence of SEQ ID NO: 3; comprises an antibody with a light chain (LC) and a heavy chain (HC), wherein said LC is the amino acid sequence of SEQ ID NO: 4 and said HC is the amino acid sequence of SEQ ID NO: 5; or comprises an antibody comprising two light chains (LCs) and two heavy chains (HCs), wherein each LC is the amino acid sequence of SEQ ID NO: 4 and each HC is the amino acid sequence of SEQ ID NO: 5;

2.) the anti-IL-17 antibody comprises an antibody with a light chain (LC) and a heavy chain (HC), wherein said LC is the amino acid sequence of SEQ ID NO: 4 and said HC is the amino acid sequence of SEQ ID NO: 5;

3.) the anti-IL-17 antibody comprises an antibody comprising two light chains (LCs) and two heavy chains (HCs), wherein each LC is the amino acid sequence of SEQ ID NO: 4 and each HC is the amino acid sequence of SEQ ID NO: 5;

4.) the anti-IL-17 antibody at a concentration in the range of about 80 mg/mL to about 150 mg/mL;

5.) the anti-IL-17 antibody at a concentration of about 80 mg/mL;

6.) the polysorbate-80 at a concentration in the range of about 0.02% (w/v) to about 0.03% (w/v);

7.) the polysorbate-80 at a concentration of about 0.03% (w/v).

In an embodiment, the present invention also provides a pharmaceutical formulation that comprises a concentration of anti-IL-17 antibody of about 80 mg/mL to about 150 mg/mL. In another embodiment, the present invention provides a pharmaceutical formulation that comprises a concentration of anti-IL-17 antibody in the range of 68 mg/mL to 92 mg/mL.. In another embodiment, the present invention provides a pharmaceutical formulation that comprises a concentration of anti-IL-17 antibody of about 80 mg/mL. In another embodiment, the present invention provides a

pharmaceutical formulation that comprises a concentration of anti-IL-17 antibody of about 120 mg/mL. In another embodiment, the present invention provides a pharmaceutical formulation that comprises a concentration of anti-IL-17 antibody of about 150 mg/mL.

In an embodiment, the present invention also provides a pharmaceutical formulation that is buffered with citrate buffer in the range of about 15 mM to about 25 mM. In another embodiment, the present invention provides a pharmaceutical formulation that is buffered with citrate buffer in the range of 15 mM to 25 mM. In another embodiment, the present invention provides a pharmaceutical formulation that is buffered with citrate buffer at a concentration of about 15 mM, about 20 mM, about 25 mM, or about 30 mM. In a further embodiment, the present invention provides a pharmaceutical formulation that is buffered with citrate buffer at a concentration of about 20 mM.

In an embodiment, the present invention also provides a pharmaceutical formulation that comprises a concentration of NaCl of about 200 mM to about 300 mM. In another embodiment, the present invention provides a pharmaceutical formulation that comprises a concentration of NaCl of 175 mM to 225 mM. In another embodiment, the present invention provides a pharmaceutical formulation that comprises a concentration of NaCl of about 200 mM, about 250 mM, or about 300 mM. In a further embodiment, the present invention provides a pharmaceutical formulation that comprises a concentration of NaCl of about 200 mM.

In an embodiment, the present invention also provides a pharmaceutical formulation that comprises a concentration of polysorbate-80 or polysorbate-20 of about 0.01 % to about 0.04 %. In another embodiment, the present invention provides a pharmaceutical formulation that comprises a concentration of polysorbate-80 or polysorbate-20 of 0.02 % to 0.04 %. In another embodiment, the present invention provides a pharmaceutical formulation that comprises a concentration of polysorbate-80 or polysorbate-20 of about 0.01 %, about 0.02 %, about 0.03 %, or about 0.04 %. In a further embodiment, the present invention provides a pharmaceutical formulation that comprises a concentration of polysorbate-80 or polysorbate-20 of about 0.03 %.

In an embodiment, the present invention also provides a pharmaceutical formulation that comprises a pH range of about 5.4 to about 6.0. In another embodiment,

the present invention provides a pharmaceutical formulation that comprises a pH in the range of 5.4 to 6.0. In another embodiment, the present invention provides a pharmaceutical formulation that comprises a pH of about 5.4, about 5.7, or about 6.0. In a further embodiment, the present invention provides a pharmaceutical formulation that comprises a pH of about 5.7.

The pharmaceutical formulations of the present invention comprise citrate buffer. Citrate buffer can be made with citric acid, trisodium citrate dihydrate, and citric acid monohydrate; or citric acid monohydrate, sodium phosphate dibasic, and citric acid. Also, citrate buffer can be made comprising sodium citrate monobasic, citric acid trisodium salt, or sodium citrate tribasic hydrate. Preferably, citrate buffer is made with sodium citrate dihydrate and citric acid.

The mAb 126 antibody is an anti-IL-17 antibody that consists of two light chains (LCs) and two heavy chains (HCs), wherein each LC is the amino acid sequence of SEQ ID NO: 4 and each HC is the amino acid sequence of SEQ ID NO: 5, and wherein the HCs are cross-linked by disulfide bonds.

The general structure of an "antibody" is very well-known in the art. For an antibody of the IgG type, there are four amino acid chains (two "heavy" chains and two "light" chains) that are cross-linked via intra- and inter-chain disulfide bonds. When expressed in certain biological systems, antibodies having unmodified human Fc sequences are glycosylated in the Fc region. Antibodies may be glycosylated at other positions as well. One of skill in the art will appreciate that antibodies for use in the formulation of the present invention may contain such glycosylation. The subunit structures and three-dimensional configurations of antibodies are well known in the art. Each heavy chain is comprised of an N-terminal heavy chain variable region ("HCVR") and a heavy chain constant region ("HCCR"). The heavy chain constant region is comprised of three domains (CH1, CH2, and CH3) for IgG, IgD, and IgA; and 4 domains (CH1, CH2, CH3, and CH4) for IgM and IgE. Each light chain is comprised of a light chain variable region ("LCVR") and a light chain constant region ("LCCR"). The variable regions of each light/heavy chain pair form the antibody binding site.

An anti-IL-17 antibody for use in the formulations of the present invention can be produced using techniques well known in the art, e.g., recombinant technologies, phage display technologies, synthetic technologies, or combinations of such technologies or

other technologies readily known in the art. Methods for producing and purifying antibodies and antigen-binding fragments are well known in the art and can be found, for example, in Harlow and Lane (1988) *Antibodies, A Laboratory Manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, chapters 5-8 and 15, ISBN 0-87969-314-2.

An anti-IL-17 antibody for use in the formulations of the present invention is an engineered antibody that has been designed to have frameworks, hinge regions, and constant regions of human origin that are identical with or substantially identical (substantially human) with frameworks and constant regions derived from human genomic sequences. Fully human frameworks, hinge regions, and constant regions are those human germline sequences as well as sequences with naturally-occurring somatic mutations and/or those with engineered mutations. An antibody for use in a formulation of the present invention may comprise framework, hinge, or constant regions derived from a fully human framework, hinge, or constant region containing one or more amino acid substitutions, deletions, or additions therein. Further, an antibody for use in a formulation of the present invention is substantially non-immunogenic in humans.

Stability of an antibody in solution depends on the chemical stability and physical stability of the antibody in the formulation in which the antibody is solubilized. Oxidation, deamidation, and hydrolysis are examples of chemical stability issues that an antibody can have in a formulation. Aggregation and gel formation are examples of physical stability issues that an antibody can have in a formulation. Another physical stability issue with antibodies in a solution formulation may be liquid-liquid phase separation (LLPS); LLPS in an antibody solution typically first appears as opalescence, followed by separation into light and heavy phases. Cloud point is the temperature where LLPS is first observed for a given condition; cloud point measures the temperature where solutions become white opaque as a result of the formation of micro-phases which ultimately resolve into the heavy and light phases traditionally associated with phase separation.

A pharmaceutical formulation is a stable formulation wherein the degree of degradation, modification, aggregation, loss of biological activity and the like, of proteins/antibodies therein is acceptably controlled, and does not increase unacceptably with time. Stability may be assessed by methods well-known in the art, including

measurement of a sample's light scattering, apparent attenuation of light (absorbance, or optical density), size (e.g. by size exclusion chromatography (SEC)), *in vitro* or *in vivo* biological activity and/or properties measured by differential scanning calorimetry (DSC). Other methods for assessing stability are well known in the art and can also be used according to the present invention. As measured by SEC, the % monomer for an anti-IL-17 pharmaceutical formulation should be greater than 90 % after storage at 5 °C for a period of 3 months, 6 months, 9 months, 12 months, 18 months, or preferably 2 years. As measured by cation exchange chromatography (CEX), the percent total acid variants should not exceed 30 % for an anti-IL-17 pharmaceutical formulation after storage at 5 °C for a period of 3 months, 6 months, 9 months, 12 months, 18 months, or preferably 2 years. For measurements of purity by reduced CE-SDS, an anti-IL-17 pharmaceutical formulation should have a purity greater than 85 % after storage at 5 °C for a period of 3 months, 6 months, 9 months, 12 months, 18 months, or preferably 2 years. Preferably, an anti-IL-17 antibody pharmaceutical formulation meets one of the aforementioned standards for stability at a temperature of 5 °C for a solution stored for two years. More preferably, an anti-IL-17 antibody pharmaceutical formulation meets all the aforementioned standards for stability at a temperature of 5 °C for a solution stored for two years.

The pharmaceutical formulations of the present invention can be in the liquid dosage form of a solution, emulsion, or suspension. Preferably, the pharmaceutical formulations of the present invention are in the liquid dosage form of a solution.

Administration of the pharmaceutical formulations of the present invention may be via parenteral administration. Parenteral administration is commonly understood in the medical literature as the injection of a dosage form into the body by a sterile syringe or some other mechanical device such as an infusion pump. Parenteral routes can include intravenous, intramuscular, subcutaneous, and intraperitoneal routes of administration. Subcutaneous administration is a preferred route.

The pharmaceutical formulations of the present invention can be used to treat subjects with RA, Ps, AS, PA or MM.. An effective amount of the anti-IL-17 antibody formulation of the present invention is the quantity which delivers an amount of the anti-IL-17 antibody that results in a desired therapeutic and/or prophylactic effect without

causing unacceptable side-effects when administered to a subject with increased IL-17 levels.

Example 1

Formulating mAb 126

Table 1: mAb 126 Drug Product Formulation

Component	Concentration (mg/mL)
mAb 126	80
Sodium Citrate Dihydrate	5.106
Citric Acid Anhydrous	0.507
Sodium Chloride	11.69
Polysorbate 80	0.30
Water for Injection	*q.s.* to 1 mL
Hydrochloric Acid	pH adjustment
Sodium Hydroxide	pH adjustment

Table 2: Buffer Excipient Composition

Component	mg/mL
Sodium Citrate Dihydrate	5.106
Citric Acid Anhydrous	0.507
Sodium Chloride	11.69
Polysorbate 80	0.414

The manufacturing process for the anti-IL-17 antibody pharmaceutical solution formulation for mAb 126 (Table 1) consists of first compounding of the buffer excipient composition (Table 2), followed by compounding of the final drug product formulation.

The buffer excipient composition (Table 2) is prepared, filtered, and stored for drug product formulation compounding. An appropriate quantity of water at a temperature of 20 +/- 5 °C is weighed into a tared empty vessel of appropriate size. The appropriate quantity of sodium citrate is added and mixed; the appropriate quantity of citric acid is then added and mixed. Then, the appropriate quantity of sodium chloride is added and mixed. Polysorbate 80 is accurately weighed out in a glass container and an appropriate quantity of water at a temperature of 20 +/- 5 °C is added into the glass container to give the concentration in Table 2, and the solution is mixed. The entire content of the polysorbate 80 solution is added to the other excipients. The polysorbate 80 solution container is rinsed with water to ensure the entire content is transferred. After

addition of the polysorbate 80 solution, the solution is mixed. After dissolution and mixing has been completed, the pH of the solution is checked to be within 5.7 +/- 0.2; adjustment with HCl or NaOH solution is done if necessary. The buffer excipient composition is passed through a filter (polyvinylidene fluoride [PVDF]) for bioburden reduction.

The buffer excipient composition is supplemented with additional polysorbate 80 to account for the lower concentration (0.2 mg/mL polysorbate-80) in the active pharmaceutical ingredient (API) compared to the final drug product formulation. Since the concentration of mAb 126 in the API will vary, the amount of buffer needed for dilution will also change. This variation requires that the concentration of polysorbate 80 be adjusted for the buffer excipient composition recipe with each batch.

The stored mAb 126 API containers (mAb 126 is expressed in cells, purified, and concentrated; the resulting API is then frozen at about 150 mg/mL to about 160 mg/mL mAb 126 in 20 mM citrate buffer, 200 mM NaCl, 0.02% polysorbate-80, at pH about 5.7) are equilibrated to a temperature of 20 +/- 5 °C. The API solution is then mixed with an appropriate amount of the buffer excipient solution to achieve 80% of the theoretical batch size. The pH of the solution is checked to be within 5.7 +/- 0.2. After pH adjustment, the solution is mixed and a sample is taken for an in-process UV assay to determine the mAb 126 concentration. An appropriate quantity of the buffer excipient solution is added to reach the final target batch weight. After mixing, the pH of the solution is checked to be within 5.7 +/- 0.2, and the osmolality of the solution is checked to be within 360-480 mOsm/Kg. The mAb 126 drug product solution is passed through a PVDF filter for bioburden reduction and stored at 5 °C.

Example 2

Phase separation

mAb 126 is found to have a propensity to phase separate while in solutions that are below 0 °C. Liquid-liquid phase separation (LLPS) needs to be solved since storage of the mAb 126 drug product will be at 5 °C. Storage of drug product at 5 °C requires stability for periodic refrigerator temperature excursions below 0 °C. Increasing the NaCl concentration is shown to lower the temperature at which LLPS occurs in mAb 126

formulations, and increasing the citrate concentration is also shown to lower the temperature at which LLPS occurs in mAb 126 formulations.

LLPS events are tested based on a technique developed specifically for the temperature range (phase separation occurring between -12 and 0 °C) encountered for mAb 126. Two milliliter (mL) samples of 10 to 200 mg/mL mAb 126 were placed in a LyoStar II (FTS Systems) lyophilization unit with the cycle shown in Table 3. Pressure was kept at atmospheric for the experiments. Sample conditions are tested at least three times and the standard deviation is approximately 0.5 °C for samples measured in triplicate. The samples are visually monitored during the lyophilization cycle for signs of phase separation, including cloud point (white opaque appearance) and the formation of a dense, protein rich layer at the bottom of the vial. Samples appear increasingly opalescent during cooling, but this effect is easily differentiable from cloud point. When cloud point occurs, the sample becomes an opaque white solution in less than a second versus a gradual increased opalescence where an object behind a vial is still visible through the sample.

Table 3: Lyophilization Cycle for Liquid-Liquid Phase Separation Testing

Step	1	2	3
Cooling Rate (°C/min)	5	1	5
Target (°C)	5	-30	20
Hold Time (min)	10	20	>20

As shown in Table 4, increasing the NaCl concentration is shown to depress the cloud point temperature. The factors which limit increasing the NaCl concentration in the anti-IL-17 antibody pharmaceutical formulation are hyper-tonicity and other non-phase-separation effects; 200 mM NaCl avoids these problems while still depressing the cloud point temperature. Also, LLPS in mAb126 is shown to be bimodal at all NaCl concentrations, except 300 mM NaCl; LLPS is strongest at a concentration of 100 mg/mL mAb 126, and the phase separation effects lessen as the concentration moves higher or lower than 100 mg/mL.

Table 4: Liquid-Liquid Phase Separation: NaCl and mAb 126 Concentration Effects (Cloud Point °C)

mAb 126 Conc. (mg/mL)	10	50	100	150	200
50 mM NaCl	-4.1	2.1	5		
100 mM NaCl		-1.2	2.7	1.1	
150mM NaCl		-7.5	-4	-5.7	-10.4
200 mM NaCl		-8.5	-7	-10.2	-10.8
250 mM NaCl			-6.8	-11.3	
300 mM NaCl		-12.5	-9.9	-12.4	-8.8

The effect of pH on cloud point of a mAb 126 solution is measured. The cloud point was found to be minimized at two pHs, pH 4 and pH6. pH 6 should be considered optimal over pH 4 when selecting a formulation for mAb 126, because chemical instability of mAb 126 at pH 4 precludes using the low cloud point at pH 4. Given the gel formation at pH 6.3 – 6.4, shown in Example 3, for the mAb 126 pharmaceutical formulations, pH 5.7 +/- 0.3 is preferred over pH 6 +/- 0.3 in order to allow for a pH range that remains stable over the shelf-life of the pharmaceutical formulation.

Effects of various commonly used buffers on liquid-liquid phase separation are explored to understand what the optimal buffer system would be for mAb 126 (Table 5); citrate buffer is found to be most effective at reducing the temperature at which LLPS occurs. These studies are conducted with 150 mM NaCl. Acetate buffer is comparable to citrate buffer at pH 5 in terms of the effect on cloud point; however, chemical instability at pH 5 makes this pH condition less favorable.

The concentration of citrate is shown to positively affect LLPS (Table 6). While citrate depresses cloud point up to 50 mM; citrate buffer is also reported to cause more pain on injection. As such, citrate concentrations higher than 30 mM are likely to be unacceptable from a patient compliance standpoint.

Table 5: Buffer Effects on Cloud Point Temperature with 150 mg/mL mAb 126

Buffer	mM	pH	Cloud Point (°C)

Acetate	10	5	-4.1
Citrate	10	5	-4.4
Histidine	10	6	-2.2
Citrate	10	6	-8.1

Table 6: Liquid-Liquid Phase Separation: Citrate Concentration Effects with 150 mg/mL mAb 126

Citrate conc.	Cloud Point (°C)
5mM	-6.3
10mM	-8.2
20mM	-10.2
30mM	-13.6
40mM	-14.6

Example 3

Gel formation

Biologic drug products are stored at 5 °C +/- 3 °C to minimize chemical and physical degradation over the shelf-life of a product. Events such as thermodynamic solid phase change or gel formation are typically not acceptable, even if reversible, because they can negatively affect stability and hinder the required visual inspection of samples prior to use.

Solid phase change is observed in high concentration samples of mAb 126 at pH conditions <pH 5 and >pH 7 at 5 °C. This thermodynamic event is shown to be reversible by equilibrating the vials at room temperature. Consequently, samples are tested at various pH conditions and monitored for thermodynamic changes in order to find the phase boundaries more precisely. These tests are conducted by dialyzing samples into pH 7, citrate buffer at 5 °C to induce phase change. The solid material is then dialyzed at the same temperature into conditions of interest to ascertain if samples would reverse to the solution state. Equilibrium testing method is preferable to long-term

sample storage with intermittent inspections because, while a particular formulation may be thermodynamically unstable, the kinetics of solid phase change may require months to occur in some cases.

Studies are conducted with 100 mg/mL or 150 mg/mL mAb 126 at 200 mM NaCl, 10 mM citrate buffer in 0.1 pH increments to find where the boundaries are for solid phase formation. The transition between phases is found between pH 6.3 and 6.4 at 5 °C. Because of the phase boundary, the target pH for a mAb 126 formulation is lowered from pH 6 to 5.7 to ensure a stable storage window.

Two experiments with 80 mg/mL mAb 126 at 5 °C are carried out in 20 mM citrate buffer, 200 mM NaCl, and 0.03% polysorbate-80; there is no gel formation at or below pH 6.1, while gel formation occurs above pH 6.1. These experiments indicate that the formulation with 80 mg/mL mAb 126 has a window from pH 5.7 +/- 0.3 pH units wide that avoids gel formation.

Example 4

Chemical instability

For a pharmaceutical formulation to achieve stability, both physical and chemical sources of instability need to be addressed in the formulation. Chemical instability can result in degradation of the antibody.

In order to assess the effect of pH on chemical stability of mAb 126 at 100 and 150 mg/mL, samples of mAb 126 are analyzed for increases in total % acid variants by chromatography. The range of pH 4 to 7 is explored in half pH unit increments. The buffer for the study includes 10 mM citrate buffer, 150 mM NaCl and 0.02% polysorbate 80. Two mL solutions are stored in 3 mL glass vials with serum stoppers. Samples in these pH environments are stored at 5 °C, 25 °C, and 40 °C in order to more accurately model the temperature effect on the different forms of degradation. Samples are analyzed using Cation Exchange (CEX) HPLC using UV detector and a Dionex ProPac WCX-10 column (4x250mm) using pH 6 10mM Bis Tris Propane (Mobile Phase A) and pH 9.6 10mM Bis Tris Propane, 50mM NaCl (Mobile phase B).

By CEX, increases in total % acid variants (%AV) are the more reliable indicator of degradation for mAb 126. Vials of mAb 126 stored at 25 °C are shown by CEX to be most stable between pH 5-6 and least stable at more alkaline pH conditions. When samples are stored at 40 °C, pH 5 and 5.5 are the most stable, with pH 6 appearing only slightly more stable than the higher pH environments. These results show that the pH of the pharmaceutical solution formulation for mAb 126 should be between pH 5 and pH 6.

Example 5

Design of Experiment (DOE) Study

The DOE study uses a multivariate approach to examine the physical and chemical stability of mAb 126 solution formulations. mAb 126 solution formulations are prepared according to Table 7. Each variable is explored at five levels to measure any curvature which might exist in the output response parameters or interactions between the input variables. The center point condition for the experiment is 20 mM citrate, 200 mM NaCl, pH 5.7, 0.02% polysorbate 80. Three center points are dispersed throughout the design. Independently preparing three center points provides an estimation of certainty in the analytical data without requiring all of the conditions to be prepared and analyzed in duplicate or triplicate. Samples are stored at four temperature conditions (5, 25, 30 and 40 °C). This range of temperatures allows for estimations of the activation energies for the results. Additionally, higher temperature storage enables earlier predictions of optimal formulation conditions.

A number of analytical techniques are selected to monitor chemical and physical stability including size exclusion chromatography (SEC), cation exchange chromatography (CEX) HPLC, HIAC-based particle analysis, digital-image based particle analysis by micro-flow imaging (MFI, Protein Simple/Brightwell Model DPA 4200 with size range of 2-100um), visual appearance, reduced and non-reduced Bioanalyzer Lab-on-a-Chip (LoC), pH, viscosity, and UV absorption (to measure protein content).

Using the data from all temperatures from the initial three month period, activation energies (Ea) are calculated employing an Arrhenius kinetic model (zero or first Order). Energies are found using non-linear regression of all Runs. The model is then employed to extrapolate trends out to 24 months at the relevant commercial storage

temperature (5 °C). Zero order Arrhenius modeling is used for SEC (monomer, polymer Rel. Sub/Impurities), CEX (acid variants), reduced/ non-reduced LoC, and UV content. The best fit for CEX basic variant trends is a first order model.

Table 7. Experimental Design

Run	pH	[PS80]	[NaCl]	[mAb 126]	[Buffer]	Buffer Type
1	5.7	0.02	200	120	20	Citrate
2	6	0.01	150	105	25	Citrate
3	6	0.03	150	105	15	Citrate
4	5.7	0	200	120	20	Citrate
5	5.4	0.03	150	135	15	Citrate
6	6	0.01	250	105	15	Citrate
7	5.7	0.02	200	90	20	Citrate
8	5.7	0.02	100	120	20	Citrate
9	6.3	0.02	200	120	20	Citrate
10	5.1	0.02	200	120	20	Citrate
11	6	0.03	250	105	25	Citrate
12	5.4	0.01	150	105	15	Citrate
13	5.4	0.03	250	135	25	Citrate
14	6	0.03	150	135	25	Citrate
15	5.7	0.02	200	120	20	Citrate
16	5.7	0.02	200	120	10	Citrate
17	5.4	0.01	250	135	15	Citrate
18	5.4	0.01	150	135	25	Citrate
19	6	0.03	250	135	15	Citrate
20	5.7	0.04	200	120	20	Citrate
21	5.4	0.03	250	105	15	Citrate
22	6	0.01	150	135	15	Citrate
23	5.4	0.03	150	105	25	Citrate
24	5.7	0.02	300	120	20	Citrate
25	5.7	0.02	200	150	20	Citrate
26	6	0.01	250	135	25	Citrate
27	5.4	0.01	250	105	25	Citrate
28	5.7	0.02	200	120	30	Citrate
29	5.7	0.02	200	120	20	Citrate

Size Exclusion Chromatography

The two variables with the strongest effect on percent monomer based on SEC results are pH and mAb 126 concentration. The effect of mAb 126 concentration is linear with increasing protein concentration resulting in decreased monomer purity.

Three input variables (pH, NaCl concentration, and buffer concentration) show curvature in their effect on percent monomer. With respect to NaCl and citrate concentration, values near the center point are the most stable. Lower pH conditions are slightly more stable than the center point, but other degradation pathway results make lowering the target pH less attractive.

Interactions between the effect of pH and protein concentration occur with the effects of protein concentration being reduced at pH conditions below 5.7. The two year prediction for monomer purity at the center point conditions of the study is slightly below 96.7%. Polysorbate 80 concentration has little effect on stability from 0.02-0.04%.

Cation Exchange Chromatography

The CEX analysis focuses on the growth of acidic species over time. Statistical modeling of CEX %AV (Ea is 23.7 kcal/g-mol) shows that little chemical modification should be expected after 24 months of storage at 5 °C. Acidic variant generation is minimized near the center point for pH, but increases with greater citrate concentration. mAb 126 and Polysorbate 80 concentration trends suggest that the center point is close to the least optimal position; however, based on the magnitude of the y-axis scale, the difference in center point stability to other conditions is essentially negligible.

Reduced Bioanalyzer LoC

Reduced LoC percent purity is a combination of the relative percentages of heavy and light chains. The two input variables with the strongest influence on the 24-month predictions are pH and NaCl concentration. Percent purity is maximized near the center point of 200 mM NaCl. The percent purity increases with increasing pH. Even at the extreme formulation conditions tested in the DOE study, the molecule is still >98% pure, indicating that the antibody is stable as measured by reduced LoC over the range of the multivariate analysis. The Ea is 21.8 kcal/g-mol.

Combined Projections

All conditions in the design space studied during this experiment have 2 year shelf life projections that predict <5% degradation. However, other physical factors preclude pH conditions above pH 6.3; therefore, the target conditions for the formulation should

not be near this pH edge. Additionally, it is important to select a target that is in an optimal global maximum for the input variables explored. Based on manufacturing considerations, which indicate that >0.01% polysorbate 80 is needed for pumping, the polysorbate 80 target is 0.03%. Based on the results of this study, the optimal formulation conditions is 20 mM citrate, 200 mM NaCl, pH 5.7 with 0.03% polysorbate 80.

Example 6

Stability at 80 mg/mL mAb 126

The stability of 80 mg/mL mAb 126 in 20 mM citrate, 200 mM NaCl, pH 5.7 with 0.03% polysorbate 80 is tested out to 24 months. For storage at 5 °C, stability of the anti-IL-17 antibody pharmaceutical formulation is measured at 0, 1, 3, 6, 9, 12, 18, and 24 months. 5 °C will be the expected storage temperature for the anti-IL-17 antibody pharmaceutical formulation. Accelerated stability studies at 25 °C are run for 1, 3, and 6 months.

A number of analytical techniques are selected to monitor chemical and physical stability including size exclusion chromatography HPLC, cation exchange chromatography HPLC, visual appearance, pH, and UV absorption. CE-SDS is performed utilizing the Beckman Coulter IgG Purity/Heterogeneity kit with a Beckman Coulter ProteomeLab PA800 Enhanced or Plus capillary electrophoresis (CE) instrument. For Reduced CE-SDS, samples are analyzed in a bare-fused silica capillary under denatured, reducing conditions by molecular sieving through a replaceable gel polymer matrix after each sample injection. For non-reduced CE-SDS, samples are diluted to approximately 5 mg/mL in water and subsequently diluted in sample diluent (20mM IAM in 100mM Tris, 1% SDS, pH 9.0) to approximately 1 mg/mL. Afterwards samples are analyzed in a bare-fused silica capillary under denatured, non-reducing conditions by molecular sieving through a replaceable gel polymer matrix at constant voltage. For both methods, UV detection is performed at 214 nm. Results are shown in Table 8.

Table 8: Stability Data for mAb 126 at 80 mg/mL

Analytical Property	Storage Condition	Month				
		0	1	3	6	9
Potency (Bioassay), %	5 °C	87	--	--	--	108
	25 °C/60% RH		106	--	109	--
Quantity (UV), mg/mL	5 °C	75.4	--	76.2	75.5	75.4
	25 °C/60% RH		75.3	76.0	76.5	--
Monomer Purity (SEC), %	5 °C	98.3	--	98.1	98.3	97.9
	25 °C/60% RH		98.3	97.6	97.6	--
Rel Subs/Impurities: Total (SEC), %	5 °C	1.7	--	1.9	1.7	2.1
	25 °C/60% RH		1.7	2.4	2.4	--
mAb 126 Purity (CE-SDS, Reduced), %	5 °C	97.8	--	97.4	97.3	97.2
	25 °C/60% RH		97.4	96.9	96.3	--
Charge Heterogeneity (CEX) [Main Peak], %	5 °C	53.9	--	53.0	54.1	55.1
	25 °C/60% RH		56.7	59.7	60.0	--
Charge Heterogeneity (CEX) [Acidic Variants], %	5 °C	13.4	--	15.4	15.3	16
	25 °C/60% RH		15.8	21.4	27.4	--
Charge Heterogeneity (CEX) [Basic Variants], %	5 °C	32.8	--	31.6	30.7	28.9
	25 °C/60% RH		27.5	18.8	13.0	--
pH	5 °C	5.7	-	5.7	5.7	5.7
	25 °C/60% RH		5.7	5.7	5.7	--
Physical Appearance	5 °C	NT	Pass[1]	--	--	Pass
	25 °C/60% RH		NT	--	--	--
Particulate Matter (greater than or equal to 10 micrometer), particles per container	5 °C	289	--	131	184	63
	25 °C/60% RH		194	177	369	--
Particulate Matter (greater than or equal to 25 micrometer), particles per container	5 °C	9	--	8	31	3
	25 °C/60% RH		4	60	20	--

[1] Physical appearance was not performed at lot release or the 1 month time point. Result shown was obtained after storage at 5 °C for approximately 2.5 months.

Sequence Listing

SEQ ID NO: 1(human IL-17)

MTPGKTSLVS LLLLLSLEAI VKAGITIPRN PGCPNSEDKN FPRTVMVNLN
IHNRNTNTNP KRSSDYYNRS TSPWNLHRNE DPERYPSVIW EAKCRHLGCI
NADGNVDYHM NSVPIQQEIL VLRREPPHCP NSFRLEKILV SVGCTCVTPI
VHHVA

SEQ ID NO: 2(LCVR)

DIVMTQTPLS LSVTPGQPAS ISCRSSRSLV HSRGNTYLHW YLQKPGQSPQ
LLIYKVSNRF IGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCSQSTHLP
FTFGQGTKLE IK

SEQ ID NO: 3(HCVR)

QVQLVQSGAE VKKPGSSVKV SCKASGYSFT DYHIHWVRQA PGQGLEWMGV
INPMYGTTDY NQRFKGRVTI TADESTSTAY MELSSLRSED TAVYYCARYD
YFTGTGVYWG QGTLVTVSS

SEQ ID NO: 4(Light chain)

DIVMTQTPLS LSVTPGQPAS ISCRSSRSLV HSRGNTYLHW YLQKPGQSPQ
LLIYKVSNRF IGVPDRFSGS GSGTDFTLKI SRVEAEDVGV YYCSQSTHLP
FTFGQGTKLE IKRTVAAPSV FIFPPSDEQL KSGTASVVCL LNNFYPREAK
VQWKVDNALQ SGNSQESVTE QDSKDSTYSL SSTLTLSKAD YEKHKVYACE
VTHQGLSSPV TKSFNRGEC

SEQ ID NO: 5(Heavy chain)

QVQLVQSGAE VKKPGSSVKV SCKASGYSFT DYHIHWVRQA PGQGLEWMGV
INPMYGTTDY NQRFKGRVTI TADESTSTAY MELSSLRSED TAVYYCARYD
YFTGTGVYWG QGTLVTVSSA STKGPSVFPL APCSRSTSES TAALGCLVKD
YFPEPVTVSW NSGALTSGVH TFPAVLQSSG LYSLSSVVTV PSSSLGTKTY
TCNVDHKPSN TKVDKRVESK YGPPCPPCPA PEFLGGPSVF LFPPKPKDTL
MISRTPEVTC VVVDVSQEDP EVQFNWYVDG VEVHNAKTKP REEQFNSTYR

VVSVLTVLHQ DWLNGKEYKC KVSNKGLPSS IEKTISKAKG QPREPQVYTL
PPSQEEMTKN QVSLTCLVKG FYPSDIAVEW ESNGQPENNY KTTPPVLDSD
GSFFLYSRLT VDKSRWQEGN VFSCSVMHEA LHNHYTQKSL SLSLG

We Claim:

1. A pharmaceutical formulation comprising an anti-IL-17 antibody at a concentration in the range of about 80 mg/mL to about 150 mg/mL, citrate buffer at a concentration of about 20 mM, sodium chloride at a concentration of about 200 mM, polysorbate-80 at a concentration in the range of about 0.02% (w/v) to about 0.03% (w/v), and pH at about 5.7, wherein the anti-IL-17 antibody comprises an antibody with a light chain (LC) and a heavy chain (HC), wherein said LC is the amino acid sequence of SEQ ID NO: 4 and said HC is the amino acid sequence of SEQ ID NO: 5.

2. The formulation of Claim 1, wherein the anti-IL-17 antibody comprises an antibody comprising two light chains (LCs) and two heavy chains (HCs), wherein each LC is the amino acid sequence of SEQ ID NO: 4 and each HC is the amino acid sequence of SEQ ID NO: 5.

3. The formulation of any one of Claims 1 to 2, wherein the concentration of anti-IL-17 antibody is about 80 mg/mL.

4. The formulation of any one of Claims 1 to 3, wherein the concentration of polysorbate-80 is about 0.03% (w/v).

5. The formulation of any one of Claims 1 to 4, wherein the formulation is an anti-IL-17 antibody pharmaceutical solution formulation.

6. A pharmaceutical formulation comprising an anti-IL-17 antibody at a concentration of about 80 mg/mL, citrate buffer at a concentration of about 20 mM, sodium chloride at a concentration of about 200 mM, polysorbate-80 at a concentration of about 0.03%, and pH at about 5.7, wherein the anti-IL-17 antibody comprises an antibody comprising two light chains (LCs) and two heavy chains (HCs), wherein each LC is the amino acid sequence of SEQ ID NO: 4 and each HC is the amino acid sequence of SEQ ID NO: 5.

7. A pharmaceutical solution formulation comprising an anti-IL-17 antibody at a concentration of about 80 mg/mL, citrate buffer at a concentration of about 20 mM,

sodium chloride at a concentration of about 200 mM, polysorbate-80 at a concentration of about 0.03%, and pH at about 5.7, wherein the anti-IL-17 antibody comprises an antibody comprising two light chains (LCs) and two heavy chains (HCs), wherein each LC is the amino acid sequence of SEQ ID NO: 4 and each HC is the amino acid sequence of SEQ ID NO: 5.

8. A pharmaceutical formulation of any one of claims 1-7 for use in therapy.

9. A pharmaceutical formulation of any one of claims 1-7 for use in the treatment of rheumatoid arthritis, psoriasis, ankylosing spondilitis, psoriatic arthritis or multiple myeloma.