CLAIMS

What is claimed is:

1. A rFVIII formulation comprising:

(a) a range of from about 1 mM to about 5 mM divalent cation;

(b) a range of from about 150 mM to about 250 mM sodium chloride or potassium chloride;

(c) a range of from about 50 ppm to about 200 ppm of a non-ionic surfactant; and

(d) a range of from about 100 IU/ml to about 5000 IU/ml of a rFVIII, wherein the rFVIII comprises an amino acid sequence that has one or more non-cysteine residues in the amino acid sequence of SEQ ID NO: 3 replaced with cysteine residues such that at least one pair of cysteine residues creates a disulfide bond not found in wild type FVIII;

wherein the rFVIII formulation has a pH in a range of from about pH 6.0 to about pH 7.5.

2. The rFVIII formulation of claim 1 further comprising:

(a) a range of from about 10 mM to about 50 mM histidine;

(b) a range of from about 10 mM to about 100 mM of a sugar or sugar alcohol; and

(c) a range of from about 150 mM to about 400 mM glycine.

3. A rFVIII formulation comprising:

(a) a range of from 10 mM to 100 mM MOPS;

(b) a range of from 0.5% to 10% by weight of a sugar or a sugar alcohol;

(c) a range of from 0.5 mM to 20 mM of a divalent cation;

(d) a range of from 10 mM to 100 mM sodium chloride or potassium chloride;

(e) a range of from 50 to 150 ppm of a non-ionic surfactant; and

(f) a range of from about 1000 IU/ml to about 1500 IU/ml of rFVIII;

wherein the rFVIII formulation contains less than 5.0 % by weight of components other than rFVIII having primary or secondary amine groups.

4. The rFVIII formulation of claim 3 that is essentially free of histidine and glycine.

5. A method for the covalent conjugation of rFVIII to a biocompatible polymer comprising:

(a) obtaining the rFVIII formulation of claim 3 or 4;

(b) adding a functionalized polymer to create a reaction mixture, wherein the polymer is functionalized with a chemical moiety reactive with amine groups on rFVIII; and

(c) incubating the reaction mixture under conditions of time and temperature such that covalent attachment of the polymer to the rFVIII occurs.

6. A rFVIII formulation comprising:

(a) a range of from 10 mM to 100 mM MOPS;

(b) a range of from 150 mM to 300 mM NaCl;

(c) a range of from 1 mM to 20 mM divalent cation; and

(d) a range of from about 100 IU/ml to about 5000 IU/ml of nonconjugated rFVIII.

7. The rFVIII formulation of claim 6 further comprising

(a) a range of from 0.5% to 10% of a sugar or sugar alcohol; and

(b) a range of from 20 ppm to 250 ppm of a non-ionic surfactant.

8. A rFVIII formulation comprising:

(a) a range of from 10 mM to 100 mM MOPS or histidine;

(b) a range of from 25 mM to 200 mM NaCl;

(c) a range of from 1 mM to 20 mM divalent cation; and

(d) a range of from about 100 IU/ml to about 5000 IU/ml of conjugated rFVIII.

9. The rFVIII formulation of claim 8 further comprising:

(a) a range of from 0.5% to 10% of a sugar or sugar alcohol; and

(b) a range of from 20 ppm to 250 ppm of a non-ionic surfactant.

10. A rFVIII formulation comprising:

(a) about 0mM, or a range of from about 1mM to about 20mM histidine;

(b) a range of from 0.5% to 20% of sucrose or trehalose;

(c) a range of from about 1 mM to about 5 mM divalent cation;

(d) about 0 mM, or a range of from about 10 mM to about 50 mM sodium chloride;

(e) about 0 mM, or a range of from about 20 ppm to about 80 ppm of a non-ionic surfactant;

(f) about 0%, or a range of from about 1.0% to about 5.0%, glycine and

(g) a range of from about 100 IU/ml to about 5000 IU/ml of conjugated rFVIII;

wherein the rFVIII formulation has a pH in a range of from about pH 6.8 to about pH 7.5.

11. The rFVIII formulation of claim 10, wherein

(a) sodium chloride is present in a range of from about 10 mM to about 50 mM;

(b) sucrose is present in a range of a range of from 0.5% to 2.0%,

(c) glycine is present at a range of from about 1.0% to about 5.0%,

(d) histidine is present in a range of from about 1mM to about 20mM, and

(e) a non-ionic surfactant is present in a range of from about 20 ppm to about 80 ppm.

12. The rFVIII formulation of claim 10, wherein

(a) sodium chloride is present at less than 1.0% by weight or is not present;

(b) sucrose or trehalose is present in a range of from 0.5% to 20%, and

(c) glycine is present at less than 1.0% by weight or is not present.

13. The rFVIII formulation of claim 12, wherein sucrose or trehalose is present at a range of from 1.0% to 10.0%.

14. A method of treating hemophilia A comprising administering a therapeutically effective amount of a rFVIII formulation of one of claims 1, 3, 6, 8 or 10 to a patient in need thereof.

What is claimed is:

1. A rFVIII formulation comprising:

(a) a range of from about 1 mM to about 5 mM divalent cation;

(b) a range of from about 150 mM to about 250 mM sodium chloride or potassium chloride;

(c) a range of from about 50 ppm to about 200 ppm of a non-ionic surfactant; and

(d) a range of from about 100 IU/ml to about 5000 IU/ml of a rFVIII, wherein the rFVIII comprises an amino acid sequence that has one or more non-cysteine residues in the amino acid sequence of SEQ ID NO: 3 replaced with cysteine residues such that at least one pair of cysteine residues creates a disulfide bond not found in wild type FVIII;

wherein the rFVIII formulation has a pH in a range of from about pH 6.0 to about pH 7.5.

2. The rFVIII formulation of claim 1 further comprising:

(a) a range of from about 10 mM to about 50 mM histidine;

(b) a range of from about 10 mM to about 100 mM of a sugar or sugar alcohol; and

(c) a range of from about 150 mM to about 400 mM glycine.

3. A rFVIII formulation comprising:

(a) a range of from 10 mM to 100 mM MOPS;

(b) a range of from 0.5% to 10% by weight of a sugar or a sugar alcohol;

(c) a range of from 0.5 mM to 20 mM of a divalent cation;

(d) a range of from 10 mM to 100 mM sodium chloride or potassium chloride;

(e) a range of from 50 to 150 ppm of a non-ionic surfactant; and

(f) a range of from about 1000 IU/ml to about 1500 IU/ml of rFVIII;

wherein the rFVIII formulation contains less than 5.0 % by weight of components other than rFVIII having primary or secondary amine groups.

4. The rFVIII formulation of claim 3 that is essentially free of histidine and glycine.

5. A method for the covalent conjugation of rFVIII to a biocompatible polymer comprising:

(a) obtaining the rFVIII formulation of claim 3 or 4;

(b) adding a functionalized polymer to create a reaction mixture, wherein the polymer is functionalized with a chemical moiety reactive with amine groups on rFVIII; and

(c) incubating the reaction mixture under conditions of time and temperature such that covalent attachment of the polymer to the rFVIII occurs.

6. A rFVIII formulation comprising:

(a) a range of from 10 mM to 100 mM MOPS;

(b) a range of from 150 mM to 300 mM NaCl;

(c) a range of from 1 mM to 20 mM divalent cation; and

(d) a range of from about 100 IU/ml to about 5000 IU/ml of nonconjugated rFVIII.

7. The rFVIII formulation of claim 6 further comprising

(a) a range of from 0.5% to 10% of a sugar or sugar alcohol; and

(b) a range of from 20 ppm to 250 ppm of a non-ionic surfactant.

8. A rFVIII formulation comprising:

(a) a range of from 10 mM to 100 mM MOPS or histidine;

(b) a range of from 25 mM to 200 mM NaCl;

(c) a range of from 1 mM to 20 mM divalent cation; and

(d) a range of from about 100 IU/ml to about 5000 IU/ml of conjugated rFVIII.

9. The rFVIII formulation of claim 8 further comprising:

(a) a range of from 0.5% to 10% of a sugar or sugar alcohol; and

(b) a range of from 20 ppm to 250 ppm of a non-ionic surfactant.

10. A rFVIII formulation comprising:

(a) about 0mM, or a range of from about 1mM to about 20mM histidine;

(b) a range of from 0.5% to 20% of sucrose or trehalose;

(c) a range of from about 1 mM to about 5 mM divalent cation;

(d) about 0 mM, or a range of from about 10 mM to about 50 mM sodium chloride;

(e) about 0 mM, or a range of from about 20 ppm to about 80 ppm of a non-ionic surfactant;

(f) about 0%, or a range of from about 1.0% to about 5.0%, glycine and

(g) a range of from about 100 IU/ml to about 5000 IU/ml of conjugated rFVIII;

wherein the rFVIII formulation has a pH in a range of from about pH 6.0 to about pH 7.5.

11. The rFVIII formulation of claim 10, wherein

(a) sodium chloride is present in a range of from about 10 mM to about 50 mM;

(b) sucrose is present in a range of a range of from 0.5% to 2.0%,

(c) glycine is present at a range of from about 1.0% to about 5.0%,

(d) histidine is present in a range of from about 1mM to about 20mM, and

(e) a non-ionic surfactant is present in a range of from about 20 ppm to about 80 ppm.

12. The rFVIII formulation of claim 10, wherein

(a) sodium chloride is present at less than 1.0% by weight or is not present;

(b) sucrose or trehalose is present in a range of from 0.5% to 20%, and

(c) glycine is present at less than 1.0% by weight or is not present.

13. The rFVIII formulation of claim 12, wherein sucrose or trehalose is present at a range of from 1.0% to 10.0%.

14. Recombinant FVIII formulation of one of claims 1, 3, 6, 8 or 10 for use in treatment of hemophilia A.

15. The use of the rFVIII formulation of one of claims 1, 3, 6, 8 or 10 in the manufacture of a medicament for the treatment of hemophilia A.