CLAIMS

1. A pharmaceutical formulation comprising a heterodimeric fusion and a lipase-resistant surfactant, wherein the heterodimeric fusion comprises:

   (i) a first heterodimerisation domain connected to at least one Relaxin A chain polypeptide or a variant thereof; and

   (ii) a second heterodimerisation domain connected to at least one Relaxin B chain polypeptide or a variant thereof,

   wherein the first heterodimerisation domain heterodimerises with the second heterodimerisation domain, and wherein the heterodimeric fusion has Relaxin activity.

2. The pharmaceutical formulation according to claim 1, wherein the Relaxin A chain polypeptide and the Relaxin B chain polypeptide are covalently bound by at least one inter-chain disulphide bond.

3. The pharmaceutical formulation according to claim 1 or 2, wherein the Relaxin A chain and the Relaxin B chain are not covalently linked to each other by an amino acid linker.

4. The pharmaceutical formulation according to any one of the preceding claims, wherein the Relaxin A chain is a Relaxin-2 A chain and the Relaxin B chain is a Relaxin-2 B chain.

5. The pharmaceutical formulation according to any one of the preceding claims, wherein the Relaxin A chain is connected to the first heterodimerisation domain via a connector and the Relaxin B chain is connected to the second heterodimerisation domain via a connector, optionally wherein one or both connectors are polypeptides.

6. The pharmaceutical formulation according to claim 5, wherein one or both of the connectors have a length of between 6 and 40 amino acids, *e.g.* one or both connectors have a length of 21 amino acids.

7. The pharmaceutical formulation according to any one of the preceding claims, wherein the first and second heterodimerisation domains are derived from an immunoglobulin Fc region ("first Fc region" and "second Fc region", respectively), optionally wherein the first and second Fc regions comprise the constant domains CH2 and CH3.

8. The pharmaceutical formulation according to claim 7, wherein the C-terminus of the first Fc region is connected to the N-terminus of the Relaxin A chain and the C-terminus of the second Fc region is connected to the N-terminus of the Relaxin B chain.

9. The pharmaceutical formulation according to claim 7 or 8, wherein the first and second Fc regions comprise heterodimerisation-promoting amino acid mutations and/or modifications, optionally wherein the heterodimerisation-promoting amino acid mutations are "Fc Knob" and "Fc Hole" mutations, *e.g.* "Fc Knob" and "Fc Hole" mutations present in the CH3 domains.

10. The pharmaceutical formulation according to any one of claims 7 to 9, wherein the first and second Fc regions are derived from a human IgG1 immunoglobulin.

11. The pharmaceutical formulation according to claim 10, wherein the heterodimerisation-promoting amino acid mutations comprise:

    a. "Fc Hole" mutations Y349C, T366S, L368A and Y407V in one CH3 domain; and

    b. "Fc Knob" mutations S354C and T366W in the other CH3 domain,

    wherein the amino acid numbering is according to the EU index as in Kabat.

12. The pharmaceutical formulation according to claim 11, wherein:

    a. the first Fc region comprises the "Fc Knob" mutations and the second Fc region comprises the "Fc Hole" mutations; or

    b. the second Fc region comprises the "Fc Knob" mutations and the first Fc region comprises the "Fc Hole" mutations.

13. The pharmaceutical formulation according to any one of claims 10 to 12, wherein the first and/or second Fc region comprises the amino acid mutations L234F, L235E, and P331S, wherein the amino acid numbering is according to the EU index as in Kabat.

14. The pharmaceutical formulation according to any one of claims 4 to 13, wherein the Relaxin-2 A chain polypeptide comprises the sequence as set forth in SEQ ID NO: 1 or a variant thereof and the Relaxin-2 B chain polypeptide comprises the sequence as set forth in SEQ ID NO: 2 or a variant thereof.

15. The pharmaceutical formulation according to claim 14, wherein the Relaxin-2 A chain polypeptide comprises the amino acid mutation K9H, K17M or K17I.

16. The pharmaceutical formulation according to any one of claims 5 to 15, wherein both connectors have the sequence GGGGSGGGGSGGGGSGGGGGS [SEQ ID NO: 5].

17. The pharmaceutical formulation according to claim 1, wherein the heterodimeric fusion comprises:

(i) an FcX-con-A fusion polypeptide; and

(ii) an FcY-con-B fusion polypeptide,

wherein:

A is a Relaxin A chain or variant thereof, *e.g.* a Relaxin-2 A chain or variant thereof;

B is a Relaxin B chain or variant thereof, *e.g.* Relaxin-2 B chain or variant thereof;

FcY is an Fc region comprising the constant domains CH2 and CH3 of a human IgG1 immunoglobulin and comprises “Fc Hole” amino acid mutations and/or modifications, optionally the amino acid mutations Y349C: T366S:L368A:Y407V;

FcX is an Fc region with “Fc Knob” amino acid mutations and/or modifications, optionally comprising the constant domains CH2 and CH3 of a human IgG1 immunoglobulin and

comprises “Fc Knob” amino acid mutations and/or modifications, optionally the amino acid mutations S354C:T366W; and

con is a connector polypeptide, optionally having the sequence GGGGSGGGGSGGGGSGGGGGS [SEQ ID NO: 5],

wherein the amino acid numbering is according to the EU index as in Kabat, and wherein FcX heterodimerises with FcY.

18. The pharmaceutical formulation according to any one of the preceding claims, wherein the heterodimeric fusion comprises a fusion polypeptide with the amino acid sequence of SEQ ID NO: 11 and a fusion polypeptide with the amino acid sequence of SEQ ID NO: 20.

19. The pharmaceutical formulation according to any one of claims 8 to 18, wherein the heterodimeric fusion further comprises one or more Fabs, optionally wherein the heterodimeric fusion comprises one Fab linked to the N-terminus of the first Fc region and a second Fab linked to the N-terminus of the second Fc region.

20. The pharmaceutical formulation according to any one of the claims 8 to 19, wherein the heterodimer further comprises a second Relaxin A chain polypeptide or variant thereof connected to the N-terminus of the first Fc region and a second Relaxin B chain polypeptide or variant thereof connected to the N-terminus of the second Fc region, optionally wherein the second Relaxin A chain is connected to the first Fc region via a connector polypeptide and the second Relaxin B chain is connected to the second Fc region via a connector polypeptide.

21. The pharmaceutical formulation according to claim 1, wherein the heterodimeric fusion comprises:

(i) FcX-B-L-A and FcY, optionally FcY-B-L-A; or

(ii) FcY-B-L-A and FcX, optionally FcX-B-L-A;

wherein:

FcY is an immunoglobulin Fc region with “Fc Hole” amino acid mutations and/or modifications, optionally comprising a CH3 domain having the amino acid mutations Y349C:T366S:L368A:Y407V;

FcX is an immunoglobulin Fc region with “Fc Knob” amino acid mutations and/or modifications, optionally comprising a CH3 domain having the amino acid mutations S354C:T366W;

B is a Relaxin B chain or a variant thereof, *e.g.* a Relaxin 2 B chain or variant thereof;

A is a Relaxin A chain or a variant thereof, *e.g.* a Relaxin 2 A chain or variant thereof; and

L is a linker polypeptide, optionally having the amino acid sequence GGGSGGGSGG [SEQ ID NO: 60],

wherein the amino acid numbering is according to the EU index as in Kabat, and wherein FcX heterodimerises with FcY.

22. The pharmaceutical formulation according to claim 21, wherein the Relaxin B chain is connected to FcX and/or FcY via a connector, optionally a connector polypeptide having a length of between 6 and 40 amino acids, *e.g.* a length of 21 amino acids.

23. The pharmaceutical formulation of any of the preceding claims, wherein the formulation comprises less than about 10,000, about 6000, about 5,000, about 1,000, about 750, about 600, about 500, about 250, about 150, about 100, or about 50 particles/mL greater than 2 µm, 5 µm, 10 µm, 15 µm, 20 µm or 25 µm diameter.

24. The pharmaceutical formulation according to any one of the preceding claims, wherein the concentration of the lipase-resistant surfactant is from 0.001% (w/v) to 1% (w/v).

25. The pharmaceutical formulation according to any one of the preceding claims, wherein the concentration of the lipase-resistant surfactant is from 0.02% (w/v) to 0.06% (w/v), optionally 0.04% (w/v).

26. The pharmaceutical formulation according to any one of the preceding claims, wherein the lipase-resistant surfactant cannot be enzymatically hydrolysed by lipase, optionally wherein the lipase is selected from lipoprotein lipase, Lipase 9, Phospholipase 2 and Phospholipase 2A.

27. The pharmaceutical formulation according to any one of the preceding claims, wherein the lipase-resistant surfactant does not comprise an ester bond capable of being enzymatically hydrolysed by lipase, optionally wherein the lipase is selected from lipoprotein lipase, Lipase 9, Phospholipase 2 and Phospholipase 2A.

28. The pharmaceutical formulation according to any one of the preceding claims, wherein the lipase-resistant surfactant is a water-soluble non-ionic triblock copolymer formed by polyethylene oxide (PEO) and polypropylene oxide (PPO) blocks, optionally wherein the water-soluble nonionic triblock copolymer is poloxamer 188 (P188).

29. The pharmaceutical formulation according to any one of claims 1 to 27, wherein the lipase-resistant surfactant is selected from P188, D-α-Tocopherol polyethylene glycol succinate (TPGS), Kolliphor HS15, Kolliphor EL, Kolliphor RH40, PEG 300, PEG400, Brij 58 and Brij 35; optionally wherein the lipase-resistant surfactant is TPGS.

30. The pharmaceutical formulation according to any one of the preceding claims, wherein the formulation further comprises a buffer at a pH from 3 to 10, optionally 5.5 to 7.5.

31. The pharmaceutical formulation according to claim 30, wherein the formulation has a pH in the range of 6 to 7.

32. The pharmaceutical formulation according to claim 31, wherein the formulation has a pH of 6.5.

33. The pharmaceutical formulation according to any one of claims 30 to 32, wherein the concentration of the buffer is from 0.1 mM to 100 mM, optionally 5 mM, 10 mM, 15 mM, 20 mM, 25 mM, 30 mM, 35 mM, 40 mM, 45 mM, or 50 mM.

34. The pharmaceutical formulation according to claim 33, wherein the concentration of the buffer is 10 mM to 30 mM, optionally 20 mM.

35. The pharmaceutical formulation according to any one of claims 30 to 34, wherein the buffer is selected from acetate, acetic acid, succinate, succinic acid, phosphate, phosphoric acid, ascorbate, ascorbic acid, lactate, lactic acid, tartartic acid, maleic acid, glycine, gluconate, citrate, histidine, imidazole, bicarbonate and carbonic acid, sodium benzoate, benzoic acid, edetate, malate, tris, glycylglycine and mixtures thereof, optionally wherein the buffer is selected from a citrate buffer and a histidine buffer.

36. The pharmaceutical formulation according to any one of claims 30 to 35, wherein the buffer is a histidine, histidine hydrochloride or histidine/histidine hydrochloride buffer, optionally a histidine/histidine hydrochloride buffer.

37. The pharmaceutical formulation according to any one of the preceding claims, wherein the formulation additionally comprises an excipient, optionally wherein the excipient is an ionic excipient.

38. The pharmaceutical formulation according to claim 37, wherein the concentration of the excipient is from 10 mM to 500 mM.

39. The pharmaceutical formulation according to claim 38, wherein the concentration of the excipient is from 140 mM to 240 mM, optionally 190 mM.

40. The pharmaceutical formulation according to any one of claims 37 to 39, wherein the excipient is an ionic excipient selected from an arginine salt or a lysine salt.

41. The pharmaceutical formulation according to claim 40, wherein the ionic excipient is selected from arginine HCl or lysine HCl, optionally arginine HCl.

42. The pharmaceutical formulation according to any one of the preceding claims, wherein the formulation further comprises a sugar, optionally wherein the sugar is sucrose.

43. The pharmaceutical formulation according to any one of the preceding claims, wherein the concentration of heterodimeric fusion is from 0.1 to 100 mg/mL, optionally 0.2 to 50 mg/mL.

44. The pharmaceutical formulation according to claim 43, wherein the formulation comprises 0.2-50 mg/mL of heterodimeric fusion, 20 mM histidine/histidine hydrochloride buffer, 190 mM arginine HCl, 0.04% (w/v) poloxamer 188 (P188), and wherein the formulation has a pH of 6.5.

45. The pharmaceutical formulation according to claim 44, wherein the heterodimeric fusion consists of a fusion polypeptide with the amino acid sequence of SEQ ID NO: 11 and a fusion polypeptide with the amino acid sequence of SEQ ID NO: 20.

46. The pharmaceutical formulation according to any one of the preceding claims, wherein the formulation comprises 50 mg/mL of heterodimeric fusion.

47. The pharmaceutical formulation according to any one of claims 1 to 45, wherein the formulation comprises 30 mg/mL of heterodimeric fusion.

48. The pharmaceutical formulation according to any one of the claims 1 to 45, wherein the formulation comprises 5 mg/mL or 1.1 mg/mL or 1 mg/mL of heterodimeric fusion.

49. A kit comprising the pharmaceutical formulation according to any one of claims 1 to 48.