

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

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Date of mailing
(day/month/year)

APR 01 2022

Applicant's or agent's file reference
L1247-20031

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/US 22/12200

International filing date (day/month/year)

12 January 2022 (12.01.2022)

Priority date (day/month/year)

12 January 2021 (12.01.2021)

International Patent Classification (IPC) or both national classification and IPC

IPC - A61K 8/735; A61Q 19/08; A61K 2800/5922 (2022.01)

CPC - A61K 8/735; A61Q 19/08; A61K 2800/5922

Applicant **LORIA PHARMACEUTICAL, LLC**

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

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Date of completion of this opinion

07 March 2022

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Box No. 1 Basis of this opinion

1. With regard to the **language**, this opinion has been established on the basis of:
 - ☒ the international application in the language in which it was filed.
 - ☐ a translation of the international application into _____ which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).
2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(b)).
3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:
 - a. ☐ forming part of the international application as filed:
 - ☐ in the form of an Annex C/ST.25 text file.
 - ☐ on paper or in the form of an image file.
 - b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file
 - c. ☐ furnished subsequent to the international filing date for the purposes of international search only:
 - ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).
 - ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).
4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
5. Additional comments:

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-21	YES
	Claims	None	NO
Inventive step (IS)	Claims	None	YES
	Claims	1-21	NO
Industrial applicability (IA)	Claims	1-21	YES
	Claims	None	NO

2. Citations and explanations:

Claims 1-5 and 7-14 lack an inventive step under PCT Article 33(3) as being obvious over US 2009/0169615 A1 to Pinsky.

Regarding claim 1, Pinsky discloses a filler composition (para [0031] - "...Additional embodiments relate to the use of bioactive collagen proteins that provide useful biological activity in addition to acting as a dermal filler...") comprising: a first silicone oil (para [0122] - "...The carrier can be in a wide variety of forms. For example, emulsion carriers, including, but not limited to... oil-in-water-in-silicone emulsions..."); water (para [0122] - "...The carrier can be in a wide variety of forms. For example, emulsion carriers, including, but not limited to... oil-in-water-in-silicone emulsions..."); a transport medium (para [0079] - "...The unique property of HA to give highly swollen cross-linked gels can be used to effect modification of the properties of cross-linked gels made of mixtures of HA with other hydrophilic polymers. These polymers include... carboxymethylcellulose..."; para [0186] - "...Non-limiting classes of thickening agents for use in the compositions of the invention include those selected from the following... carboxymethyl cellulose..."; see instant claim 8); a surfactant (para [0112] - "...To prepare non-phospholipid paucilamellar lipid vesicles formed of non-phospholipid surfactant material and containing an aqueous-based collagen and/or HA material, any suitable method known in the art can be used..."; para [0131] - "...In certain embodiments, oil-in-water emulsions that contain at least one hydrophilic surfactant which can disperse the hydrophobic materials in the water phase (percentages by weight of the topical carrier). The surfactant, at a minimum, must be hydrophilic enough to disperse in water..."; para [0172] - "...The compositions of the present invention may also contain a safe and effective amount of a topical anesthetic. Examples of topical anesthetic drugs include... lidocaine..."); and optionally a second silicone oil (para [0123] - "...Anti-foaming agents include high molecular weight silicones and other materials well known in the art for such use..."; Note: As silicones are described as being used as components in the emulsion and as anti-foaming agents, more than one silicone is considered present), wherein: the filler composition is a pharmaceutically acceptable oil-in-water emulsion (para [0122] - "...The carrier can be in a wide variety of forms. For example, emulsion carriers, including, but not limited to... oil-in-water-in-silicone emulsions..."), and that the composition may deliver collagen to a human through the dermis of the skin (Abstract - "...Compositions and methods for administering collagen to a human subject have been developed..."; para [0030] - "...In one embodiment, the present invention provides a skin care composition with a safe and effective amount of one or more collagen fragments, and/or variants thereof, wherein the formulation facilitates the passage of the collagen protein through the epidermis and thus being delivered to the dermis of the skin..."), but does not further specifically disclose the filler composition comprising: 1-80 vol.% of a first silicone oil having a first viscosity; 15-98 vol.% of water; 1-3 wt.% of a transport medium; 0.05-10 vol.% of a surfactant; and optionally a second silicone oil having a second viscosity lower than the first viscosity, wherein: the second silicone oil is provided in an amount of 1-80 vol.% when the first viscosity is 30,000 cSt or less; the second silicone oil is provided in an amount of 0-80 vol.% when the first viscosity is greater than 30,000 cSt; at least one of the first silicone oil and the second silicone oil is dispersed in the water as droplets having an average diameter of less than 30 microns; and the transport medium is sufficiently biodegradable when implanted intradermally or subcutaneously in a human to provide a temporary scaffold for collagen growth between the droplets. However, as Pinsky discloses that the emulsions may comprise droplets (para [0126] - "...In emulsion technology, the term "dispersed phase" is a term well-known to one skilled in the art that means that the phase exists as small particles or droplets that are suspended in and surrounded by a continuous phase..."), having 0.5 to 2 micron diameter (para [0116] - "...If an aqueous center is used, the paucilamellar lipid vesicles will normally range in diameter from about 0.5-2 u..."), that the composition may comprise thickeners (para [0185] - "...The compositions of the present invention can contain one or more thickening agents, preferably from about 0.1% to about 5%..."), that the composition may degrade in the living body slowly (para [0086] - "...Delivery of a drug from these systems occurs when the gel is degraded in the living body. The degradation process is usually slower than diffusion. The rate of the degradation process can be controlled by several means..."), it would have been obvious to one of ordinary skill in the art to create the filler composition comprising: 1-80 vol.% of a first silicone oil having a first viscosity; 15-98 vol.% of water; 1-3 wt.% of a transport medium; 0.05-10 vol.% of a surfactant; and optionally a second silicone oil having a second viscosity lower than the first viscosity, wherein: the second silicone oil is provided in an amount of 1-80 vol.% when the first viscosity is 30,000 cSt or less; the second silicone oil is provided in an amount of 0-80 vol.% when the first viscosity is greater than 30,000 cSt; at least one of the first silicone oil and the second silicone oil is dispersed in the water as droplets having an average diameter of less than 30 microns; and the transport medium is sufficiently biodegradable when implanted intradermally or subcutaneously in a human to provide a temporary scaffold for collagen growth between the dropletst, through routine experimentation.

-- See Supplemental Box --

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In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Box V.2 Citations and Explanations

Regarding claim 2, Pinsky discloses the filler composition of claim 1, as disclosed above, but does not further specifically disclose the composition which comprises 3 vol.% of the second silicon oil and 27 vol.% of the first silicone oil, wherein the second viscosity is 1,000 cSt and the first viscosity is 12,500 cSt. However, as Pinsky discloses the use of multiple silicones (para [0122] - '...The carrier can be in a wide variety of forms. For example, emulsion carriers, including, but not limited to... oil-in-water-in-silicone emulsions...'; para [0123] - '...Anti-foaming agents include high molecular weight silicones and other materials well known in the art for such use...'), and that the composition may comprise thickeners (para [0185] - '...The compositions of the present invention can contain one or more thickening agents, preferably from about 0.1% to about 5%...'), it would have been obvious to one of ordinary skill in the art to create the filler composition which comprises 3 vol.% of the second silicon oil and 27 vol.% of the first silicone oil, wherein the second viscosity is 1,000 cSt and the first viscosity is 12,500 cSt, through routine experimentation.

Regarding claim 3, Pinsky discloses the filler composition of claim 1, as disclosed above, but does not further specifically disclose the composition which comprises 5 vol.% of the second silicon oil and 25 vol.% of the first silicone oil, wherein the second viscosity is 12,500 cSt and the first viscosity is 100,000 cSt. However, as Pinsky discloses the use of multiple silicones (para [0122] - '...The carrier can be in a wide variety of forms. For example, emulsion carriers, including, but not limited to... oil-in-water-in-silicone emulsions...'; para [0123] - '...Anti-foaming agents include high molecular weight silicones and other materials well known in the art for such use...'), and that the composition may comprise thickeners (para [0185] - '...The compositions of the present invention can contain one or more thickening agents, preferably from about 0.1% to about 5%...'), it would have been obvious to one of ordinary skill in the art to create the filler composition which comprises 5 vol.% of the second silicon oil and 25 vol.% of the first silicone oil, wherein the second viscosity is 12,500 cSt and the first viscosity is 100,000 cSt, through routine experimentation.

Regarding claim 4, Pinsky discloses the filler composition of claim 1, as disclosed above, but does not further specifically disclose the composition which comprises 30 vol.% of the first silicon oil and none of the second silicone oil, wherein the first viscosity is 100,000 cSt. However, as Pinsky discloses the use of multiple silicones (para [0122] - '...The carrier can be in a wide variety of forms. For example, emulsion carriers, including, but not limited to... oil-in-water-in-silicone emulsions...'; para [0123] - '...Anti-foaming agents include high molecular weight silicones and other materials well known in the art for such use...'), and that the composition may comprise thickeners (para [0185] - '...The compositions of the present invention can contain one or more thickening agents, preferably from about 0.1% to about 5%...'), it would have been obvious to one of ordinary skill in the art to create the filler composition which comprises 30 vol.% of the first silicon oil and none of the second silicone oil, wherein the first viscosity is 100,000 cSt, through routine experimentation.

Regarding claim 5, Pinsky discloses the filler composition of claim 1, as disclosed above, but does not further specifically disclose the composition wherein the first viscosity is from 12,500 cSt to 20,000,000 cSt and the second viscosity is from 65 cSt to 5000 cSt. However, as Pinsky discloses the use of multiple silicones (para [0122] - '...The carrier can be in a wide variety of forms. For example, emulsion carriers, including, but not limited to... oil-in-water-in-silicone emulsions...'; para [0123] - '...Anti-foaming agents include high molecular weight silicones and other materials well known in the art for such use...'), and that the composition may comprise thickeners (para [0185] - '...The compositions of the present invention can contain one or more thickening agents, preferably from about 0.1% to about 5%...'), it would have been obvious to one of ordinary skill in the art to create the filler composition wherein the first viscosity is from 12,500 cSt to 20,000,000 cSt and the second viscosity is from 65 cSt to 5000 cSt, through routine experimentation.

Regarding claim 7, Pinsky discloses the filler composition of any one of claims 1-5, as disclosed above, wherein the transport medium may be a water-soluble polymer (para [0079] - '...The unique property of HA to give highly swollen cross-linked gels can be used to effect modification of the properties of cross-linked gels made of mixtures of HA with other hydrophilic polymers. These polymers include... carboxymethylcellulose...'; para [0186] - '...Nonlimiting classes of thickening agents for use in the compositions of the invention include those selected from the following... carboxymethyl cellulose...').

Regarding claim 8, Pinsky discloses the filler composition of any one of claims 1-5, as disclosed above, wherein the transport medium may be at least one member selected from the group consisting of carboxymethylcellulose (CMC) (para [0079] - '...The unique property of HA to give highly swollen cross-linked gels can be used to effect modification of the properties of cross-linked gels made of mixtures of HA with other hydrophilic polymers. These polymers include... carboxymethylcellulose...'; para [0186] - '...Nonlimiting classes of thickening agents for use in the compositions of the invention include those selected from the following... carboxymethyl cellulose...'), hyaluronic acid, hydroxyethyl cellulose, methyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, polyvinylalcohol, guar gum, hydroxypropyl guar gum, xanthan gum, croscarmellose sodium, and alginate acid.

Regarding claim 9, Pinsky discloses the filler composition of claim 8, as disclosed above, wherein the transport medium may be CMC (para [0079] - '...The unique property of HA to give highly swollen cross-linked gels can be used to effect modification of the properties of cross-linked gels made of mixtures of HA with other hydrophilic polymers. These polymers include... carboxymethylcellulose...'; para [0186] - '...Nonlimiting classes of thickening agents for use in the compositions of the invention include those selected from the following... carboxymethyl cellulose...').

Regarding claim 10, Pinsky discloses the filler composition of claim 9, as disclosed above, but does not further specifically disclose wherein the CMC is cross-linked. However, as Pinsky discloses that cross-linking takes place (para [0076] - '...The swelling ratio depends upon the degree of cross-linking of the gel...'), and the use of cross-linking agents (para [0077] - '...An even more preferred cross-linking agent is 1,4-butanediol diglycidyl ether (BDDE)...'; see instant claim 17), it would have been obvious to one of ordinary skill in the art to create the filler composition wherein the CMC is cross-linked, through routine experimentation.

-- See Supplemental Box --

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Continuation of:

Box V.2 Citations and Explanations

Regarding claim 11, Pinsky discloses the filler composition of any one of claims 1-5, as disclosed above, but does not further specifically disclose wherein the temporary scaffold dissolves in 7 to 35 days. However, as Pinsky discloses that the composition may degrade in the living body slowly (para [0086] - '...Delivery of a drug from these systems occurs when the gel is degraded in the living body. The degradation process is usually slower than diffusion. The rate of the degradation process can be controlled by several means...'), it would have been obvious to one of ordinary skill in the art to create the filler composition wherein the temporary scaffold dissolves in 7 to 35 days, through routine experimentation.

Regarding claim 12, Pinsky discloses the filler composition of any one of claims 1-5, as disclosed above, wherein the surfactant may be lidocaine (para [0172] - '...The compositions of the present invention may also contain a safe and effective amount of a topical anesthetic. Examples of topical anesthetic drugs include... lidocaine...').

Regarding claim 13, Pinsky discloses the filler composition of any one of claims 1-5, as disclosed above, but does not further specifically disclose wherein the average diameter of the droplets is from 1 nanometer to 1 micron. However, as Pinsky discloses the use of droplets having 0.5 to 2 micron diameter (para [0116] - '...If an aqueous center is used, the paucilamellar lipid vesicles will normally range in diameter from about 0.5-2 u...'), it would have been obvious to one of ordinary skill in the art to create the filler composition wherein the average diameter of the droplets is from 1 nanometer to 1 micron, through routine experimentation.

Regarding claim 14, Pinsky discloses the filler composition of any one of claims 1-5, as disclosed above, wherein: the first silicone oil and the second silicone oil are polydimethylsiloxane; the transport medium may be an optionally cross-linked water-soluble polymer selected from the group consisting of carboxymethylcellulose (CMC) (para [0079] - '...The unique property of HA to give highly swollen cross-linked gels can be used to effect modification of the properties of cross-linked gels made of mixtures of HA with other hydrophilic polymers. These polymers include... carboxymethylcellulose...'; para [0186] - '...Nonlimiting classes of thickening agents for use in the compositions of the invention include those selected from the following... carboxymethyl cellulose...'), hyaluronic acid, hydroxyethyl cellulose, methyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, polyvinylalcohol, guar gum, hydroxypropyl guar gum, xanthan gum, croscarmellose sodium, and alginic acid; the surfactant is lidocaine; and/or the average diameter of the droplets may be from 1 nanometer to 1 micron (para [0116] - '...If an aqueous center is used, the paucilamellar lipid vesicles will normally range in diameter from about 0.5-2 u...').

Claims 6 and 15-21 lack an inventive step under PCT Article 33(3) as being obvious over Pinsky in view of US 9,993,578 B1 to Lorstan Pharmaceutical, LLC (hereinafter 'Lorstan').

Regarding claim 6, Pinsky discloses the filler composition of any one of claims 1-5, as disclosed above, but does not further specifically disclose wherein the first silicone oil and the second silicone oil are polydimethylsiloxane. Lorstan discloses a similar filler composition (Abstract - '...The present invention relates to compositions in the form of oil-in-water dispersions comprising a silicone oil...'; col 1 In 10-12 - '...This invention relates to compositions comprising silicone oil-in-water emulsions and to methods of making and using such compositions as a dermal filler...'), wherein the composition may comprise polydimethylsiloxane (col 4 In 49-55 - '...In certain embodiments of the filler composition, the silicone oil comprises at least one member selected from the group consisting of polydimethylsiloxane... In certain embodiments of the filler composition, the silicone oil comprises polydimethylsiloxane with a viscosity of 5000 cSt...'). It would have therefore been obvious to one of ordinary skill in the art to combine these references, and to create the filler composition wherein the first silicone oil and the second silicone oil are polydimethylsiloxane, because PDMS is a known lubricant with personal care uses as skin conditioners that provide a smooth feel (see Lorstan, col 2 In 46-61).

-- See Supplemental Box --

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Box V.2 Citations and Explanations

Regarding claim 15, Pinsky discloses the filler composition of any one of claims 1-5, as disclosed above, but does not further specifically disclose a method for preparing the filler composition according to any one of claims 1-5, comprising the steps of: (i) preparing an oil phase comprising the steps of: (a) providing an active ingredient that is substantially sterile and substantially free of pyrogen, wherein the active ingredient is the second silicone oil or the first silicone oil when there is no second silicone oil; (b) mixing the active ingredient with 1-5 volumes of sterile injectable water for 4 to 6 minutes at 1200 to 1500 rpm; (c) allowing the active ingredient and water mixture to separate into a lower water layer and an upper layer containing the active ingredient; (d) removing the lower water layer and collecting the upper layer; and (e) repeating steps (b) through (d) on the active ingredient at least once to obtain the oil phase; (ii) preparing a water phase solution comprising the sequential steps of: (a) dissolving with stirring a transport medium in a sterile solvent selected from the group consisting of injectable water, normal saline, Ringer's solution, and lactated Ringer's solution, to form a preliminary water phase solution; (b) sterilizing the preliminary water phase solution to form a sterilized water phase solution; and (c) optionally freezing and thawing the sterilized water phase solution; and (iii) preparing an oil-in-water emulsion by combining 35-45 parts by volume of the oil phase with 55-65 parts by volume of the water phase solution with agitation to form an emulsion of the active ingredient within the water. Lorstan discloses a similar filler composition (Abstract - "...The present invention relates to compositions in the form of oil-in-water dispersions comprising a silicone oil..."; col 1 In 10-12 - "...This invention relates to compositions comprising silicone oil-in-water emulsions and to methods of making and using such compositions as a dermal filler..."), wherein a method for preparing the filler composition comprising the steps of: (i) preparing an oil phase comprising the steps of: (a) providing an active ingredient that is substantially sterile and substantially free of pyrogen, wherein the active ingredient is the second silicone oil or the first silicone oil when there is no second silicone oil (col 11 In 21-25 - "...The processes comprise the general steps of (i) preparing a silicone oil phase comprising the steps of: (a) sterilizing and depyrogenizing a sample of silicone oil until essentially sterile and pyrogen-free..."); (b) mixing the active ingredient with 1-5 volumes of sterile injectable water for 4 to 6 minutes at 1200 to 1500 rpm (col 11 In 26-29 - "...mixing the resultant sterile and pyrogen-free silicone oil sample with from about an equal volume to about four to five volumes of sterile injectable water, for approximately 5 minutes at about 1200 to 1500 rpm..."); (c) allowing the active ingredient and water mixture to separate into a lower water layer and an upper layer containing the active ingredient (col 11 In 30-31 - "...allowing the silicone oil and water mixture to separate into two layers..."); (d) removing the lower water layer and collecting the upper layer (col 11 In 32-33 - "...removing the lower water layer and collecting the upper silicone layer..."); and (e) repeating steps (b) through (d) on the active ingredient at least once to obtain the oil phase (col 11 In 38-39 - "...repeating steps (b) through (d) on the silicone oil one or more additional times..."); (ii) preparing a water phase solution comprising the sequential steps of: (a) dissolving with stirring a transport medium in a sterile solvent selected from the group consisting of injectable water, normal saline, Ringer's solution, and lactated Ringer's solution, to form a preliminary water phase solution (col 11 In 41-44 - "...dissolving a thickening agent in sterile injectable water or a sterile solution selected from normal saline, Ringer's solution, or lactated Ringers solution, solution with stirring to form a thickened water phase solution..."); (b) sterilizing the preliminary water phase solution to form a sterilized water phase solution (col 11 In 45 - "...sterilizing the thickened water phase solution..."); and (c) optionally freezing and thawing the sterilized water phase solution (col 11 In 46-47 - "...optionally freezing and thawing the sterilized thickened water phase solution..."); and (iii) preparing an oil-in-water emulsion by combining 35-45 parts by volume of the oil phase with 55-65 parts by volume of the water phase solution with agitation to form an emulsion of the active ingredient within the water (col 11 In 51-54 - "...adding approximately 40 parts by volume of the silicone oil phase to approximately 60 parts by volume of the thickened water phase with agitation to form a dispersion of the silicone oil within the water..."). It would have therefore been obvious to one of ordinary skill in the art to combine these references, and to create a method for preparing the filler composition according to any one of claims 1-5, comprising the steps of: (i) preparing an oil phase comprising the steps of: (a) providing an active ingredient that is substantially sterile and substantially free of pyrogen, wherein the active ingredient is the second silicone oil or the first silicone oil when there is no second silicone oil; (b) mixing the active ingredient with 1-5 volumes of sterile injectable water for 4 to 6 minutes at 1200 to 1500 rpm; (c) allowing the active ingredient and water mixture to separate into a lower water layer and an upper layer containing the active ingredient; (d) removing the lower water layer and collecting the upper layer; and (e) repeating steps (b) through (d) on the active ingredient at least once to obtain the oil phase; (ii) preparing a water phase solution comprising the sequential steps of: (a) dissolving with stirring a transport medium in a sterile solvent selected from the group consisting of injectable water, normal saline, Ringer's solution, and lactated Ringer's solution, to form a preliminary water phase solution; (b) sterilizing the preliminary water phase solution to form a sterilized water phase solution; and (c) optionally freezing and thawing the sterilized water phase solution; and (iii) preparing an oil-in-water emulsion by combining 35-45 parts by volume of the oil phase with 55-65 parts by volume of the water phase solution with agitation to form an emulsion of the active ingredient within the water, because the procedure can readily be modified to incorporate further cross-linking agents to aid in thickening (see Lorstan, col 5 In 29-31; col 11 In 55-67).

Regarding claim 16, Pinsky in view of Lorstan discloses the method of claim 15, as disclosed above. Pinsky further discloses wherein the sterile solvent may contain a cross-linking agent which forms cross-links in the transport medium (para [0077] - "...An even more preferred cross-linking agent is 1,4-butanediol diglycidyl ether (BDDE)..."; see instant claim 17).

Regarding claim 17, Pinsky in view of Lorstan discloses the method of claim 16, as disclosed above. Pinsky further discloses wherein the cross-linking agent may be 1,4-butanediol diglycidyl ether (para [0077] - "...An even more preferred cross-linking agent is 1,4-butanediol diglycidyl ether (BDDE)..."), but does not further specifically disclose wherein it is present in an amount from 0.01 to 10% by weight of the composition. However, it would have been obvious to one of ordinary skill in the art to create the method wherein the cross-linking agent may be 1,4-butanediol diglycidyl ether present in an amount from 0.01 to 10% by weight of the composition, through routine experimentation.

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Box V.2 Citations and Explanations

Regarding claim 18, Pinsky discloses the filler composition of any one of claims 1-5, as disclosed above, but does not further specifically disclose a soft tissue augmentation method comprising intradermally and/or subcutaneously injecting into a patient the filler composition of any one of claims 1-5. Lorstan discloses a similar filler composition (Abstract - '...The present invention relates to compositions in the form of oil-in-water dispersions comprising a silicone oil...'; col 1 ln 10-12 - '...This invention relates to compositions comprising silicone oil-in-water emulsions and to methods of making and using such compositions as a dermal filler...'), wherein the composition may be used in a soft tissue augmentation method comprising intradermally and/or subcutaneously injecting into a patient the filler composition (col 5 ln 36-38 - '...A third aspect of the invention is directed to a soft tissue augmentation method comprising subcutaneously injecting into a patient a filler composition of the invention...'). It would have therefore been obvious to one of ordinary skill in the art to combine these references, and to create a soft tissue augmentation method comprising intradermally and/or subcutaneously injecting into a patient the filler composition of any one of claims 1-5, because liquid injectable silicone is a known soft tissue filler and is both versatile and cost-effective (see Lorstan, col 7 ln 25-32).

Regarding claim 19, Pinsky in view of Lorstan discloses the soft tissue augmentation method of claim 18, as disclosed above. Lorstan further discloses wherein a volume of 20 to 60 ml of the filler composition is injected into a single injection site (col 5 ln 39-41 - '...In certain embodiments of the soft tissue augmentation method, a volume of 20 to 60 ml is injected into a single injection site...').

Regarding claim 20, Pinsky in view of Lorstan discloses the soft tissue augmentation method of claim 18, as disclosed above. Lorstan further discloses wherein: the filler composition stimulates collagen growth (col 5 ln 42-43 - '...In certain embodiments of the soft tissue augmentation method, the filler composition stimulates collagen growth...'); the transport medium forms a temporary scaffold for collagen growth between active ingredient droplets (col 4 ln 37-38 - '...In certain embodiments of the filler composition, the thickening agent is carboxymethyl cellulose...'; col 5 ln 44-45 - '...the filler composition stimulates collagen growth growth between silicone oil droplets...'); and a collagen matrix anchors the active ingredient droplets in place as the temporary scaffold dissolves within 7-35 days (col 5 ln 45-47 - '...a collagen matrix anchors the silicone oil droplets in place as the temporary scaffold dissolves within 14-28 days...').

Regarding claim 21, Pinsky in view of Lorstan discloses the soft tissue augmentation method of claim 18, as disclosed above. Lorstan further discloses wherein the filler composition is injected into a penis or a scrotum for penis or scrotum enhancement (col 5 ln 48-50 - '...In certain embodiments of the soft tissue augmentation method, the filler composition is injected into a penis or a scrotum for penis or scrotum enhancement...').

Claims 1-21 have industrial applicability under PCT Article 33(4) because the subject matter can be made or used in industry.