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(54) Title: METHODS OF STABILIZING EPINEPHRINE

(57) Abstract: The present invention is directed to methods of stabilizing a pharmaceutical composition comprising epinephrine con-
taining the steps filling a container, capping the container, assembling the container and placing the assembled capped container (as-
sembled device) in a secondary packaging system.

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METHODS OF STABILIZING EPINEPHRINE

BACKGROUND OF THE INVENTION

[001] Epinephrine stimulates the alpha- and beta-adrenergic receptors of the sympathetic nervous system. Epinephrine binds to these adrenergic receptors leading to relief of many life-threatening symptoms of anaphylaxis including: relaxation of the smooth muscle in the bronchi of the lungs opening the constricted airways; constriction of the blood vessels leading to decreased swelling of the tongue and throat and increased blood pressure; and finally, increased heart rate preventing or reversing cardiovascular collapse.

[002] Currently, Epinephrine is commercially available as an injection (Adrenalin® a trademark of and available from Par Sterile Products, LLC) and an auto-injector (EpiPen® a trademark of and available from Mylan, Inc. and AuviQ® a trademark of and available from Sanofi Corporation). Epinephrine was previously available as a nasal spray (Adrenalin®) and an aerosol spray (Primatene® Mist trademark of Armstrong Pharmaceuticals, Inc.). The injection pens and the previous nasal spray have limited stability at room temperature.

[003] The need to store many epinephrine products in a refrigerator is a major disadvantage for a pharmaceutical product. Accordingly, there is a need for developing a room temperature stable epinephrine product that addresses problems associated with the storage of an epinephrine at refrigerated conditions and patient convenience.

SUMMARY OF THE INVENTION

[004] The present invention is directed to a method of stabilizing a pharmaceutical composition comprising:

from about 0.1% to about 12% w/w epinephrine base or a salt thereof; and optionally, from about 50% to about 99% w/w water, from about 0.1% to about 2% w/w sodium chloride, from about 0.001 to about 0.02% w/w benzalkonium chloride ("BAC"), from about 0.1% to about 0.5% w/w sodium bisulfite, from about 0.01% to about 0.1% edetate disodium dihydrate and from about 20% to about 50% of 0.5 N hydrochloric acid ("HCl"), or

optionally, from about 10% to about 60% w/w ethanol, from about 11% to about 20% w/w water, from about 2% to about 20 % w/w propylene glycol, from about 0.001% to about 0.02% w/w BAC, from about 0.01% to about 0.1% w/w edetate disodium dihydrate and from about 20% to about 50% w/w 0.5 N HCl,

comprising the steps of:

- a. filling a container with the pharmaceutical composition under a vacuum or a gas overlay;
- b. closing the container;
- c. placing the closed container in a holder and actuator to create an assembled device;
- d. placing the assembled device in a secondary packaging system under one or more conditions selected from the group consisting of with or without a gas overlay, with or without an oxygen absorbing means, and with or without oxygen indicator; and
- e. sealing the secondary packaging system,

wherein the container is selected from the group consisting of a glass vial, plastic vial, glass bottle and a plastic bottle and the secondary packaging system is selected from the group consisting of a pouch and a blister package.

[005] The present invention is further directed to a container comprising a pharmaceutical composition comprising:

from about 0.1% to about 12% w/w epinephrine base or a salt thereof; and optionally, from about 50% to about 99% w/w water, from about 0.1% to about 2% w/w sodium chloride, from about 0.001 to about 0.02% w/w benzalkonium chloride ("BAC"), from about 0.1% to about 0.5% w/w sodium bisulfite, from about 0.01% to about 0.1% edetate disodium dihydrate and from about 20% to about 50% of 0.5 N hydrochloric acid ("HCl"), or optionally, from about 10% to about 60% w/w ethanol, from about 11% to about 20% w/w water, from about 2% to about 10% w/w propylene glycol, from about 0.001% to about 0.02% w/w BAC, from about 0.01% to about 0.1% w/w edetate disodium dihydrate and from about 20% to about 50% w/w 0.5 N HCl.

DETAILED DESCRIPTION OF THE INVENTION

[006] The present invention provides room temperature stable epinephrine compositions through novel packaging methods.

[007] The epinephrine may be included in its free form or in the following forms: a salt; an acid addition salt of an ester; an amide; an enantiomer; an isomer; a tautomer; a prodrug; a derivative of an active agent of the present invention; different isomeric forms, including, but not limited to enantiomers and diastereoisomers, both in pure form and in admixture, including racemic

mixtures; and enols. The term "epinephrine" is also meant to encompass derivatives that are produced from another compound of similar structure by the replacement of one atom, molecule or group by another.

[008] As used herein, all numerical values relating to amounts, weights, and the like, that are defined as "about" each particular value is plus or minus 10 %. For example, the phrase "about 10 % w/w" is to be understood as "9 % w/w to 11 % w/w." Therefore, amounts within 10 % of the claimed value are encompassed by the scope of the claims.

[009] All weights herein refer to % w/w or percent weight of the total composition.

[010] The present invention is directed to a method of stabilizing a pharmaceutical composition comprising:

from about 0.1% to about 12% w/w epinephrine base or a salt thereof; and optionally, from about 50% to about 99% w/w water, from about 0.1% to about 2% w/w sodium chloride, from about 0.001 to about 0.02% w/w benzalkonium chloride ("BAC"), from about 0.1% to about 0.5% w/w sodium bisulfite, from about 0.01% to about 0.1% edetate disodium dihydrate and from about 20% to about 50% of 0.5 N hydrochloric acid ("HCl"), or

optionally, from about 10% to about 60% w/w ethanol, from about 11% to about 20% w/w water, from about 2% to about 20 % w/w propylene glycol, from about 0.001% to about 0.02% w/w BAC, from about 0.01% to about 0.1% w/w edetate disodium dihydrate and from about 20% to about 50% w/w 0.5 N HCl,

comprising the steps of:

- a. filling a container with the pharmaceutical composition under a vacuum or a gas overlay;
- b. closing the container;
- c. placing the closed container in a holder and actuator to create an assembled device;
- d. placing the assembled device in a secondary packaging system under one or more conditions selected from the group consisting of with or without a gas overlay, with or without an oxygen absorbing means, and with or without oxygen indicator; and
- e. sealing the secondary packaging system,

wherein the container is selected from the group consisting of a glass vial, a plastic vial, a glass bottle and a plastic bottle and the secondary packaging system is selected from the group consisting of a pouch and a blister package.

[011] The present invention is further directed to a container comprising a pharmaceutical composition comprising:

from about 0.1% to about 12% w/w epinephrine base or a salt thereof; and optionally, from about 50% to about 99% w/w water, from about 0.1% to about 2% w/w sodium chloride, from about 0.001 to about 0.02% w/w benzalkonium chloride ("BAC"), from about 0.1% to about 0.5% w/w sodium bisulfite, from about 0.01% to about 0.1% edetate disodium dihydrate and from about 20% to about 50% of 0.5 N hydrochloric acid ("HCl"), or optionally, from about 10% to about 60% w/w ethanol, from about 11% to about 20% w/w water, from about 2% to about 10% w/w propylene glycol, from about 0.001% to about 0.02% w/w BAC, from about 0.01% to about 0.1% w/w edetate disodium dihydrate and from about 20% to about 50% w/w 0.5 N HCl.

[012] In a preferred embodiment, the gas used in the methods of the present invention is nitrogen or an inert gas. As used herein, the term "inert gas" refers to the gaseous form of an element in which the atoms have a full valence shell. More preferably the inert gas used in the methods of the present invention is selected from the group consisting of helium, neon, argon, krypton, xenon and radon.

[013] In another preferred embodiment, the assembled device is an intranasal device. In a more preferred embodiment, the assembled device is an intranasal device comprising a glass vial, a rubber stopper, a vial holder and an actuator.

[014] In another preferred embodiment, the secondary packaging system contains an oxygen absorbing means. Preferably, the oxygen absorbing means is provided by one or more walls of the secondary packaging system or by an auxiliary oxygen absorber placed between two or more walls of the secondary packaging system. In another preferred embodiment, the oxygen absorbing means is selected from the group consisting of a pellet, a strip, a sheet and a packet.

[015] In a preferred embodiment, the auxiliary oxygen absorber is an iron based or polymer based oxygen absorber. In a more preferred embodiment, the auxiliary oxygen absorber is an iron based oxygen absorber. In an even more preferred embodiment, the iron based auxiliary

oxygen absorber provides absorption of from about 1 to about 3,000 cubic centimeters of oxygen, yet more preferably from about 10 to about 1,000 cubic centimeters of oxygen, even more preferably from about 50 to about 500 cubic centimeters of oxygen and most preferably about 100 cubic centimeters of oxygen.

[016] In another preferred embodiment, the secondary packaging system contains an oxygen indicator. In another preferred embodiment, the oxygen indicator means is selected from the group consisting of a pellet, a strip, a sheet and a packet.

[017] The disclosed embodiments are simply exemplary embodiments of the inventive concepts disclosed herein and should not be considered as limiting, unless the claims expressly state otherwise.

[018] The following examples are intended to illustrate the present invention and to teach one of ordinary skill in the art how to use the compositions of the invention. They are not intended to be limiting in any way.

EXAMPLES

[019] Preferred compositions of the present invention are described in Tables 1 and 2, below.

Table 1 - Composition 1

Ingredients	% w/w	Function
Epinephrine Base	2.962	Active Ingredient
Benzalkonium Chloride	0.010	Preservative
Sodium Chloride	0.600	Tonicity Agent
Sodium Bisulfite	0.150	Anti-Oxidant
Edetate Disodium Dihydrate (EDTA)	0.050	Chelating agent
Hydrochloric acid (0.5N)	32.930	pH modifier
Purified Water	63.298	Vehicle
Solution containing 2.0 N NaOH and 0.5 N HCl	Adjust to pH 4.5 ± 0.1	pH adjustment

Table 2 - Composition 2

Ingredients	% w/w	Function
Epinephrine Base	3.178	Active Ingredient
Benzalkonium Chloride	0.010	Preservative
Dehydrated Alcohol (Ethanol)	40.000	Co-Solvent
Propylene Glycol	5.000	Co-Solvent
Sodium Bisulfite	0.150	Anti-Oxidant
Edetate Disodium Dihydrate	0.050	Chelating agent

Hydrochloric acid (0.5N)	35.471	pH modifier
Purified Water	16.141	Vehicle
Solution containing 2.0 N NaOH and 0.5 N HCl	Adjust pH to 4.5 ± 0.1	pH adjustment

Example 1. Preparation of a Composition of the Present Invention

[020] All the solvents were degassed and purged with nitrogen prior to use. All the excipients including propylene glycol, ethanol, 0.5 N hydrochloric acid, edetate disodium dihydrate, sodium bisulfite and benzalkonium chloride were then dissolved in water while stirring at room temperature. Epinephrine base was then added to the excipient solution. Finally, sodium hydroxide / hydrochloric acid was used to adjust final pH to 4.5 ± 0.1 to create the compositions in Tables 1 and 2, above.

Example 2. Nasal Spray Device Filling Procedure

[021] A composition of the present invention is filled into unit dose nasal spray device vials under vacuum or a gas atmosphere such as nitrogen. Thereafter a rubber stopper is inserted, and a vial holder and actuator attached. These unit dose nasal spray devices are then packaged in a secondary packaging material.

Example 3. Packaging Procedure

[022] The Epinephrine nasal spray devices are packaged in a secondary packaging system (e.g. a pouch, blister or any other enclosed package) under a gas overlay. There are several ways in which the skilled in the art may practice the packaging step. The description below refers to only some embodiments of the invention and is not limiting in any way.

[023] The secondary packaging system may be comprised of oxygen absorbers or may hold an oxygen absorber. The gas overlay may be provided by a tank placed externally to the packaging. The gas is transferred from the tank to the packaging via a hose, tube or other means at a pressure above 0.01 pounds per square inch ("p.s.i."), preferably from about 0.1 to about 5 p.s.i.

[024] If an oxygen absorber is introduced into the packaging system, then the oxygen absorber is placed into the secondary packaging under a gas overlay. The secondary packaging system may also hold an oxygen indicator.

[025] If an oxygen absorber and or oxygen indicator are held in the secondary packaging, then the presence of the oxygen absorber and or oxygen indicator may be assured by visual inspection or an external sensor.

Example 4. Stability Testing

[026] The formulations listed in Table 1 and 2 were filled into unit dose nasal spray device vials under vacuum or a gas overlay such as nitrogen. Thereafter a rubber stopper is inserted, and a vial holder and actuator attached. The assembled devices were packaged in a secondary packaging system (e.g. a pouch, blister or any other enclosed package) under a gas overlay, vacuum or normal atmospheric conditions with the appropriate placement of an oxygen absorber in the pouch. These units were then subjected to stability testing at $55^{\circ}\text{C} \pm 2^{\circ}\text{C}$, $40^{\circ}\text{C} \pm 2^{\circ}\text{C} / 75\% \pm 5\% \text{RH}$ and $25^{\circ}\text{C} \pm 2^{\circ}\text{C} / 60\% \pm 5\% \text{RH}$.

[027] The stability data was collected at zero time point, 3 months and 6 months at 25°C as well as zero-time point, 2 months, 3 months and 6 months at 40°C for the hydro-alcoholic formulation. Furthermore, for the aqueous formulation, the stability data was collected at zero time point, 3months and 6 months at 25°C as well as zero time point, 2 months and 6 months at 40°C . Assay and impurities were detected using high performance liquid chromatography with an ultraviolet detector. The assay was performed at 280 nm and is indicated as a % of initial concentration. For all impurities, analysis was performed at 210 nm and 280nm and expressed as a % area. Amounts of individual impurities are listed in Tables 3 to 6 as a percentage of the area of each formulation along with amount of total impurities. “BQL” refers to “Below Quantifiable Limit” and “ND” refers to “Not Detected.” The BQL designation is used to describe those peaks that are less than 0.05%.

Table 3: Stability Data for Pouched Epinephrine Nasal Spray Formulation of Table 2 stored at $25^{\circ}\text{C} \pm 2^{\circ}\text{C}/60\% \pm 5\%$ relative humidity with oxygen absorbers

(25°C)				
	RRT	T=0	3M	6M
Assay		101.32	92.83	101.79
Appearance		Clear, colorless	Clear, colorless	Clear, colorless

Imp-F	0.19	0.16	1.08	2.32
Epinephrone	1.34	ND	BQL	BQL
Methoxy	1.77	0.07	0.05	0.06
Unknown Impurities (%)	0.21	ND	0.03	0.07
	0.23	ND	ND	BQL
	1.20	ND	ND	BQL
	2.45	ND	ND	BQL
Total Impurities (%)		0.23	1.16	2.45

Table 4: Stability Data for Pouched Epinephrine Nasal Spray Formulation of Table 2 stored at 40°C ± 2°C/75 % ± 5 % relative humidity with oxygen absorbers

(40°C)					
	RRT	T=0	2M	3M	6M
Assay		101.32	83.12	91.78	100.20
Appearance		Clear, colorless	Clear, colorless	Clear, colorless	Clear, colorless
Imp-F	0.19	0.16	4.56	6.40	7.56
Epinephrone	1.34	ND	BQL	BQL	BQL
Methoxy	1.77	0.07	0.06	0.05	0.05
Unknown Impurities (%)	0.20	ND	ND	ND	0.13
	0.21	ND	0.26	0.05	0.08
	0.26	ND	0.13	0.12	0.30
	1.19	ND	0.06	BQL	BQL

	1.71	ND	BQL	BQL	0.05
	1.95	ND	ND	ND	0.07
	2.45	ND	0.06	0.05	0.73
	2.92	ND	ND	ND	0.19
	2.95	ND	ND	ND	0.13
	2.97	ND	ND	ND	0.16
Total Impurities (%)		0.23	5.13	6.67	9.45

Table 5: Stability Data for Pouched Epinephrine Nasal Spray Formulation of Table 1 stored at 25°C ± 2°C/60 % ± 5 % relative humidity with oxygen absorbers

(25°C)				
	RRT	T=0	3M	6M
Assay		101.32	103.80	104.79
Appearance		Clear, colorless	Clear, colorless	Clear, colorless
Imp-F	0.19	0.16	1.54	4.00
Epinephrone	1.34	ND	BQL	BQL
Methoxy	1.77	0.07	0.06	0.05
Unknown Impurities (%)	0.21	ND	BQL	BQL
	0.72	ND	BQL	BQL
	0.83	ND	BQL	ND
	3.09	ND	BQL	0.05
Total impurities (%)		0.23	1.60	4.10

Table 6: Stability Data for Pouched Epinephrine Nasal Spray Formulation of Table 1 stored at 40°C ± 2°C/75 % ± 5 % relative humidity with oxygen absorbers

(40°C)				
	RRT	T=0	2M	6M
Assay		101.32	91.40	103.10
Appearance		Clear, colorless	Clear, colorless	Clear, colorless
Imp-F	0.19	0.16	6.81	6.90
Epinephrone	1.34	ND	BQL	BQL
Methoxy	1.77	0.07	0.06	0.05
Unknown Impurities (%)	0.21	ND	0.09	0.07
	0.70	ND	BQL	ND
	1.71	ND	ND	0.07
	1.92	ND	ND	0.07
	1.95	ND	ND	0.05
	2.00	ND	ND	0.05
	2.09	ND	ND	0.06
	2.27	ND	ND	0.05
	2.41	ND	ND	0.08
	2.84	ND	ND	0.19
	2.90	ND	ND	0.29
2.93	ND	ND	0.31	
2.98	ND	ND	0.25	
Total Impurities (%)		0.23	6.96	8.49

[028] Compositions exhibit less than 20% of total impurities at 25^o C 60% RH ± 5% RH and 40^o C 75 % RH ± 5% RH after 6 months. See, Tables 3-6.

[029] Further, it is known Epinephrine is highly susceptible to oxidative degradation in solutions. Various anti-oxidants were used to stabilize Epinephrine in formulations during accelerated and long-term stability studies. Among the tested anti-oxidants and stabilizers, sodium bisulfite, in

combination with edetate disodium dihydrate, was promising. Sodium bisulfite was used in the above listed formulations as an antioxidant at a concentration of 0.15% w/w to stabilize the formulations. Edetate disodium dihydrate was used as stabilizer at 0.05%w/w. However, sulfite and bisulfite ions are known to react with the optically active side chain of epinephrine, in turn forming Epinephrine Sulfonic acid, also known as impurity F. Temperature plays a significant role in the formation of impurity F, as is evident from the stability data. Most of the marketed products use either sodium bisulfite or sodium metabisulfite as anti-oxidants at higher concentrations to stabilize epinephrine formulations and as a result high amounts of impurity F were seen in those formulations towards the end of their shelf life.

[030] For the hydro-alcoholic formulations, 2.32% and 7.56% of impurity F was observed after a period of 6 months at 25°C / 60%RH ± 5%RH, and 40°C / 75%RH ± 5%RH, respectively. In the case of aqueous formulation, 4.00% and 6.90% of impurity F was observed after a period of 6 months at 25°C / 60%RH ± 5%RH and 40°C / 75%RH ± 5%RH, respectively. The lower percentage of impurity F formation in the case of hydro alcoholic formulations may be attributed to the change in solvent system. All other impurities were within acceptable limits and both the aqueous and hydro-alcoholic formulations were clear and colorless during stability studies. In conclusion, the use of said packaging technique significantly improved the stability of Epinephrine formulations.

WHAT IS CLAIMED IS:

1. A method of stabilizing a pharmaceutical composition comprising from about 1% to about 12% w/w epinephrine comprising the steps of:
 - a. filling a container with the pharmaceutical composition under a vacuum or a gas overlay;
 - b. closing the container;
 - c. placing the closed container in a holder and actuator to create an assembled device;
 - d. placing the assembled device in a secondary packaging system under one or more conditions selected from the group consisting of under a gas overlay, with an oxygen absorbing means and with oxygen indicator; and
 - e. sealing the secondary packaging system,wherein the container is selected from the group consisting of a glass, a plastic vial, a glass bottle and a plastic bottle and the secondary packaging system is selected from the group consisting of a pouch and a blister package.
2. The method of claim 1, wherein the composition further comprises from about 50% to about 99% w/w water, from about 0.1% to about 2% w/w sodium chloride, from about 0.001% to about 0.02% w/w benzalkonium chloride, from about 0.1% to about 0.5% w/w sodium bisulfite from about 0.01% to about 0.1% w/w edetate disodium dihydrate and from about 20% to about 50% w/w 0.5 N hydrochloric acid.
3. The method of claim 1, wherein the composition further comprises from about 10% to about 60% w/w ethanol, from about 11% to about 20% w/w water, from about 2% to about 20 % w/w propylene glycol, from about 0.001% to about 0.02% w/w benzalkonium chloride, from about 0.01% to about 0.1% w/w edetate disodium dihydrate and from about 20% to about 50% w/w 0.5 N hydrochloric acid.
4. The method of claim 1, wherein the gas is selected from the group consisting of helium, neon, argon, krypton, xenon, radon and nitrogen.
5. The method of claim 4, wherein the gas is nitrogen.
6. The method of claim 1, wherein the assembled device comprises a glass vial, a rubber stopper, a vial holder and an actuator.

7. The method of claim 1, wherein the secondary packaging system contains an oxygen absorbing means.
8. The method of claim 7, wherein the oxygen absorbing means is provided by one or more walls of the secondary packaging system.
9. The method of claim 7, wherein the oxygen absorbing means is provided by an auxiliary oxygen absorber displaced between two or more walls of the secondary packaging system.
10. The method of claim 9, wherein the oxygen absorbing means is in a form selected from the group consisting of a pellet, a strip, a sheet and a packet.
11. The method of claim 9, wherein the auxiliary oxygen absorber is iron based or polymer based.
12. The method of claim 11, wherein the auxiliary oxygen absorber is iron based.
13. The method of claim 12, wherein the iron based auxiliary oxygen absorber provides absorption of from about 1 to about 3,000 cubic centimeters of oxygen.
14. The method of claim 12, wherein the iron based auxiliary oxygen absorber provides absorption of from about 10 to about 1,000 cubic centimeters of oxygen.
15. The method of claim 12, wherein the iron based auxiliary oxygen absorber provides absorption of from about 50 to about 500 cubic centimeters of oxygen.
16. The method of claim 12, wherein the iron based auxiliary oxygen absorber provides absorption of about 100 cubic centimeters of oxygen.
17. The method of claim 1, wherein the secondary packaging system contains an oxygen indicator.
18. The method of claim 17, comprising an oxygen indicator in the form of a pellet, a strip, a sheet and a packet.
19. A container comprising a pharmaceutical composition comprising from about 0.1% to about 12% w/w epinephrine base or a salt thereof.
20. The container of claim 19, further comprising from about 50% to about 99% w/w water, from about 0.1% to about 2% w/w sodium chloride, from about 0.001 to about 0.02% w/w benzalkonium chloride, from about 0.1% to about 0.5% w/w sodium bisulfite, from about 0.01% to about 0.1% edetate disodium dihydrate and from about 20% to about 50% of 0.5 N hydrochloric acid.

21. The container of claim 19, further comprising from about 10% to about 60% w/w ethanol, from about 11% to about 20% w/w water, from about 2% to about 20% w/w propylene glycol, from about 0.001% to about 0.02% w/w benzalkonium chloride, from about 0.01% to about 0.1% w/w edetate disodium dihydrate and from about 20% to about 50% w/w 0.5 N hydrochloric acid.
22. The container of claim 21, wherein container is an intranasal device.
23. The container of claim 22, wherein the intranasal device comprises a glass vial, a rubber stopper, a vial holder and an actuator.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 19/12602

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/01, A61K 31/138 (2019.01)
CPC - A61K 31/01, A61K 31/138, A61K 36/61

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	US 2010/0174268 A1 (Wilmot et al.) 08 July 2010 (08.07.2010) Abstract, para [0008], [0018], [0021]-[0022], [0024]-[0025], [0027], [0043], [0048]-[0051], [0054]-[0056], [0059]-[0060]; Figure 1; Figure 2; Figure 3; and Figure 11.	1-18, 23
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Further documents are listed in the continuation of Box C. See patent family annex.

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