(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 January 2014 (03.01.2014)

WIPO | PCT

(10) International Publication Number
WO 2014/004250 A1

(51) International Patent Classification:
A61M 15/06 (2006.01) *B65D 83/06* (2006.01)

(21) International Application Number:
PCT/US2013/046779

(22) International Filing Date:
20 June 2013 (20.06.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/664,013 25 June 2012 (25.06.2012) US
13/776,558 25 February 2013 (25.02.2013) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

WO 2014/004250 A1

(54) Title: POWDER DISPERSION DEVICES AND METHODS

(57) Abstract: A dry powder inhaler may include a powder storage, an inlet channel, a dispersion chamber, and an outlet channel. A geometry of the inhaler may be such that a flow profile is generated within the dispersion chamber that causes an actuator to oscillate, enabling the actuator when oscillating to deaggregate powdered medicament within the dispersion chamber to be aerosolized and entrained by the air and delivered to a patient through the outlet channel.

POWDER DISPERSION DEVICES AND METHODS

CROSS-REFERENCE TO RELATED APPLICATION

This PCT application claims the benefit of U.S. Non-Provisional Patent Application No. 13/773,558, filed February 25, 2013, entitled, "Powder Dispersion Devices and Method" which claim priority to U.S. Provisional Patent Application No. 61/664,013, filed 25 June 2012, entitled "Powder Dispersion Devices and Method," the entirety of which is hereby incorporated by reference for all purposes.

This application is related to U.S. Nonprovisional Patent Application No. 13/776,546, attorney docket number 93933-863197, filed on February 25, 2013, entitled "Powder Dispersion Devices and Method," the entirety of which is hereby incorporated by reference for all purposes.

BACKGROUND

In the field of dry powder inhalers, there is generally a trade-off between performance, as defined by the efficiency of the nominal or loaded dose in the inhaler that is delivered to the lung, and device complexity, in terms of the internal geometry, specifically, the powder flow path that the dose travels as it exits the device. In many instances, inhalers with relatively uncomplicated flow paths may be characterized by poor efficiency, as generally less than 30% of the nominal dose is delivered to the deep lung. Alternatively, inhalers with relatively more complex internal flow paths, may provide increased efficiency, such as less than or equal to 40% of the nominal dose, though the increased complexity of the internal flow path may lead to increased deposition within the inhaler, effectively lowering the overall dose delivered to the patient and contaminating the device.

SUMMARY

This Summary does not in any way limit the scope of the claimed subject matter.

The present disclosure is directed to a powder dispersion mechanism that is compact, breath-actuated, and effective or sufficient at promoting efficient particle dispersion across a range of doses such as from, for example, low microgram doses to doses requiring many milligrams. Accordingly, in some embodiments, a powder dispersion mechanism is disclosed that employs a bead contained within a "small" volume dispersion chamber, with a straight flow path, and that

is breath-actuated. The bead may oscillate, generally linearly in certain embodiments, along an axis of the dispersion chamber when the patient inhales through the device, such that it does not require an energy source other than a patient's inspiratory maneuver to function. This may be referred to as "passive" bead activation or actuation. However, the present disclosure is not so limiting. For example, bead activation may be "active," where an external energy source is coupled with the patients inhalation flow stream to induce oscillation.

In an aspect, a dry powder inhaler is disclosed. The dry powder inhaler may include a powder storage that is configured to hold a powdered medicament. The dry powder inhaler may include an inlet channel that is adapted to receive air and powdered medicament from the powder storage. The dry powder inhaler may include a dispersion chamber that is adapted to receive air and powdered medicament from the inlet channel, the chamber holding an actuator that is movable within the dispersion chamber. The dry powder inhaler may include an outlet channel through which air and powdered medicament exit the inhaler to be delivered to a patient. Geometry of the inhaler may be such that a flow profile is generated within the dispersion chamber that causes the actuator to oscillate, thus enabling the oscillating actuator to deaggregate the powdered medicament passing through the dispersion chamber to be entrained by the air and delivered to the patient through the outlet channel.

In an aspect, a method for aerosolizing a powdered medicament is disclosed. The method may include providing an inhaler comprising an inlet channel, a chamber that is adapted to receive air and powdered medicament from the inlet channel, an actuator disposed in the chamber, and an outlet channel. The method may include supplying a powdered medicament to the inlet channel. The method may include inducing air to flow through the outlet channel to cause air and the powdered medicament to enter into the chamber through the inlet channel, and to cause the actuator to oscillate within the chamber to effectively disperse powdered medicament passing through the chamber to be entrained by the air and delivered to the patient through the outlet channel.

In an aspect, a powder dispersion device is disclosed. The powder dispersion device may include a housing having a central, longitudinal axis. The housing may include a chamber, a flow inlet in fluid communication with the chamber and a flow outlet in fluid communication with the chamber. The powder dispersion device may include a powder storage compartment that is configured to store a powdered medicament for introduction into the chamber through the flow

inlet. The powder dispersion device may include a bead positioned within the chamber such that it may rapidly move back and forth within the chamber along the longitudinal axis. The bead may be sized in dimension so that the bead when oscillating deagglomerates the powdered medicament so that a desired aerodynamic particle size distribution is achieved upon exit from the flow outlet.

In an aspect, a method for aerosolizing a powder is disclosed. The method may include providing a powder dispersion device including a housing having a central, longitudinal axis, the housing may include a chamber, a flow inlet in fluid communication with the chamber and a flow outlet in fluid communication with the chamber, and an actuator positioned within the chamber. The actuator may be selected to have a size such that upon oscillation it produces a desired range of aerodynamic particle sizes of the powdered medicament. The method may include introducing the amount of powdered medicament into the chamber. The method may include inducing a flow through the chamber and out the flow outlet. The flow may enter the chamber from the flow inlet and rapidly expand when entering the chamber. The flow through the chamber may cause the actuator to oscillate within the chamber along the longitudinal axis to aerosolize and deagglomerate the powdered medicament to the desired range of aerodynamic particle sizes so that a desired aerodynamic particle size distribution is achieved upon exit from the flow outlet.

BRIEF DESCRIPTION OF THE DRAWINGS

A further understanding of the nature and advantages of various embodiments may be realized by reference to the following figures. In the appended figures, similar components or features may have the same reference label. Further, various components of the same type may be distinguished by following the reference label by a dash and a second label that distinguishes among the similar components. When only the first reference label is used in the specification, the description is applicable to any one of the similar components having the same first reference label irrespective of the second reference label.

FIG. 1 shows a cross-section of an example tubular body having an inlet and a dispersion chamber.

FIG. 2 shows the tubular body of **FIG. 1** in multiple views.

FIG. 3 shows a bead positioned within a chamber of the tubular body of **FIG. 1**.

FIG. 4 shows a first view of an example powder dispersion device in cross-section.

FIG. 5 shows a perspective view of the device of **FIG. 4**.

FIG. 6 shows a first example experimental set-up in accordance with the present disclosure.

FIG. 7 shows a second example experimental set-up in accordance with the present disclosure.

FIG. 8 shows a second view of the device of **FIG. 4** in cross-section.

FIG. 9 shows a third view of the device of **FIG. 4** in cross-section.

FIG. 10 shows the device of **FIG. 4** incorporated internally into an existing inhaler system.

FIG. 11 shows a simplified, conceptual, example schematic diagram of the device of **FIG. 4** in multiple configurations.

FIG. 12 shows a first stage-by-stage particle deposition distribution profile.

FIG. 13 shows a second stage-by-stage particle deposition distribution profile.

FIG. 14 shows a first perspective view of a first example powder dispersion device.

FIG. 15 shows a second perspective view of the device of **FIG. 14**.

FIG. 16 shows a first end view of the device of **FIG. 14**.

FIG. 17 shows a second end view of the device of **FIG. 14**.

FIG. 18 shows a first perspective view of a second housing of the device of **FIG. 14**.

FIG. 19 shows a second perspective view of the housing of **FIG. 18**.

FIG. 20 shows a first end view of the housing of **FIG. 18**.

FIG. 21 shows a second end view of the housing of **FIG. 18**.

FIG. 22 shows a first perspective view of a first housing of the device of **FIG. 14**.

FIG. 23 shows a second perspective view of the housing of **FIG. 22**.

FIG. 24 shows a first end view of the housing of **FIG. 22**.

FIG. 25 shows a second end view of the housing of **FIG. 22**.

FIG. 26 shows a first perspective view of a second example powder dispersion device.

FIG. 27 shows a second perspective view of the device of **FIG. 26**.

FIG. 28 shows a first end view of the device of **FIG. 26**.

FIG. 29 shows a second end view of the device of **FIG. 26**.

FIG. 30 shows a first perspective view of a second housing of the device of **FIG. 26**.

FIG. 31 shows a second perspective view of the housing of **FIG. 30**.

FIG. 32 shows a first end view of the housing of **FIG. 30**.

FIG. 33 shows a second end view of the housing of **FIG. 30**.

FIG. 34 shows a first perspective view of a first housing of the device of **FIG. 26**.

FIG. 35 shows a second perspective view of the housing of **FIG. 34**.

FIG. 36 shows a first end view of the housing of **FIG. 34**.

FIG. 37 shows a second end view of the housing of **FIG. 34**.

FIG. 38 shows a first perspective view of a third example powder dispersion device.

FIG. 39 shows a second perspective view of the device of **FIG. 38**.

FIG. 40 shows a third perspective view of the device of **FIG. 38**.

FIG. 41 shows a fourth perspective view of the device of **FIG. 38**.

FIG. 42 shows a fifth perspective view of the device of **FIG. 38**.

FIG. 43 shows a sixth perspective view of the device of **FIG. 38**.

DETAILED DESCRIPTION

The present disclosure relates to the field of pulmonary drug delivery, and more specifically to dry powder inhalers that deliver a medicament into the lungs of a patient. In example embodiments, such a powder dispersion mechanism may comprise of a bead positioned within a chamber that is arranged and configured to induce a sudden, rapid, or otherwise abrupt expansion of a flow stream upon entering the chamber.

In general, the chamber may be coupled to any form or type of dose containment system or source that supplies powdered medicament into the chamber. For example, in one embodiment, the dose containment source may comprise or be incorporated within, for example, a powder dispersion device such as the TOBI® Podhaler®, the FORADIL® Aerolizer®, the SPIRIVA® HandiHaler®, the FLOVENT® Diskus®, the SEREVENT® Diskus®, the ADVAIR® Diskus®, the ASMANEX® Twisthaler®, the SYMBICORT® Turbuhaler®, the Budelin® Novolizer®, and many others. The bead when oscillating within the chamber may then disrupt and aerosolize powder agglomerates within the chamber, as passed from the source, to provide for more effective deposition of medicament into the lungs of a patient. Still other embodiments are possible.

Referring now to **FIG. 1**, a cross-section of an example tubular body **100** having an inlet **102** and a dispersion chamber **104** is shown according to the principles of the present disclosure. In this example, a fluid (e.g., air) flow path of the inlet **102** is defined by a first internal diameter **106**, and a fluid flow path of the chamber **104** is defined by a second internal diameter **108**. Although shown approximately constant in **FIG. 1**, at least one of the first internal diameter **106** and the second internal diameter **108** may vary in dimension as defined with respect to a longitudinal

axis **L** of the tubular body **100**. In addition to providing desirable fluid flow characteristics, as discussed further below, these configurable dimensions may be defined such as to provide for a draft angle for injection molding.

For example, the first internal diameter **106** may taper inwardly, towards and as measured with reference to the longitudinal axis **L**, beginning approximately at a reference point **L1** of the longitudinal axis **L** and ending approximately at a reference point **L2** of the longitudinal axis **L**. Other embodiments are possible. For example, the first internal diameter **106** may taper inwardly towards the longitudinal axis **L** beginning approximately at the reference point **L2**, and ending approximately at the reference point **L1**. In a similar manner, the second internal diameter **108** may taper inwardly, towards and as measured with reference to the longitudinal axis **L**, beginning approximately at the reference point **L2**, and ending approximately at a reference point **L3** of the longitudinal axis **L**. In another embodiment, the second internal diameter **108** may taper inwardly towards the longitudinal axis **L** beginning approximately at the reference point **L3** and ending approximately at the reference point **L2**. Still other embodiments are possible.

For example, it is contemplated that an internal structural profile of at least one of the inlet **102** and the chamber **104** may be defined, as desired, such as to obtain or otherwise realize particular fluid flow characteristics within the tubular body **100**. For example, as depicted in **FIG. 1**, the tubular body **100** may be arranged and configured such that a sudden flow stream expansion may occur when the relatively "small" cross-sectional fluid flow path of or defined by the inlet **102** opens abruptly into a "larger" cross-sectional fluid flow path of or defined by the chamber **104**. In this example, and as discussed in further detail below, high-energy forces may develop by within the chamber **104.** In one aspect, this may be due to relatively "low" pressure regions induced by relatively "high" velocity fluid entering the chamber **104**, where a portion of the flow stream detaches. Other mechanisms may contribute to the development of high-energy fluid flow within the chamber **104** as well. Further, such high-energy fluid flow, along with mechanical impact forces, may disrupt and aerosolize medicament powder agglomerates within the chamber **104** to provide for more effective deposition of medicament into the lungs of a patient.

Still other embodiments of the example tubular body **100** are possible as well. For example, in some embodiments, a difference between the reference point **L1** of the longitudinal axis **L** and the reference point **L2** may approach zero (0). In this example, the tubular body **100** may consist

only of the chamber **104**. Here, instead of an "inlet tube," the tubular body **100** may consist of an "inlet hole."

Referring now additionally to **FIG. 2**, the tubular body **100** of **FIG. 1** is shown in multiple views. In particular, the tubular body **100** of **FIG. 1** is shown in perspective view **202**, side view **204**, and cross-section view **206**. In this example, the cross-section view **206** is taken along an axis **A-A** of the side view **204**. Additionally, and as illustrated in **FIG. 1**, the fluid flow path of or defined by the inlet **102** is coaxially aligned with the fluid flow path of or defined by the chamber **104**. This is in contrast with a substantially "off-axis" alignment of the inlet **102** and the chamber **104**, illustrated conceptually in **FIG. 2** by a finite angle **B** defined with respect to the longitudinal axis **L**. A coaxial alignment may provide a number of advantages over such an "off-axis" alignment, such as facilitating or otherwise assisting in the development of high-energy forces within the chamber **104**. The coaxial alignment may further enable the efficient transfer of powder into the chamber **104**. However, other embodiments are possible. For example, in some embodiments, a central longitudinal axis of the inlet **102** may be at least slightly offset yet parallel to a central longitudinal axis of the chamber **104**. Other benefits and/or advantages associated with the alignment of the inlet **102** and the chamber **104** may be understood from the preceding description provided in connection with **FIGS. 1-2**, and from the following description provided in connection with **FIGS. 3-42**.

For example, referring now additionally to **FIG. 3**, a bead **302** may be positioned within the chamber **104** of the tubular body **100** of **FIGS. 1-2**. In this example, the bead **302** may be approximately spherical, at least on the macroscale, and oscillate in a manner similar to that described in U.S. Application No. 13/469,963, filed 11 May 2012, and entitled "Bead-Containing Dry Powder Inhaler," the complete disclosure of which is herein incorporated by reference.

Further, a relationship between the diameter **304** of the bead **302**, the first internal diameter **106** of the inlet **102**, and the second internal diameter **108** of the chamber **104** may be of the form: $d_{bead}^2 \cong (d_{inlet})(d_{chamber})$. In general, this relationship may hold in scenarios where d_{bead} and d_{inlet} and $d_{chamber}$ are of similar order of magnitude. For example, in one embodiment d_{bead} may be about 5 mm, d_{inlet} may be about 3.39 mm, and $d_{chamber}$ may be about 7.37 mm, within manufacturing tolerance. In this example, a length of the chamber **104**, $l_{chamber}$, such as defined by a distance approximately between the reference point **L2** and the reference point **L3** of the

longitudinal axis **L** (see **FIG. 1**), may be less than or equal to about less than twice the diameter **304** of the bead **302**.

In some embodiments, a preferred diameter of the bead **302** may be within a range of about 0.5 mm to about 15 mm. The relationship $d_{bead}^2 \cong (d_{inlet})(d_{chamber})$ may then be used to determine d_{inlet} and $d_{chamber}$. In some embodiments, a preferred diameter of the bead **302** may be within a range of about 1.5 mm to about 6 mm. Still other embodiments are possible.

In some embodiments, a preferred ratio of the diameter of the chamber **104** to that of the inlet **102** may be within a range of about 1.1 to about 3.0. At respective extremes, the relationship $d_{bead}^2 \cong (d_{inlet})(d_{chamber})$ may thus be rewritten as, based on substitution, $d_{bead}^2 \cong (d_{chamber})^2/1.1$ and $d_{bead}^2 \cong (d_{chamber})^2/3$.

In some embodiments, it may be preferred that the length of the chamber **104**, $l_{chamber}$, is about 1.2 times to about 5 times the diameter of the bead **302**. In other embodiments, it may be preferred that the length of the chamber **104**, $l_{chamber}$, is about 1.5 times to about 3 times the diameter of the bead **302**. In other embodiments, it may be preferred that the length of the chamber **104**, $l_{chamber}$, is about 2 times to about 2.5 times the diameter of the bead **302**.

In example embodiments, the length of the chamber **104** may determine whether the bead **302** freely oscillates, without physical interaction with ends of the chamber **104**. In this manner, the length of the chamber **302** may facilitate free oscillation of the bead **302**. A substantially "freely" oscillating bead **302** may even more effectively disrupt and aerosolize powder agglomerates within the chamber **104**, as passed from the source, to provide for more effective deposition of medicament into the lungs of a patient.

For example, a study was performed to evaluate the length of the chamber **104** and to determine whether a particular length of chamber **104** would allow the bead **302** to "freely" oscillate within the chamber **104**. In particular, using a device similar to the device **400**, a bead of fixed diameter, about 4 mm, was used across the study. The length of the chamber however was varied as 1.5x, 2.0x, 3.0x, 3.5x, 4.0x, and 9.8x diameter of the bead. In this manner, the study included evaluating at least six different device configurations. In general, it was found that oscillation of the bead within the chamber was similar for lengths up to and including 3.5x diameter of the bead, yet varied for lengths 4.0x and 9.8x diameter of the bead. For example, a similar flow rate through the device was needed to allow the bead to "freely" oscillate within the chamber at least for chamber lengths of 2.0x and 3.0x diameter of the bead. However, a "higher" or "greater"

flow rate was needed to allow the bead to "freely" oscillate within the chamber for a chamber length of 4.0x diameter of the bead. Further the bead did not appear to "freely" oscillate within the chamber for a chamber length of 9.8x diameter of the bead, for any flow rate through the device. At this chamber length, the bead may not be fully influenced by pressure at the inlet of the device. Other mechanisms may be possible as well.

In another example, a study was performed to evaluate the length of the chamber **104** and to determine whether a particular diameter of the bead **302**, for a fixed length of the chamber **104**, would allow the bead **302** to "freely" oscillate within the chamber **104**. In particular, using a device similar to the device **400**, a chamber of fixed length and diameter, about 10 mm length and about 6 mm diameter, was used across the study. The diameter of the bead however was varied as 3.7 mm, 4 mm, and 4.7 mm. In this manner, the study included evaluating at least three different device configurations. In general, it was found that oscillation of the bead within the chamber for a 4 mm bead did "freely" oscillate within the chamber at a first particular flow rate. At this flow rate for this device configuration, a distinct audible pitch produced by oscillation of the bead within the chamber may be observed. Operation and characteristics of the device **400** having a 4 mm bead diameter is discussed in further detail below.

Further, it was found that oscillation of the bead within the chamber for a 3.7 mm bead did "freely" oscillate within the chamber **104** at or about the first particular flow rate. However, a flow rate greater than the first particular flow rate was needed to observe an audible pitch similar to the distinct audible pitch produced by oscillation of the bead within the chamber for the 4 mm bead. Here, a greater flow rate may be required to produce the audible pitch due to a reduced effective cross-sectional area of the 3.7 mm bead, as compared to the 4 mm bead. Other mechanisms may be possible as well. Further, it was found that oscillation of the bead within the chamber for a 4.7 mm bead did not "freely" oscillate within the chamber at or about the first particular flow rate. Here, the effective cross-sectional area of the 4.7 mm bead may be too large such as to prohibit "free" oscillation within the chamber. Other mechanisms may be possible as well.

Continuing with the above dimensional example, the length of the chamber **104** may thus be about 10 mm. In this example, and when the power law relationship between the diameters of the bead **302**, the inlet **102**, and the chamber **104** is observed, the bead **302** may oscillate within the chamber **104** generally without experiencing continuous physical collisions with either end of the

chamber **104**. Such an arrangement may further facilitate development of high energy forces within the chamber **104** to more efficiently disrupt and aerosolize medicament powder agglomerates within the chamber **104** for more effective deposition of medicament into the lungs of a patient.

In general, high-energy forces may refer to dispersive forces that may strip drug from the bead **302**, and deaggregation or deagglomeration forces that may break-up or break-apart aggregates in powder fed into the chamber **104**. Here, the terms deaggregation or deagglomeration, and aggregation or agglomeration may be used interchangeably. The high-energy forces may be generated by the bead **302** when rapidly oscillating within the chamber **104** via formation of turbulence and eddies within the chamber **104**, compression and decompression zones within the chamber **104**, and the like.

When a DPF (Dry Powder Formulation) is passed through the chamber **104** containing the bead **302**, which is oscillating "rapidly" such as, for example, at a frequency greater than about 100 Hz, these high frequency oscillations of the bead **302** may produce high-energy forces within the chamber **104**. This may disrupt agglomerates of drug particles that may be held together at least by cohesive forces, such as by van der Waals forces, static electrical forces, etc. Additionally, physical collisions between the bead **302**, when rapidly oscillating, and potentially aggregated or agglomerated powder particles as they pass through the chamber **104** may promote de-aggregation of the agglomerates. Details associated with interaction(s) between the bead **302** and powder particles as transferred through the chamber **104** are discussed further below. The oscillation frequency may typically be between about 1 to about 1,000 Hz, and may preferably be between about 25 to about 500 Hz, although other frequencies may also occur. However, in some cases, the oscillation frequency could be up to about 2,000 Hz.

The powder dispersion devices and methods in accordance with the present disclosure may be applicable in many scenarios. For example, APIs (Active Pharmaceuticals Ingredients), or active agents, that may be used with any of the mechanisms described within the context of the present disclosure may include analgesic anti-inflammatory agents such as, acetaminophen, aspirin, salicylic acid, methyl salicylate, choline salicylate, glycol salicylate, 1-menthol, camphor, mefenamic acid, fluphenamic acid, indomethacin, diclofenac, alclofenac, ibuprofen, ketoprofen, naproxene, pranoprofen, fenoprofen, sulindac, fenbufen, clidanac, flurbiprofen, indoprofen,

protizidic acid, fentiazac, tolmetin, tiaprofenic acid, bendazac, bufexamac, piroxicam, phenylbutazone, oxyphenbutazone, clofezone, pentazocine, mepirizole, and the like.

Other drugs that may be used include drugs having an action on the central nervous system, for example sedatives, hypnotics, antianxiety agents, analgesics and anesthetics, such as, chloral, buprenorphine, naloxone, haloperidol, fluphenazine, pentobarbital, phenobarbital, secobarbital, amobarbital, cydobarbital, codeine, lidocaine, tetracaine, dyclonine, dibucaine, cocaine, procaine, mepivacaine, bupivacaine, etidocaine, prilocaine, benzocaine, fentanyl, nicotine, and the like.

Local anesthetics such as, benzocaine, procaine, dibucaine, lidocaine, and the like.

Still other drugs include antihistaminics or antiallergic agents such as, diphenhydramine, dimenhydrinate, perphenazine, triprolidine, pyrilamine, chlorcyclizine, promethazine, carbinoxamine, tripelennamine, brompheniramine, hydroxyzine, cyclizine, meclizine, clorprenaline, terfenadine, chlorpheniramine, and the like.

Anti-allergenics such as, antazoline, methapyrilene, chlorpheniramine, pyrilamine, pheniramine, and the like.

Decongestants such as, phenylephrine, ephedrine, naphazoline, tetrahydrozoline, and the like.

Other drugs include antipyretics such as, aspirin, salicylamide, non-steroidal anti-inflammatory agents, and the like.

Antimigrane agents such as, dihydroergotamine, pizotyline, and the like.

Acetonide anti-inflammatory agents, such as hydrocortisone, cortisone, dexamethasone, fluocinolone, triamcinolone, medrysone, prednisolone, flurandrenolide, prednisone, halcinonide, methylprednisolone, fludrocortisone, corticosterone, paramethasone, betamethasone, ibuprophen, naproxen, fenoprofen, fenbufen, flurbiprofen, indoprofen, ketoprofen, suprofen, indomethacin, piroxicam, aspirin, salicylic acid, diflunisal, methyl salicylate, phenylbutazone, sulindac, mefenamic acid, meclofenamate sodium, tolmetin, and the like.

Muscle relaxants such as, tolperisone, baclofen, dantrolene sodium, cyclobenzaprine, and the like.

Steroids may also be used, including androgenic steroids, such as, testosterone, methyltestosterone, fluoxymesterone, estrogens such as, conjugated estrogens, esterified estrogens, estropipate, 17-β estradiol, 17-β estradiol valerate, equilin, mestranol, estrone, estriol, 17β ethinyl estradiol, diethylstilbestrol, progestational agents, such as, progesterone, 19-

norprogesterone, norethindrone, norethindrone acetate, melengestrol, chlormadinone, ethisterone, medroxyprogesterone acetate, hydroxyprogesterone caproate, ethynodiol diacetate, norethynodrel, 17-α hydroxyprogesterone, dydrogesterone, dimethisterone, ethinylestrenol, norgestrel, demegestone, promegestone, megestrol acetate, and the like.

Respiratory agents that may be used include: theophilline and β2 -adrenergic agonists, such as, albuterol, terbutaline, metaproterenol, ritodrine, carbuterol, fenoterol, quinterenol, rimiterol, solmefamol, soterenol, tetroquinol, tacrolimus, and the like.

Sympathomimetics such as, dopamine, norepinephrine, phenylpropanolamine, phenylephrine, pseudoephedrine, amphetamine, propylhexedrine, arecoline, and the like.

Antimicrobial agents that may be used include antibacterial agents, antifungal agents, antimycotic agents and antiviral agents; tetracyclines such as, oxytetracycline, penicillins, such as, ampicillin, cephalosporins such as, cefalotin, aminoglycosides, such as, kanamycin, macrolides such as, erythromycin, chloramphenicol, iodides, nitrofrantoin, nystatin, amphotericin, fradiomycin, sulfonamides, purrolnitrin, clotrimazole, itraconazole, miconazole chloramphenicol, sulfacetamide, sulfamethazine, sulfadiazine, sulfamerazine, sulfamethizole and sulfisoxazole; antivirals, including idoxuridine; clarithromycin; and other anti-infectives including nitrofurazone, and the like.

Antihypertensive agents that may be used include clonidine, α-methyldopa, reserpine, syrosingopine, rescinnamine, cinnarizine, hydrazine, prazosin, and the like.

Other possible drugs include antihypertensive diuretics such as, chlorothiazide, hydrochlorothrazide, bendoflumethazide, trichlormethiazide, furosemide, tripamide, methylclothiazide, penfluzide, hydrothiazide, spironolactone, metolazone, and the like.

Cardiotonics such as, digitalis, ubidecarenone, dopamine, and the like.

Coronary vasodilators such as, organic nitrates such as, nitroglycerine, isosorbitol dinitrate, erythritol tetranitrate, and pentaerythritol tetranitrate, dipyridamole, dilazep, trapidil, trimetazidine, and the like.

Vasoconstrictors such as, dihydroergotamine, dihydroergotoxine, and the like.

β-blockers or antiarrhythmic agents such as, timolol pindolol, propranolol, and the like.

Humoral agents such as, the prostaglandins, natural and synthetic, for example PGE1, PGE2α, and PGF2α, and the PGE1 analog misoprostol, and the like.

Antispasmodics such as, atropine, methantheline, papaverine, cinnamedrine, methscopolamine, and the like.

Other drugs that may be used include calcium antagonists and other circulatory organ agents, such as, aptopril, diltiazem, nifedipine, nicardipine, verapamil, bencyclane, ifenprodil tartarate, molsidomine, clonidine, prazosin, and the like.

Anti-convulsants such as, nitrazepam, meprobamate, phenytoin, and the like.

Agents for dizziness such as, isoprenaline, betahistine, scopolamine, and the like.

Tranquilizers such as, reserprine, chlorpromazine, and antianxiety benzodiazepines such as, alprazolam, chlordiazepoxide, clorazeptate, halazepam, oxazepam, prazepam, clonazepam, flurazepam, triazolam, lorazepam, diazepam, and the like.

Antipsychotics such as, phenothiazines including thiopropazate, chlorpromazine, trifluprom azine, mesoridazine, piperracetazine, thioridazine, acetophenazine, fluphenazine, perphenazine, trifluoperazine, and other major tranqulizers such as, chlorprathixene, thiothixene, haloperidol, bromperidol, loxapine, and molindone, as well as, those agents used at lower doses in the treatment of nausea, vomiting, and the like.

Drugs for Parkinson's disease, spasticity, and acute muscle spasms such as levodopa, carbidopa, amantadine, apomorphine, bromocriptine, selegiline (deprenyl), trihexyphenidyl hydrochloride, benztropine mesylate, procyclidine hydrochloride, baclofen, diazepam, dantrolene, and the like.

Respiratory agents such as, codeine, ephedrine, isoproterenol, dextromethorphan, orciprenaline, ipratropium bromide, cromglycic acid, and the like.

Non-steroidal hormones or antihormones such as, corticotropin, oxytocin, vasopressin, salivary hormone, thyroid hormone, adrenal hormone, kallikrein, insulin, oxendolone, and the like.

Vitamins such as, vitamins A, B, C, D, E and K and derivatives thereof, calciferols, mecobalamin, and the like, for use dermatologically for example.

Enzymes such as, lysozyme, urokinaze, and the like.

Herb medicines or crude extracts such as, Aloe vera, and the like.

Antitumor agents such as, 5-fluorouracil and derivatives thereof, krestin, picibanil, ancitabine, cytarabine, and the like.

Anti-estrogen or anti-hormone agents such as, tamoxifen or human chorionic gonadotropin, and the like.

Miotics such as pilocarpine, and the like.

Cholinergic agonists such as, choline, acetylcholine, methacholine, carbachol, bethanechol, pilocarpine, muscarine, arecoline, and the like.

Antimuscarinic or muscarinic cholinergic blocking agents such as, atropine, scopolamine, homatropine, methscopolamine, homatropine methylbromide, methantheline, cyclopentolate, tropicamide, propantheline, anisotropine, dicyclomine, eucatropine, and the like. Mydriatics such as, atropine, cyclopentolate, homatropine, scopolamine, tropicamide, eucatropine, hydroxyamphetamine, and the like.

Psychic energizers such as 3-(2-aminopropy)indole, 3-(2-aminobutyl)indole, and the like, such as ipratropium, tiotropium, glycopyrrolate (glycopyrronium), aclidinium, and the like.

Antidepressant drugs such as, isocarboxazid, phenelzine, tranylcypromine, imipramine, amitriptyline, trimipramine, doxepin, desipramine, nortriptyline, protriptyline, amoxapine, maprotiline, trazodone, and the like.

Anti-diabetics such as, insulin, and anticancer drugs such as, tamoxifen, methotrexate, and the like.

Anorectic drugs such as, dextroamphetamine, methamphetamine, phenylpropanolamine, fenfluramine, diethylpropion, mazindol, phentermine, and the like. Anti-malarials such as, the 4-aminoquinolines, alphaaminoquinolines, chloroquine, pyrimethamine, and the like.

Anti-ulcerative agents such as, misoprostol, omeprazole, enprostil, and the like.

Antiulcer agents such as, allantoin, aldioxa, alcloxa, N-methylscopolamine methylsuflate, and the like.

Antidiabetics such as insulin, and the like. Anti-cancer agent such as, cis-platin, actinomycin D, doxorubicin, vincristine, vinblastine, etoposide, amsacrine, mitoxantrone, tenipaside, taxol, colchicine, cyclosporin A, phenothiazines or thioxantheres, and the like.

Other possibilities include those for use with vaccines, one or more antigens, such as, natural, heat-killer, inactivated, synthetic, peptides and even T cell epitopes (e.g., GADE, DAGE, MAGE, etc.), and the like.

Example therapeutic or active agents also include drugs of molecular weight from about 40 to about 1,100 including the following: Hydrocodone, Lexapro, Vicodin, Effexor, Paxil, Wellbutrin, Bextra, Neurontin, Lipitor, Percocet, Oxycodone, Valium, Naproxen, Tramadol, Ambien, Oxycontin, Celebrex, Prednisone, Celexa, Ultracet, Protonix, Soma, Atenolol, Lisinopril, Lortab, Darvocet, Cipro, Levaquin, Ativan, Nexium, Cyclobenzaprine, Ultram,

Alprazolam, Trazodone, Norvasc, Biaxin, Codeine, Clonazepam, Toprol, Zithromax, Diovan, Skelaxin, Klonopin, Lorazepam, Depakote, Diazepam, Albuterol, Topamax, Seroquel, Amoxicillin, Ritalin, Methadone, Augmentin, Zetia, Cephalexin, Prevacid, Flexeril, Synthroid, Promethazine, Phentermine, Metformin, Doxycycline, Aspirin, Remeron, Metoprolol, Amitriptyline, Advair, Ibuprofen, Hydrochlorothiazide, Crestor, Acetaminophen, Concerta, Clonidine, Norco, Elavil, Abilify, Risperdal, Mobic, Ranitidine, Lasix, Fluoxetine, Coumadin, Diclofenac, Hydroxyzine, Phenergan, Lamictal, Verapamil, Guaifenesin, Aciphex, Furosemide, Entex, Metronidazole, Carisoprodol, Propoxyphene, Digoxin, Zanaflex, Clindamycin, Trileptal, Buspar, Keflex, Bactrim, Dilantin, Flomax, Benicar, Baclofen, Endocet, Avelox, Lotrel, Inderal, Provigil, Zantac, Fentanyl, Premarin, Penicillin, Claritin, Reglan, Enalapril, Tricor, Methotrexate, Pravachol, Amiodarone, Zelnorm, Erythromycin, Tegretol, Omeprazole, and Meclizine.

Monospecific antibodies, such as monoclonal antibodies and phages, and the like.

Cholinesterase family of enzymes, such as acetalcholinesterase and butyryl acetalcholinesterase, and the like

Other active agents include those listed as BCS Class II agents, such as Glibenclamide for example, and the like.

The active agents mentioned above may be used in combination as required. Moreover, the above drugs may be used either in the free form or, if capable of forming salts, in the form of a salt with a suitable acid or base. When the drugs have a carboxyl group, their esters may be employed.

It is contemplated that at least all possible types of dry powder formulations for pulmonary delivery are within the scope of the present disclosure.

This may include, but is not limited to, pure micronized drug formulations, no excipients are included (e.g., drug particles may or may not be crystalline, the formulation may include one or more drugs, co-crystals – multiple APIs in a single crystalline particle); binary, ternary, etc., formulations where the drug is but one component of the formulation, two or more drugs are blended together, and which also may or may not include one or more excipients.; and engineered powders including low density powders, spray-dried powder, etc., designed to be dispersed effectively relative to traditional micronized formulations, the PulmoSphere® technology used in the TOBI® Podhaler®. However, the oscillating bead dispersion mechanism

as described throughout the present disclosure may be used with other aerosol dispersion methods, not just powders, including but not limited to, aqueous and/or propellant-based inhalers, such as liquid or powder nebulizers, pMDIs and powder or liquid nasal sprays. Still other embodiments are possible.

Further it is contemplated that the dry powder formulations for pulmonary delivery in accordance with the present disclosure may be used to counter effects of various types of agents that may at least initially affect the respiratory system including, but are not limited to: harassing agents such as tear agents and vomiting agents; incapacitating agents such as psychological agents; and lethal agents such as blister agents, blood agents, choking (pulmonary) agents, and nerve agents.

Examples of tear agents may include a-Chlorotoluene, Benzyl bromide, Bromoacetone (BA), Bromobenzylcyanide (CA), Bromomethylethyl ketone, Capsaicin (OC), Chloracetophenone (MACE; CN), Chloromethyl chloroformate, Dibenzoxazepine (CR), Ethyl iodoacetate, Ortho-chlorobenzylidene malononitrile (Super tear gas; CS), Trichloromethyl chloroformate, Xylyl bromide, and the like.

Examples of vomiting agents may include Adamsite (DM), Diphenylchloroarsine (DA), Diphenylcyanoarsine (DC), and the like.

Examples of psychological agents may include 3-Quinuclidinyl benzilate (BZ), Phencyclidine (SN), Lysergic acid diethylamide (K), and the like.

Examples of blister agents may include nitrogen mustards such as Bis(2-chloroethyl)ethylamine (HN1), Bis(2-chloroethyl)methylamine (HN2), Tris(2-chloroethyl)amine (HN3), Sulfur Mustards such as 1,2-Bis(2-chloroethylthio) ethane (Sesquimustard; Q), 1,3-Bis(2-chloroethylthio)-n-propane,1,4-Bis(2-chloroethylthio)-n-butane,1,5-Bis(2-chloroethylthio)-n-pentane, 2-Chloroethylchloromethylsulfide, Bis(2-chloroethyl) sulfide (Mustard gas; HD), Bis(2-chloroethylthio) methane, Bis(2-chloroethylthiomethyl) ether, Bis(2-chloroethylthioethyl) ether (O Mustard; T), and the like, and Arsenicals such as Ethyldichloroarsine (ED), Methyldichloroarsine (MD), Phenyldichloroarsine (PD), 2-Chlorovinyldichloroarsine (Lewisite; L), and the like.

Examples of blood agents may include Cyanogen chloride (CK), Hydrogen cyanide (AC), Arsine (SA), and the like.

Examples of choking agents may include but are not limited to, Chlorine (CL); Chloropicrin (PS), Diphosgene (DP), Phosgene (CG), and the like.

Examples of nerve agents may include G series such as Tabun (GA), Sarin (GB), Soman (GD), Cyclosarin (GF), GV series such as Novichok agents, GV (nerve agent), V series such as VE, VG, VM, and the like.

As mentioned above, the example bead **302** disposed within the example chamber **104** may oscillate in a manner similar to that described in U.S. Application No. 13/469,963, filed 11 May 2012, entitled "Bead-Containing Dry Powder Inhaler." However, in accordance with the present disclosure, the bead **302** may not include a pre-coated powder on its surface. Rather, powder may be separately introduced into the chamber **104** from a receptacle such as dose containment or dosing chamber, or other temporary holding compartment or region, or from another dry powder inhaler, as described further below. With this configuration, the powder may be initially placed into a dose containment chamber. When a patient inhales from a mouthpiece, air may be drawn through the dose containment chamber which moves the powder into the chamber **104**, where it encounters the bead **302** oscillating primarily along the longitudinal axis **L** (see e.g., **FIG. 3**).

In some embodiments, however, the bead **302** may be coated with drug. This may act as a detachment platform for the drug coated on its surface, as well as a dispersion mechanism for drug formulation located and introduced upstream of the bead. For example, for a combination drug product, such as delivering two or more drugs in a single inhalation maneuver, where one drug is delivered in a larger dose, such as an inhaled corticosteroid, than the other drug, such as a long-acting beta-agonist, the lower dose drug may be coated onto the surface of the bead **302**, while the larger dose drug is located in a dose containment container, such as a capsule, blister, reservoir, etc., upstream of the chamber **104** containing the drug-coated bead. Thus, during inhalation, oscillation of the bead **302** may serve as a detachment platform to the drug adhered to its surface, and as a dispersion mechanism to the powder that is located upstream.

Additionally, the bead **302** may be coated with a layer of durable material. An example of such a material may include, but is not limited to, gelatin, sugars, any pharmaceutically acceptable film coating materials, including polymers, metallic coatings, anti-static coatings, plasma coatings, etc. This may be beneficial for example when bead material can erode or fragment. In this example, the layer thickness may depend on the density of the material to be added, such that the

addition of the coated layer does not eliminate or substantially impair or inhibit the ability of the bead **302** to oscillate within the dispersion chamber **104**.

Using the bead **302** as a dispersion mechanism may provide a number of advantages. For example, by employing the oscillating bead in the capacity of a dispersion engine, large doses such as, for example, about 1 mg to about 25 mg or greater, may be delivered by storing them in capsules or blisters. However, it will be appreciated that smaller doses may also be delivered. For example, doses greater than about 1 μg of active drug may be delivered. In some cases, the active drug may be blended with a carrier, such as lactose. Also, when the bead **302** is not coated with drug and used as a dispersion mechanism, there is no retention mechanism required to hold the bead **302** tightly within the inhaler, decreasing the complexity of the DPF. Still further, using the bead **302** as a dispersion mechanism may require no additional or complicated processing steps for the DPF formulations, as the powder may be produced by traditionally employed methods. Additionally, the bead **302** in the present disclosure may oscillate generally within the center of the chamber **104**, along the longitudinal axis **L**, where physical contact between the bead **302** and inner walls of the chamber **104**, and possibly ends of the chamber **104**, may occur infrequently, if at all. This type of dispersion mechanism may be beneficial as collisions between walls of the chamber **104** and the bead **302** could serve to rub powder onto either the surface of the bead **302** or inner walls of the chamber **104** when powder is caught therebetween during a physical collision, thereby decreasing an amount of powder available for transfer into the lungs of a patient. Alternatively the frequent collision of the bead **302** with the walls of the chamber **104** may act to scrub off any drug adhered to the wall(s), thus increasing an amount of powder available for transfer into the lungs of a patient.

Referring now back to **FIGS. 1-3**, and as mentioned above, alignment of the inlet **102** and the chamber **104,** may provide significant advantages over inhalers having an "off-axis" alignment. In particular, the tubular body **100** of the present disclosure may produce an approximately symmetrical flow stream expansion that drives oscillation of the bead **302**. Such a configuration may enable a powder dispersion device, or dry powder inhaler, incorporating aspects of the tubular body **100**, to be constructed with minimal bulk. For example, the chamber **104** in example embodiments of the present disclosure may be modeled as a cylinder of the dimensions detailed above (e.g., $d_{chamber} \sim 7.37$ mm, $l_{chamber} \sim 10$ mm) for a similar 5 mm bead. Accordingly,

a maximum volume occupied by the chamber **104** is about 427 cubic mm based on the expression $v_{cylinder} = \pi r^2 l$.

Referring now to **FIGS. 4-5**, an example powder dispersion device or inhaler **400** is shown in accordance with the principles of the present disclosure. In particular, **FIG. 4** shows a first view of the device **400** of **FIG. 4** in cross-section. **FIG. 5** shows a perspective view of the device **400** of **FIG. 4**.

The device **400** may generally incorporate aspects of the example tubular body **100** described above in connection with **FIGS. 1-3**. For example, the device **400** may include a first housing **402** comprising the inlet **102** and the chamber **104** of the tubular body **100**. Additionally, although not expressly shown, the bead **302** may be positioned within the chamber **104**, such as shown in **FIG. 3**. The device **400** may further include a second housing **404** comprising a sheath flow channel **406** that surrounds and is not in fluid connection with a primary or main powder flow channel **408**. In some embodiments, the first housing **402** may be integrally formed with the second housing **404**. In one embodiment, the chamber **104** and the main powder flow channel **408** may have at least one common structural dimension, such as internal diameter for example. Additionally, the second housing **404** may itself comprise of, be coupled to, or otherwise incorporated within, a mouthpiece adapted to be placed within the mouth of a patient, or in a nasal adapter adapted to conform to the nostrils of a patient. The device **400** may further include a plurality of flow bypass channels **410** that are formed within the second housing **404**. The flow bypass channels **410** may be in fluid connection with the sheath flow channel **406**.

The device **400** may further include a dosing chamber **412**, a retaining member **416**, and a piercing member **418** disposed at an end of the chamber opposite the inlet **102**. The piercing member **418** may puncture or otherwise perforate a capsule, blister, or powder reservoir **414** as arranged or positioned within the dosing chamber **412**. In general, the retaining member **416** may include at least one opening or aperture sized to permit air and powdered or otherwise aerosolized medicament to pass through the retaining member **416**, and to prevent the possibility of the bead **302** from exiting the chamber **104**. The at least one opening or aperture may, in some embodiments, be arranged and configured (e.g., diameter, pattern, etc.) to maintain desired fluid flow characteristics with the device **400**, such that the bead **302** may disrupt and aerosolize medicament powder agglomerates within the chamber **104** to provide for more effective deposition of medicament into the lungs of a patient.

In one example, referring specifically to **FIG. 4**, a patient may prime the device **400** by puncturing the capsule, blister, or transfer of a dose from a powder reservoir **414**, and then inhale, drawing air through the chamber **104** which in turn draws the DPF from the dosing chamber **412** into the adjacent chamber **104** via the inlet **102**, where the bead **302** is rapidly oscillating, creating high-energy forces that may strip drug from the surface of carrier particles in the DPF, or when the bead **302** is drug-covered, and/or de-agglomerate drug powder aggregates and drug-on-drug aggregates. Drug particles may then be deposited in lungs and airways of a patient from the primary or main powder flow channel **408** based on direction of air flow through the device such as shown in **FIG. 4**. Such a "self-dosing" scenario may be useful for effectively dispensing both traditional binary or ternary DPF formulations, drug and carrier/excipient particles, and pure drug-powder formulations where there are no carrier particles are present. Other embodiments having similar effects are possible, as discussed further below in connection with **FIG. 9**.

In general, the resistance to flow of the device **400** may be adjusted by altering the geometry and/or arrangement of at least one of the inlet **102**, the bead **302**, the sheath flow channel **406**, the main powder flow channel **408**, and the flow bypass channel(s) **410**. Additionally, as shown in **FIG. 5**, the flow bypass channels **410** may be located radially around the body of the second housing **404**, and fluidly connected to the sheath flow channel **406**. In some embodiments however, the device **400** may not include any flow bypass channels. In one embodiment, the flow bypass channels **410** may comprise of twelve individual channels located radially around the body of the second housing **404**. However, other embodiments are possible. For example, the flow bypass channels **410** may comprise of different numbers and diameters of individual channels and entry points into the sheath flow channel **406**. Further, one or more of the flow bypass channels **410** may be parallel through the main powder flow channel **408**, or may be in fluid connection with, and then diverge from, the main powder flow channel **408**. Still other embodiments are possible.

One or more of the flow bypass channels **410** may be "opened" or "closed" such as by removal or insertion of a resilient material therein to "unplug" or "plug" the same. This may result in changes in the overall resistance of the device **400**, thereby influencing flow rate through the device **400**. For example, a person may inhale through a "high" resistance inhaler with a lower inspiratory flow rate than they would through a "low" resistance inhaler, despite inhaling with

the same inhalation effort. In this manner, the device **400** may be "tuned" to respond "optimally" to the needs of a patient. In other words, the device **400** in accordance with the present disclosure may be tailored to suit particular patient needs. For example, resistance of the device **400** may be approximately inversely proportional to diameter of the bead **302**. Thus, for a "larger" diameter bead **302**, one or more of the flow bypass channels **410** may be "closed" to increase resistance of the device such that a patient may receive a proper dose of medicament irrespective of possibly diminished inhalation capacity.

Experimental Study A

Performance of the example powder dispersion device or inhaler **400** of **FIG. 4** was evaluated to assess how the bead **302** as an oscillating mechanism functions to disperse drug powder within the chamber **104**. In this example, no powder was coated onto the surface of the bead **302**. During inhalation, powder travels from a dosing chamber **412** (see **FIG. 4**), where the powder is stored, into the chamber **104**, where the bead **302** when oscillating creates high-energy forces that may strip the drug particles from, for example, a lactose carrier, and/or disrupt aggregated particles and disperse them into sizes that may more easily penetrate patient airways. Additionally, physical collisions between the bead **302** and coarse "carrier" particles and/or aggregates may also promote drug dispersion, and increased physical collisions between lactose carrier particles.

In general, the bead **302** may comprise of an uncoated "low" density expanded polystyrene bead, with the chamber **104** being downstream of the dosing chamber **412**, where the powder may be contained in the powder reservoir **414**. Other embodiments are possible. For example, a density of the bead **302** may be selected as desired, where the density of bead **302** may or may not affect performance of the device **400**. In the example of a capsule, capsule material may include gelatin or HPMC (hydroxypropylmethylcellulose). Examples of commercial dry powder inhaler products where the powder is stored in capsules include the FORADIL® Aerolizer® and the SPIRIVA® HandiHaler®. In general, the capsules may each contain one dose, or multiple capsules can be used to contain the equivalent of one dose, as with the TOBI® Podhaler®, where each dose consists of four capsules, each containing 28 mg of powder for example. In the example of an individual blister, one blister may contain one dose. Examples of commercial dry powder inhaler products where the powder is stored in blisters include the FLOVENT® Diskus®, SEREVENT® Diskus®, and the ADVAIR® Diskus®. In the example of a reservoir, a

particular reservoir may contains sufficient powder for multiple doses. Examples of commercial dry powder inhaler products where the powder is stored in reservoirs include the ASMANEX® Twisthaler®, SYMBICORT® Turbuhaler® and the Budelin® Novolizer®. Still other embodiments are possible.

In practice, a patient may prime the device **400** by puncturing the capsule/blister contained within the powder reservoir **414** or transferring drug from the powder reservoir **414**, and then inhale, drawing powder into the adjacent chamber **104** via the inlet **102** where the bead **302** is rapidly oscillating, creating high-energy forces that may strip the drug from the surface of carrier particles (e.g., when the bead **302** is drug-covered), and/or de-agglomerate powder aggregates. Thus, this approach may be useful for effectively dispersing both traditional binary or ternary DPF formulations, drug and carrier/excipient particles, and pure drug-powder formulations where there are no carrier particles are present.

In the example study, the capsule chamber of the Handihaler® (see e.g., **FIG. 6**) as described generally in U.S. Patent No. 7,252,087, was employed to puncture an HPMC capsule containing 20 mg (±1 mg) of a 2% binary blend of micronized budesonide and inhalation-grade lactose (Respitose® ML006). As a control, the powder was dispersed only from the Handihaler®, with no bead-dispersion chamber downstream. For the experimental sets, the chamber **104** was included downstream of the Handihaler® capsule chamber with a single 4 mm expanded polystyrene bead, placed inside. Thus the experimental configurations were: Handihaler® alone (herein referred to as "No Attachment"); and Handihaler® with the example device **400** as an attachment (herein referred to as "Attachment").

Due to placing of "narrow" inlets in series, the resistance of the "Attachment" was relatively "high," with a 4 kPa pressure drop of approximately 26 LPM. In this example, the flow bypass channels **410** of the device **400** were used to lower the resistance, making the 4 kPa pressure drop flow rate at approximately 70 LPM; the cutoff of Stage 2 is about 4.1 μm, and the cutoff of Stage 1 is about 7.4 μm. The Stage 2 cutoff of 39 LPM is about 5.6 μm.

The results with N = 3 (+/- stdev):

"No Attachment" : FPF (Fine Particle Fraction) (< 5.6 μm) = 48.2% (3.0%); and

"Attachment" : FPF (< 4.1 μm) = 70.9% (1.2%).

Here, it may be understood that the FPF increased at Stage 2 cutoff from 48.2%, using the "No Attachment" arrangement or configuration, to 70.9%, using the "Attachment" arrangement or

configuration. Thus, it may be understood that the "Attachment" arrangement or configuration more efficiently deaggregated powder passing through arrangement or configuration, such that a greater percentage of "smaller" particles were created that would then be available to penetrate into a patients lung.

Additionally, when Stage 2 was also included in the FPF, changing the cutoff size to < about 7.4 μm), the FPF would increase to 77.7% (1.0%).

It was expected there would be significant drop-off in measurable or otherwise recovered dose due to loss in the chamber **104**. There was however no noticeable difference in recovered dose. This surprising and unexpected result may indicate that the device **400**, a compact device, having straight powder flow path containing a breath-actuated, approximately linearly oscillating, bead as the dispersion mechanism, may serve as an effective powder dispersion mechanism for at least dry powder formulations. This may be beneficial in many respects. For example, since it has been found that FPF output increases using the "Attachment" arrangement or configuration, a patient may be more capable of obtaining a proper dosage of medicament. Other benefits are possible as well.

Experimental Study B

Performance of the example powder dispersion device or inhaler **400** of **FIG. 4** was evaluated to assess the influence of size of the bead **302** on the example device **400**. In this example, a particular powder dispersion device configured to incorporate a bead of a particular size was produced via stereolithography from the material DSM Somos® NeXT. A particular powder dispersion device was attached to the capsule chamber of the HandiHaler® dry powder inhaler. This allowed testing the dispersion of powder from capsules that could be perforated by the piercing mechanism of the HandiHaler®.

FIG. 6 shows a first example experimental set-up in accordance with the present disclosure. In particular, **FIG. 6** shows the example device **400** of **FIG. 4** attached to a capsule chamber (e.g., dosing chamber **412**) of the HandiHaler® dry powder inhaler **602**. Although, it will be appreciated that element **602** may generally be any type of dose containment system or powder source. **FIG. 6** further shows the device **400** arranged and configured to incorporate or otherwise exhibit a 3.2 mm bead, a 4.0 mm bead, and a 5.2 mm bead. Powder contained in a capsule was punctured using the piercing mechanism of the HandiHaler® dry powder inhaler. During inhalation, powder is pulled or otherwise caused to flow out from the perforations in the capsule

wall, traveling into the chamber **104** of the device **400**, where forces created by the bead **302**, when the bead is rapidly oscillating, at least disrupts powder agglomerates.

In general, the resistance of the device **400** varied inversely with bead size. The device **400** was tested at a constant 4 kPa pressure drop across the device **400** by altering the volumetric flow rate through the device **400** to compensate for difference in device resistance, summarized in the following **Table 1**:

Configuration	Bead Size	4 kPa Flow Rate	Device Resistance $(cmH_20)^{0.5}$ / L min^{-1}
No Attachment	No Attachment	39 L min^{-1}	0.173
Attachment	3.2 mm	81 L min^{-1}	0.079
Attachment	4.0 mm	86 L min^{-1}	0.073
Attachment	5.2 mm	95 L min^{-1}	0.069

Here, it may be understood that even though an "Attachment" in accordance with the present disclosure is being coupled to an inhaler, device resistance including the "Attachment" does not increase. Rather, device resistance decreases. This may be beneficial in many respects. For example, a patient with decreased or otherwise diminished lung capacity may be more capable of using the "Attachment" arrangement or configuration. Further, since it has been found that FPF output increases using the "Attachment" arrangement or configuration (see Experimental Study A), a patient of decreased or otherwise diminished lung capacity may be more capable of obtaining a proper dosage of medicament. Other benefits are possible as well.

Experimental Study B1

Performance of the example powder dispersion device or inhaler **400** of **FIG. 4** was evaluated to assess the influence of size of the bead **302** in delivering a high dose of a pure micronized beta agonist, not containing any excipients.

In this example study, 15 mg (± 1 mg) of pure micronized albuterol sulfate (beta-agonist) was placed into Size 3 HPMC capsules. Powder was dispersed via the "No Attachment" or "Attachment" configurations as discussed above, with the device **400** including either a 3.2 mm bead, 4.0 mm bead, or 5.2 mm bead, and attached to the capsule chamber of the HandiHaler® dry powder inhaler **602** (see **FIG. 6**) through a next generation cascade impactor connected to a high vacuum pump. The volumetric flow rate through the different configurations was adjusted such that a pressure drop of approximately 4 kPa was produced across the respective device **400**,

such as listed in **Table 1** above. The devices were activated or otherwise actuated for a time interval that allowed 4 L of air to flow therethrough. Following actuation, the drug depositing on the different regions of the experimental setup was collected by rinsing each region with deionized water, and quantified by UV-VIS spectrophotometry at 230 nm.

The FPF of the emitted dose, which may refer to the fraction of a dose that leaves the inhaler that deposits in the lungs, because if its size, for each configuration is summarized in the following **Table 2**:

Configuration/Bead Size	FPF (emitted), N =3
No Attachment	24.1% (3.4 +/- 1 std deviation)
Attachment/3.2 mm bead	75.3% (2.9 +/- 1 std deviation)
Attachment/4.0 mm bead	75.8% (3.1 +/- 1 std deviation)
Attachment/5.2 mm bead	73.0% (5.5 +/- 1 std deviation)

Here, it may be understood that the FPF increased from about 24%, using the "No Attachment" arrangement or configuration, to between about 73% to 76%, using the "Attachment" arrangement or configuration. Similar to the above-conclusion (see Experimental Study A), it may be understood that the "Attachment" arrangement or configuration more efficiently deaggregated powder passing through arrangement or configuration, such that a greater percentage of "smaller" particles were created that would then be available to penetrate into a patients lung.

Experimental Study B2

Performance of the example powder dispersion device or inhaler **400** of **FIG. 4** was evaluated to assess the influence of size of the bead **302** in delivering a high dose of a pure inhaled corticosteroid, no excipients.

In this example study, 10 mg (± 0.5 mg) of pure micronized mometasone furoate (inhaled corticosteroid) was placed into Size 3 HPMC capsules. Powder was dispersed via the "No Attachment" or "Attachment" configuration as discussed above, with the device **400** including either a 3.2 mm bead or 5.2 mm bead, and attached to the capsule chamber of the HandiHaler® dry powder inhaler **602** (see **FIG. 6**) through a next generation cascade impactor connected to a high vacuum pump. The volumetric flow rate through the different configurations was adjusted such that a pressure drop of approximately 4 kPa was produced across the respective device **400**, such as listed in **Table 1** above. The devices were actuated for a time interval that allowed 4 L of

air to flow through the inhaler. Following actuation, the drug depositing on the different regions of the experimental setup was collected by rinsing each region with methanol and quantified by UV-VIS spectrophotometry at 250 nm. Other preferred solvents may be used depending on type of studied drug.

The FPF of the emitted dose for each configuration is summarized in the following **Table 3**:

Device Configuration/Bead Size	FPF (emitted), N =3
No Attachment	31.5% (4.0 +/- 1 std deviation)
Attachment/3.2 mm bead	75.6% (2.8 +/- 1 std deviation)
Attachment/5.2 mm bead	70.3% (1.7 +/- 1 std deviation)

Here, it may be understood that the FPF increased from about 32%, using the "No Attachment" arrangement or configuration, to between about 70% to 76%, using the "Attachment" arrangement or configuration. Similar to the above-conclusion (see Experimental Study A), it may be understood that the "Attachment" arrangement or configuration more efficiently deaggregated powder passing through arrangement or configuration, such that a greater percentage of "smaller" particles were created that would then be available to penetrate into a patients lung.

Experimental Study B3

Performance of the example powder dispersion device or inhaler **400** of **FIG. 4** was evaluated to assess the influence of size of the bead **302** in delivering a low dose of beta-agonist delivered from a traditional DPF formulation, with coarse lactose particles as an excipient.

In this example study, a 2% (w/w) binary blend of albuterol sulfate in lactose was prepared by blending 490 mg of inhalation-grade lactose (LactoHale 300) with 10 mg of pure micronized albuterol sulfate via geometric dilution in a 25 mL glass scintillation vial. The vial was then placed into a Turbula® Orbital blender for 40 minutes at 46 RPM. 20 mg (± 1 mg) of the 2% albuterol sulfate blend was placed into Size 3 HPMC capsules. Powder was dispersed via the "No Attachment" or "Attachment" configuration as discussed above, with the device **400** including either a 3.2 mm bead, a 4.0 mm bead, or 5.2 mm bead, and attached to the capsule chamber of the HandiHaler® dry powder inhaler **602** (see **FIG. 6**) through a next generation cascade impactor connected to a high vacuum pump. The volumetric flow rate through the different configurations was adjusted such that a pressure drop of approximately 4 kPa was produced across the respective device **400**, such as listed in **Table 1** above. The devices were

actuated for a time interval that allowed 4 L of air to flow through the inhaler. Following actuation, the drug depositing on the different regions of the experimental setup was collected by rinsing each region with deionized H_2O and quantified by UV-VIS spectrophotometry at 230 nm. The fine particle fraction of the emitted dose for each configuration is summarized in the following **Table 4**:

Device Configuration/Bead Size	FPF (emitted), N =3
No Attachment	29.7% (2.8 +/- 1 std deviation)
Attachment/3.2 mm bead	72.7% (0.9 +/- 1 std deviation)
Attachment/4.0 mm bead	71.8% (2.6 +/- 1 std deviation)
Attachment/5.2 mm bead	71.6% (4.3 +/- 1 std deviation)

Here, it may be understood that the FPF increased from about 30%, using the "No Attachment" arrangement or configuration, to between about 72% to 73%, using the "Attachment" arrangement or configuration. Similar to the above-conclusion (see Experimental Study A), it may be understood that the "Attachment" arrangement or configuration more efficiently deaggregated powder passing through arrangement or configuration, such that a greater percentage of "smaller" particles were created that would then be available to penetrate into a patients lung.

Experimental Study C

To evaluate the influence of drug dose on the powder dispersion performance of the device **400**, powder was dispersed via the "Attachment" configuration as discussed above, with the device **400** including a 3.2 mm bead, and attached to the capsule chamber of the HandiHaler® dry powder inhaler **602** (see **FIG. 6**) through a next generation cascade impactor connected to a high vacuum pump. In particular, 1, 5, 10 or 25 mg of pure micronized albuterol sulfate were dispersed with volumetric flow rate set to produce a 4 kPa pressure across the device 400, about 81 LPM. The device **400** was actuated for a time period to allow 4 L of air to flow through the device **400**. Samples were rinsed with deionized H_2O and analyzed via UV-VIS Spectroscopy at 230 nm. Results showed that the drug delivery efficiency as measured by FPF of the emitted dose was both "high" and relatively consistent, even as the dose increased to 25 mg of pure micronized drug powder, summarized in the following **Table 5**:

Device Configuration/Bead Size	Dose	FPF (emitted), N =3
Attachment/3.2 mm bead	1 mg	83.7% (2.0 +/- 1 std deviation)
Attachment/3.2 mm bead	5 mg	85.4% (2.8 +/- 1 std deviation)

Attachment/3.2 mm bead	10 mg	83.7% (2.6 +/- 1 std deviation)
Attachment/3.2 mm bead	25 mg	78.0% (1.9 +/- 1 std deviation)

For a bead of approximately equal density, changing the bead diameter will change the bead mass. It is contemplated that beads of lower mass may oscillate with greater frequency than heavier beads. Thus, smaller beads may have a greater oscillation frequency than larger beads. It is contemplated that particle size distributions differ between bead sizes, and with smaller beads, due to the greater oscillation frequency of the smaller beads, higher energy localized eddies may be produced, which may be more effective at de-aggregating powder particles than lower energy localized eddies produced by larger beads that oscillate with a lower frequency. However, larger beads may travel a greater distance during their oscillation, by the power law relation governing bead diameter described above, and coupled with the greater diameter, may displace a larger volume of air when they move. Accordingly, overall force produced by a larger bead may be much greater than that produced by a smaller bead, despite the higher energy eddies produced by the smaller beads, such that a larger bead may influence a greater proportion of powder passing through the dispersion chamber **104**, but to a lesser extent than the smaller beads. This may be summarized as: smaller beads → greater oscillation frequency → more effective dispersion, influences less powder; and larger beads → lower oscillation frequency → less effective dispersion, influence more powder. The above description may be one possible explanation as to the operation of the device **400** in accordance with the present disclosure and other mechanisms of action may be possible.

Referring now to **FIG. 7**, a second example experimental set-up is shown in accordance with the present disclosure. In particular, **FIG. 7** shows the example device **400** of **FIG. 4** attached to a mouthpiece **704** of a particular commercial dry powder inhaler **702**, namely the Flovent® Diskus® inhaler. Although, it will be appreciated that element **702** may generally be any type of dose containment system or powder source

In previous examples, the device **400** was connected directly to the capsule chamber of the HandiHaler®, bypassing the mouthpiece of the HandiHaler®, which powder may flow through under "normal" operation. In contrast, as shown in **FIG. 7**, the example device **400** of **FIG. 4** is coupled to the mouthpiece **704** of the inhaler **702** by a coupling **706**, thereby allowing powder to flow through the inhaler **702** as during "normal" operation, and then into the chamber **304** containing the bead **302** (see e.g., **FIG. 3**). During inhalation, powder is pulled or otherwise

caused to flow out through the inhaler **702**, traveling into the chamber **104** of the device **400**, where forces created by the bead **302**, as rapidly oscillating, at least disrupts powder agglomerates.

Experimental Study D

Performance of the example powder dispersion device or inhaler **400** of **FIG. 4** was evaluated to assess the ability of the example device **400** in increasing FPD (Fine Particle Dose) and emitted FPF (Fine Particle Fraction) when coupled in series with the inhaler **702**. The fraction of a dose that leaves the inhaler that deposits in the lungs, because of its size, may be referred to as the (FPF), or FPD when expressed in terms of mass. In particular, flow rate through the inhaler **702**, with API (Active Pharmaceutical Ingredient) Fluticasone propionate, with and without the example device **400** coupled to the mouthpiece **704** was set to produce a 4 kPa pressure drop across the device **400** of 49 LPM when coupled to the inhaler **702** (referred to as "No Attachment"), and 83 LPM when decoupled from the inhaler **702** (referred to as "Attachment"). Samples were collected via rinsing with ethanol and analyzed by UV-VIS spectrophotometer at 238 nm. The example device **400** when coupled in series with the inhaler **702** improved the FPD by 33 mcg (49%), and improved FPF by 52%, summarized in the following **Table 6**:

Device Configuration	Fine Particle Dose, N = 5	FPF (emitted), N = 5
No Attachment	68.2 (2.7) mcg	26.4 % (1.0 +/- 1 std deviation)
Attachment	101.5 (4.3) mcg	40.0 % (1.4 +/- 1 std deviation)

Here, it may be understood that the device or inhaler **400** of **FIG. 4** may enhance the performance (FPF emitted) of a commercial inhaler. This may be beneficial since the device or inhaler **400** of **FIG. 4** may be considered as an "add-on," such that a patient may not be required to purchase another device when a particular commercial inhaler does not provide the performance required or desired by the patient. This may be because the device or inhaler **400** of **FIG.** 4 is configured to more efficiently break-up powder agglomerates, and reduce or otherwise minimize the resistance of an or other device that the device or inhaler **400** is coupled to. Other benefits are possible as well.

Referring now to **FIG. 8**, a second view of the device **400** of **FIG. 4** is shown in cross-section. In particular, a cross section of the second example experimental set-up of **FIG. 7** is shown. Similar to **FIG. 7**, the example device **400** of **FIG. 4** is coupled to the mouthpiece **704** of the inhaler **702** by the coupling **706**, thereby allowing powder to flow through the inhaler **702** as during

"normal" operation, and then into the chamber **304** containing the bead **302** (see also **FIG. 3**). In particular, a piercing member **712** may puncture or otherwise perforate a capsule, blister, or powder reservoir **714** as contained within a dosing chamber **716** of the inhaler **702**. Powder may then be caused to flow through the inhaler **702** into the chamber **304** containing the bead **302** via the mouthpiece **704** and coupling **706**. The bead **302** may then disrupt and aerosolize medicament powder agglomerates within the chamber **104** to provide for more effective deposition of medicament into the lungs of a patient in a manner such as described above. Other embodiments are possible.

In general, the coupling **706** may be a rigid or flexible coupling formed of any material, or combination thereof, such as thermoplastic/thermosetting plastics, metals, glasses, elastomers, etc., and may be coupled to the mouthpiece **704** of the inhaler **702** on a first end **708**, and to the device **400** on a second end **710**. Here, it may be preferred that the material has surface properties that do not attract powder particles. The coupling **706** may be permanently fastened to, such as being integrally formed therewith, at least one of the inhaler **702** and the device **400**, or may be removable fastened with least one of the inhaler **702** and the device **400**. For example, the coupling **706** may be fastened to the inhaler **702** by one of a "snap-fit" or a "pressure-fit" or a "twist-to-fit" mechanism, etc., such as in a "quick" connect/disconnect implementation. Still other embodiments are possible. For example, it will be appreciated that the device **400** may not be limited to being "clipped" or otherwise "coupled" to other inhalers. Further, aspects of the present disclosure may be used in combination with any type of dose containment system, and may not be limited to a capsule, blister, or reservoir.

As discussed above in connection with **FIG. 4**, a patient may prime the device **400** by puncturing the capsule, blister, or powder reservoir **414**, and then inhale, drawing the powder from the dosing chamber **412** into the adjacent chamber **104** via the inlet **102**, where the bead **302** is rapidly oscillating, creating high-energy forces that may strip drug from the surface of carrier particles (e.g., when the bead **302** is drug-covered), and/or de-agglomerate powder aggregates. Drug particles may then be deposited in lungs and airways of a patient from the primary or main powder flow channel **408** based on direction of air flow through the device such as shown in **FIG. 4**. Such a "self-dosing" scenario may at least be useful for effectively dispensing both traditional binary or ternary DPF formulations, drug and carrier/excipient particles, and pure

drug-powder formulations where there are no carrier particles are present. Other embodiments are however possible.

For example, referring now specifically to **FIG. 9**, a "forced-dosing" scenario is described in accordance with the present disclosure. In particular, a third view of the device **400** of **FIG. 4** is shown in cross-section in **FIG. 9**. In this example, a coupling **902** is shown that is removably coupled to the first housing **402** of the device **400**. The coupling **902** includes an inlet **904** that is removably coupled to an air source **906**. In one embodiment, an individual other than a patient may prime the device **400** by puncturing a capsule, blister, or reservoir **908** of the coupling **902** using a piercing member **910**. The source **906** may then be employed to force air through the device **400**, drawing powder from the reservoir **908** into the adjacent chamber **104** via the inlet **102**, where the bead **302** is rapidly oscillating, creating high-energy forces that may strip drug from the surface of carrier particles (e.g., when the bead **302** is drug-covered), and/or de-agglomerate powder aggregates. Drug particles may then be deposited in lungs and airways of the patient from the primary or main powder flow channel **408** based on direction of air flow through the device such as shown in **FIG. 9**.

Such a "forced-dosing" scenario may beneficial when, for example, emergency treatment of unconscious or otherwise unresponsive personnel may be necessary. For example, the device **400** may enable a responder to administer treatment agent to the lungs of a patient. Additionally, the second housing **404** may itself comprise of, be coupled to, or otherwise incorporated within, a mouthpiece adapted to be placed within the mouth of a patient, or in a nasal adapter adapted to conform to the nostrils of a patient. In the example of **FIG. 9**, the second housing **404** of the device **400** may be securely positioned within or on the mouth or nasal passages of a patient. With air expelled from the lungs of a responder into the inlet **604**, the device **400** may be activated or actuated such as to deposit a treatment agent into the lungs and airways of the patient. In this example, the source **906** corresponds to the lungs of an individual. Other embodiment are possible. For example, in some embodiments. the source **906** may comprise of a ventilation bag, mechanical ventilator, mechanical pump, etc. Still other embodiments are possible.

At least **FIGS. 6-9** illustrate a scenario in which the example device **400** is coupled to, or fitted onto, an external feature of a dose containment system or powder source **602**. Other embodiments are however possible. For example, referring now to **FIG. 10**, a scenario is

illustrated in which the example device **400** is coupled to, or fitted onto, an internal feature of a dose containment system or powder source. In particular, the device **400** may replace a powder dispersion mechanism internal to an existing inhaler. An example of an existing inhaler may include the HandiHaler®, ASMANEX® Twisthaler®, SYMBICORT® Turbuhaler® and the Budelin® Novolizer® dry powder inhalers and others. Other embodiments are possible.

For example, a dose containment system or powder source **912** may generally include a dose module **914** that holds a portion of DPF, a powder dispersion module **916**, and a mouthpiece module **918** that would in practice be used to deliver a dose of the DPF to a patient. In general, the powder dispersion module **916** may exhibit a tortuous path the DPF needs to navigate between its introduction into the flow path and release from the mouthpiece module **918**. The tortuous path may possibly deaggregate DPF aggregates to some degree, but may also add flow resistance. In accordance with the principles of the present disclosure, the dose containment system or powder source **912** may be modified to replace the powder dispersion module **916** with the device **400**, or subassemblies of the device **400**, including an inlet, chamber with a bead, and an outlet similar to the device **400**. Further, this may or may not include the second housing **404** of the device **400**, where an existing element of an inhaler being modified may instead be used. In this example, the device **400** may enhance the efficiency of de-aggregation of DPF of the dose containment system or powder source **912**, and may lower the resistance to flow within the dose containment system or powder source **912**. Other benefits and advantages are possible as well.

Referring now to **FIG. 11**, a simplified, conceptual, example schematic diagram of the example device **400** of **FIG. 4** in multiple configurations is shown. In particular, the chamber **104** of the device **400** is shown in a series configuration **1002** with another chamber **104**, and in a parallel configuration **1004** with another chamber **104**. In this example, it is contemplated that multiple drugs in each their own (e.g., two or more) dispersion chambers (e.g., in addition to other elements of the example device **400** as desired) configured in accordance with the principles of the present disclosure may be coupled in series or parallel. Further, it is contemplated that any desired series/parallel combination may also be formed. For example, the series configuration **1002** may be coupled in series with the parallel configuration **1004**. In another example, the parallel configuration **1004** may be coupled in series with a single particular chamber **104**, and etc.

In addition, it is contemplated that the type and configuration of the bead **302** may vary in the context of **FIG. 11**. For example, when multiple ones of the chamber **104** are connected in series and/or parallel, one or more of the respective dispersion chambers may have similar bead sizes, different bead sizes, similar bead materials, different bead materials, and etc. Further, it is contemplated that any desired series/parallel combination may be formed. In general, type and configuration of the bead **302** may vary as desired.

Such an implementation may be beneficial in many respects. For example, for combination therapies, one drug may pass through a particular dispersion chamber and another other drug may pass through a separate dispersion chamber, or both drugs can pass through the same dispersion chamber. Additionally, "downstream" of the dispersion chambers may merge into a single dispersion chamber, or be kept separate throughout the length of the device **400**, such that the powders do not mix until they are emitted from the device. Still other benefits and/or advantages are possible as well.

Referring now to **FIG. 12**, a first example stage-by-stage particle deposition distribution profile **1100** is shown. In particular, **FIG. 12** shows an example of a simulated stage-by-stage particle distribution profile of the 15 mg pure micronized albuterol sulfate formulation discussed above in connection with Experimental study B1, for powder emitted from the "No Attachment" configuration, or the "Attachment" configuration, as described above. The stage-by-stage particle distribution profile is simulated because an experimental set-up or particle sizing apparatus using a number of meshed screens arranged to pass a particular range of particles size were positioned with respect to each other such as to model the lungs of a patient.

In **FIG. 12**, the first or leftmost bar in each category is associated with the "No Attachment" configuration, the second or middle bar in each category is associated with the "Attachment" configuration using a 3.2 mm bead, and the third bar or rightmost bar in each category is associated with the "Attachment" configuration using a 5.2 mm bead. In general, particle sizes become smaller as the stage number increases. Accordingly, Stage 1 will contain the largest particles at a greater concentration than Stage 2, then Stage 2, Stage 3, etc. As seen within the profile **1100**, Stage 1, Stage 2, and Stage 3 show a greater deposition for the 5.2 mm bead relative to its 3.2 mm counterpart, which then switches at Stage 5 and Stage 6, where the 3.2 mm bead exhibits greater deposition than the larger bead. The Stages may correspond to particle deposition locations within the human anatomy where induction port, preseparator, Stage 1, and

Stage 2 may approximate deposition within the mouth, throat, and upper airways, and Stages 3-8 may approximate deposition within the lung.

Referring now to **FIG. 13**, a second example stage-by-stage particle deposition distribution profile **1200** is shown. In particular, **FIG. 13** shows an example of a simulated stage-by-stage particle distribution profile of the 10 mg (± 0.5 mg) of pure micronized mometasone furoate, discussed above in connection with Experimental study B2, for powder emitted from the "No Attachment" configuration, or the "Attachment" configuration, as described above. In **FIG. 13**, the first or leftmost bar in each category is associated with the "No Attachment" configuration, the second or middle bar in each category is associated with the "Attachment" configuration using a 3.2 mm bead, and the third bar or rightmost bar in each category is associated with the "Attachment" configuration using a 5.2 mm bead. As may be understood upon inspection of the profile **1200**, a similar trend as observed in the profile **1100** is observed with the pure micronized mometasone furoate. Further it may be understood from the profile **1200**, and the profile **1100**, that using the diameter of the bead **302** the particle size distribution may be tailored to a particular target profile. As an example, certain drugs may require central lung deposition, whereas other drugs may require more peripheral lung deposition. In one example, the term particle size distribution may refer to an aerodynamic particle size distribution. In general, an aerodynamic particle size may equal the diameter of a sphere that has the same or similar drag coefficient as a given particle. In this example, the bead **302** may be selected to have a size such that upon oscillation it produces a desired aerodynamic particle size distribution of powdered medicament. Further, a desired aerodynamic particle size distribution may obtained as a function of a diameter of the bead **302**.

Altering the bead size can influence the aerodynamic particle size distribution profile of the emitted drug and thus may enable regional targeting of the lung by altering the diameter of the bead size, while maintaining the chamber and inlet diameters proportional, rather than by altering the formulation, which can be a more costly and time intensive process. In the above example experimental studies, the proportions of the inlet and dispersion chamber diameters were kept constant to the diameter of the bead as: $d_{bead}^2 \cong (d_{inlet})(d_{chamber})$, where the ratio of the diameter of the dispersion chamber (chamber **104**) to that of the inlet is approximately or about 2.1. However, other embodiments are possible. For example, the ratio of the diameter of the dispersion chamber to that of the inlet may be within a range of about greater than 1.1 to about

3.0. In other embodiments, the ratio of the diameter of the dispersion chamber to that of the inlet may be within a range of about 1.5 to about 2.5. Still other embodiments are possible.

Referring now to **FIGS. 14-17**, a first example powder dispersion device or inhaler **1300** is shown in accordance with the principles of the present disclosure. In general, the device **1300** may be configured to be coupled to another inhaler device. In particular, **FIG. 14** shows a first perspective view of the device **1300**. **FIG. 15** shows a second perspective view of the device **1300**. **FIG. 16** shows a first end view of the device **1300**. **FIG. 17** shows a second end view of the device **1300**.

In general, the device **1300** may be similar to or otherwise correspond to the device **400** discussed above in connection with **FIGS. 1-13**. For example, the device **1300** may include a first housing **1302** comprising an inlet **1304** and a chamber **1306**. The inlet **1304** and a chamber **1306** may be arranged and/or configured in a manner similar to the inlet **102** and chamber **104** of the device **400**. Additionally, although not expressly shown, the bead **302** may be positioned within the chamber **1306**, such as shown in **FIG. 3**. The device **1300** may further include a second housing **1308** comprising a sheath flow channel **1310** that surrounds a primary or main powder flow channel **1312**. The device **400** may further include a plurality of flow bypass channels **1314** that are formed within the second housing **1308**. The flow bypass channels **1314** may be in fluid connection with the sheath flow channel **1310**.

FIGS. 18-21 show the second housing **1308** of the device **1300** in multiple views. In particular, **FIG. 18** shows a first perspective view of the second housing **1308**. **FIG. 19** shows a second perspective view of the second housing **1308**. **FIG. 20** shows a first end view of the second housing **1308**. **FIG. 21** shows a second end view of the second housing **1308**.

FIGS. 22-25 show the first housing **1302** of the device **1300** in multiple views. In particular, **FIG. 22** shows a first perspective view of the first housing **1302**. **FIG. 23** shows a second perspective view of the first housing **1302**. **FIG. 24** shows a first end view of the first housing **1302**. **FIG. 25** shows a second end view of the first housing **1302**.

A locking mechanism that may be used to couple or otherwise fasten the first housing **1302** with the second housing **1308** may be understood upon inspection of at least **FIGS. 18-25**. In particular, the second housing **1308** may include a first locking member **1316** and a second locking member **1318**. The first housing **1302** may include a first bar **1320** and a second bar **1322**. In practice, the first housing **1302** and the second housing **1308** may be positioned or

orientated with respect to each other and manipulated such that the first bar **1320** is engaged with a first stop surface **1324** of the first locking member **1316** (see **FIG. 18**), and the second bar **1322** is engaged with a first stop surface **1326** of the second locking member **1318**. The first housing **1302** and the second housing **1308** may then be manipulated such as to rotate the first housing **1302** with respect to the second housing **1308** (or vice versa) until the first bar **1320** is engaged with a second stop surface **1328** of the first locking member **1316**, and the second bar **1322** is engaged with a second stop surface **1330** of the second locking member **1318**. In this position, the first bar **1320** may be secured by compression fitting with the first locking member **1316**, and the second bar **1322** may be secured by compression fitting with the second locking member **1318**, thereby coupling the first housing **1302** with the second housing **1308**. A reverse process may be implemented to decouple the first housing **1302** from the second housing **1308**. Such interchangeability may be beneficial in many respects. For example, when a bead **302** of different size is desired, the first housing **1302** may be removed and replaced with another first housing **1302** having a bead **302** of different size than the original housing. Other benefits are possible as well.

Additionally, referring specifically to **FIG. 18**, a retaining member **1332** of the second housing **1308** may include one or more openings sized to permit air and powdered or otherwise aerosolized medicament to pass through the retaining member **1332**, and to prevent the bead **302** from passing through the retaining member **1332**. Other embodiments are possible. For example, in some embodiments, a different mechanism may be used and to prevent the bead **302** from exiting the chamber **1306** into the second housing **1308**.

Referring now to **FIGS. 26-29**, a second example powder dispersion device or inhaler **2500** is shown in accordance with the principles of the present disclosure. In general, the device **2500** may be configured to be coupled to another inhaler device. In particular, **FIG. 26** shows a first perspective view of the device **2500**. **FIG. 27** shows a second perspective view of the device **2500**. **FIG. 28** shows a first end view of the device **2500**. **FIG. 29** shows a second end view of the device **2500**.

In general, the device **2500** may be similar to or otherwise correspond to the powder dispersion device or inhaler **400** discussed above in connection with **FIGS. 1-13**. For example, the device **2500** may include a first housing **2502** comprising an inlet **2504** and a chamber **2506**. Additionally, although not expressly shown, the bead **302** may be positioned within the chamber

2506, such as shown in **FIG. 3**. The device **2500** may further include a second housing **2508** comprising a sheath flow channel **2510** that surrounds a primary or main powder flow channel **2512**. The device **2500** may further include a plurality of flow bypass channels **2514** that are formed within the second housing **2508** or enter the sheath flow channel **2510** parallel to a longitudinal axis of the main powder flow channel **2512**. The flow bypass channels **2514** may be in fluid connection with the sheath flow channel **2510**. Further, referring specifically to **FIG. 26**, in some embodiments, the flow bypass channels **2514** may be formed anywhere along a length **2513** of the second housing **2508**. Still further, the flow bypass channels **2514** may be formed at any predetermined and desired angle C within the second housing **2508** as measured with reference to a central axis D, and an axis E perpendicular to the central axis D, of the device **2500**. For example, in **FIG. 26**, while the flow bypass channels **2514** are illustrated as approximately normal to the central axis D, the flow bypass channels **2514** may be angled with respect to the central axis D (as measured with respect to the axis E). Angled flow bypass channels **2514** may in some instances be more easily fabricated via an injection molding process. Other ones of the devices **400**, **1300**, etc., of the present disclosure may exhibit such characteristics as well.

FIGS. 30-33 show the second housing **2508** of the device **2500** in multiple views. In particular, **FIG. 30** shows a first perspective view of the second housing **2508**. **FIG. 31** shows a second perspective view of the second housing **2508**. **FIG. 32** shows a first end view of the second housing **2508**. **FIG. 33** shows a second end view of the second housing **2508**.

FIGS. 34-37 show the first housing **2502** of the device **2500** in multiple views. In particular, **FIG. 34** shows a first perspective view of the first housing **2502**. **FIG. 35** shows a second perspective view of the first housing **2502**. **FIG. 36** shows a first end view of the first housing **2502**. **FIG. 37** shows a second end view of the first housing **2502**.

A coupling mechanism that may be used to fasten the first housing **2502** with the second housing **2508** may be understood upon inspection of at least **FIGS. 30-37**. In particular, the second housing **2508** may include a first locking member **2516** and a second locking member **2518** (see **FIG. 30**). The first housing **2502** may include a first bar **2520** and a second bar **2522**. The first locking member **2516** may also include a first stop surface **2524** and a second stop surface **2528**, and the second locking member **2518** may also include a first stop surface **2526** and a second stop surface **2530**. In practice, the first housing **205** and the second housing **2508** may be coupled

and decoupled in manner similar to that described above in connection with the first example powder dispersion device or inhaler **1300**. Such interchangeability may be beneficial in many respects. For example, when a bead **302** of different size is desired, the first housing **2502** may be removed and replaced with another first housing **2502** having a bead **302** of different size than the original housing. Other benefits are possible as well.

Additionally, referring specifically to **FIG. 30**, a retaining member **2532** of the second housing **2508** may include one or more openings sized to permit air and powdered or otherwise aerosolized medicament to pass through the retaining member **2532**, and to prevent the bead **302** from passing through the retaining member **2532**. Other embodiments are possible. For example, in some embodiments, a different mechanism may be used and to prevent the bead **302** from exiting the chamber **2506** into the second housing **2508**.

Referring now to **FIGS. 38-43**, a third example powder dispersion device or inhaler **3700** is shown in accordance with the principles of the present disclosure. In general, the device **3700** may be configured to be coupled to another inhaler device. In particular, **FIG. 38** shows a first perspective view of the device **3700**. **FIG. 39** shows a second perspective view of the device **3700**. **FIG. 40** shows a third perspective view of the device **3700**. **FIG. 41** shows a fourth perspective view of the device **3700**. **FIG. 42** shows a fifth perspective view of the device **3700**. **FIG. 43** shows a sixth perspective view of the device **3700**.

In general, the device **3700** may be similar to the device **400**, the device **1300**, and/or the device **2500**, respectively, as discussed above in connection with **FIGS. 1-37**. In particular, the device **3700** may be similar to or otherwise correspond to the first housing **402** of the device **400**, the first housing **1302** of the device **1300**, and/or the first housing **2502** of the device **2500**. For example, the device **3700** may include a housing **3702** comprising an inlet **3704** and a chamber **3706**. Additionally, although not expressly shown, the bead **302** may be positioned within the chamber **3706**, such as shown in **FIG. 3**. In this example, the device **3700** may be coupled to either of the second housing **404** of the device **400**, the second housing **1308** of the device **1300**, and the second housing **2508** of the device **2500**. For example, the housing **3702** may include a first bar **3708** and a second bar **3710**. In practice, the housing **3704** may be, for example, coupled and decoupled to the second housing **2508** of the device **2500** in manner similar to that described above in connection with the device **1300**. Such interchangeability may be beneficial in many respects. For example, when a bead **302** of different size is desired, the first housing **2502** may

be removed and replaced with another first housing **2502** having a bead **302** of different size than the original housing. Other benefits are possible as well.

Although the subject matter has been described in language specific to structural features and/or methodological acts, it is to be understood that the subject matter defined in the appended claims is not necessarily limited to the specific features or acts described above. Rather, the specific features and acts described above are disclosed as example forms of implementing the claims.

WHAT IS CLAIMED IS:

1. A dry powder inhaler, comprising:

a powder storage that is configured to hold a powdered medicament;

an inlet channel that is adapted to receive air and powdered medicament from the powder storage;

a dispersion chamber that is adapted to receive air and powdered medicament from the inlet channel, the chamber holding an actuator that is movable within the dispersion chamber; and

an outlet channel through which air and powdered medicament exit the inhaler to be delivered to a patient;

wherein the geometry of the inhaler is such that a flow profile is generated within the dispersion chamber that causes the actuator to oscillate, thus enabling the oscillating actuator to deaggregate the powdered medicament passing through the dispersion chamber to be entrained by the air and delivered to the patient through the outlet channel.

2. The dry powder inhaler of claim **1**, wherein a cross-sectional area of a flow path through the inhaler undergoes a step increase at the entrance to the dispersion chamber.

3. The dry powder inhaler of claim **1**, wherein a ratio of the diameter of the dispersion chamber to that of the inlet channel is within a range of about greater than 1.0 to about 3.0.

4. The dry powder inhaler of claim **1**, wherein the inlet channel comprises a tube.

5. The dry powder inhaler of claim **1**, wherein the inlet channel comprises a tube with a cross-section that varies along the length of the tube.

6. The dry powder inhaler of claim **1**, wherein the outlet channel comprises a tube with a cross-section that varies along the length of the tube.

7. The dry powder inhaler of claim **1**, wherein the outlet channel is integral to a mouthpiece adapted to be placed within the mouth of the patient.

8. The dry powder inhaler of claim **1**, wherein the outlet channel is integral to a nasal adapter adapted to conform to at least one nostril of the patient.

9. The dry powder inhaler of claim **1**, further comprising one or more bypass channels that receive supplemental air from external the inhaler, and deliver the supplemental air to the patient

without the supplemental air having passed through at least one of a powder storage chamber and the dispersion chamber.

10. The dry powder inhaler of claim **1**, further comprising a second chamber in fluid connection with the dispersion chamber.

11. The dry powder inhaler of claim **1**, further comprising a second chamber in fluid connection with the dispersion chamber, wherein air and powdered medicament exiting the dispersion and second chambers are delivered to the outlet channel.

12. The dry powder inhaler of claim **1**, further comprising a second chamber in fluid connection with the dispersion chamber, and wherein the dispersion and second chambers are similar in at least one dimension.

13. The dry powder inhaler of claim **1**, wherein the powder storage is a receptacle containing an amount of the powdered medicament.

14. The dry powder inhaler system of claim **1**, further comprising a piercing member configured to perforate the powder storage, containing an amount of the powdered medicament, to transfer air and powdered medicament to the inlet channel.

15. The dry powder inhaler system of claim **1**, wherein the powder storage is selected from one of: a capsule; a blister; and a powder reservoir.

16. The dry powder inhaler system of claim **1**, wherein the actuator comprises a second powdered medicament adhered thereto.

17. The dry powder inhaler system of claim **1**, wherein the actuator comprises a second powdered medicament adhered thereto, and wherein the geometry of the inhaler is such that a flow profile is generated within the chamber that causes the actuator to oscillate, thus enabling the oscillating actuator to effectively disperse powdered medicament passing through the chamber, and the second powdered medicament, to be entrained by the air and delivered to the patient through the outlet channel.

18. The dry powder inhaler system of claim **1**, further comprising a retaining member disposed at an end of the dispersion chamber opposite the inlet channel, the retaining member having one or more openings sized to permit air and powdered medicament to pass through the retaining member, and to prevent the actuator from passing through the retaining member.

19. A method for aerosolizing a powdered medicament, comprising:

providing an inhaler comprising an inlet channel, a chamber that is adapted to receive air and powdered medicament from the inlet channel, an actuator disposed in the chamber, and an outlet channel;

supplying a powdered medicament to the inlet channel; and

inducing air to flow through the outlet channel to cause air and the powdered medicament to enter into the chamber through the inlet channel, and to cause the actuator to oscillate within the chamber to effectively disperse powdered medicament passing through the chamber to be entrained by the air and delivered to the patient through the outlet channel.

20. A method as in claim **19**, wherein the powdered medicament is stored within a storage compartment, and wherein the powdered medicament is transferred from the storage compartment through the inlet channel and into the chamber as flow is induced through the chamber.

21. A method as in claim **19**, further comprising inhaling from a mouthpiece to induce the flow through the chamber.

22. A powder dispersion device, comprising:

a housing having a central, longitudinal axis, wherein the housing includes a chamber, a flow inlet in fluid communication with the chamber and a flow outlet in fluid communication with the chamber;

a powder storage compartment that is configured to store a powdered medicament for introduction into the chamber through the flow inlet; and

a bead positioned within the chamber such that it may rapidly move back and forth within the chamber along the longitudinal axis, wherein the bead is sized in dimension so that the bead when oscillating deagglomerates the powdered medicament so that a desired aerodynamic particle size distribution is achieved upon exit from the flow outlet.

23. A powder dispersion device as in claim **22**, wherein the desired aerodynamic particle size distribution is obtained as a function of a diameter of the bead.

24. A powder dispersion device as in claim **22**, wherein an inner diameter of the flow inlet is less than an inner diameter of the chamber.

25. A powder dispersion device as in claim **22**, wherein the flow inlet is one of cylindrical and tapered in geometry.

26. A powder dispersion device as in claim **22**, wherein the inlet is axially aligned with the chamber along the longitudinal axis.

27. A powder dispersion device as in claim **22**, wherein the bead is approximately spherical.

28. A powder dispersion device as in claim **22**, wherein the chamber has a volume flow path that is larger than that of the inlet so as to induce a sudden expansion of a flow stream entering into the chamber from the inlet.

29. A method for aerosolizing a powder, comprising:

providing a powder dispersion device comprising: a housing having a central, longitudinal axis, wherein the housing includes a chamber, a flow inlet in fluid communication with the chamber and a flow outlet in fluid communication with the chamber; and an actuator positioned within the chamber, wherein the actuator is selected to have a size such that upon oscillation it produces a desired range of aerodynamic particle sizes of the powdered medicament;

introducing the amount of powdered medicament into the chamber; and

inducing a flow through the chamber and out the flow outlet, wherein the flow enters the chamber from the flow inlet and rapidly expands when entering the chamber, wherein the flow through the chamber causes the actuator to oscillate within the chamber along the longitudinal axis to aerosolize and deagglomerate the powdered medicament to the desired range of aerodynamic particle sizes so that a desired aerodynamic particle size distribution is achieved upon exit from the flow outlet.

30. A method as in claim **29**, wherein the desired aerodynamic particle size distribution is obtained as a function of a diameter of the bead.

31. A method as in claim **29**, wherein the powdered medicament is stored within a storage compartment, and wherein the powdered medicament is transferred from the storage compartment through the inlet channel and into the chamber as flow is induced through the chamber.

32. A method as in claim **29**, further comprising inhaling from one of a mouthpiece and a nasal adaptor to induce the flow through the chamber.

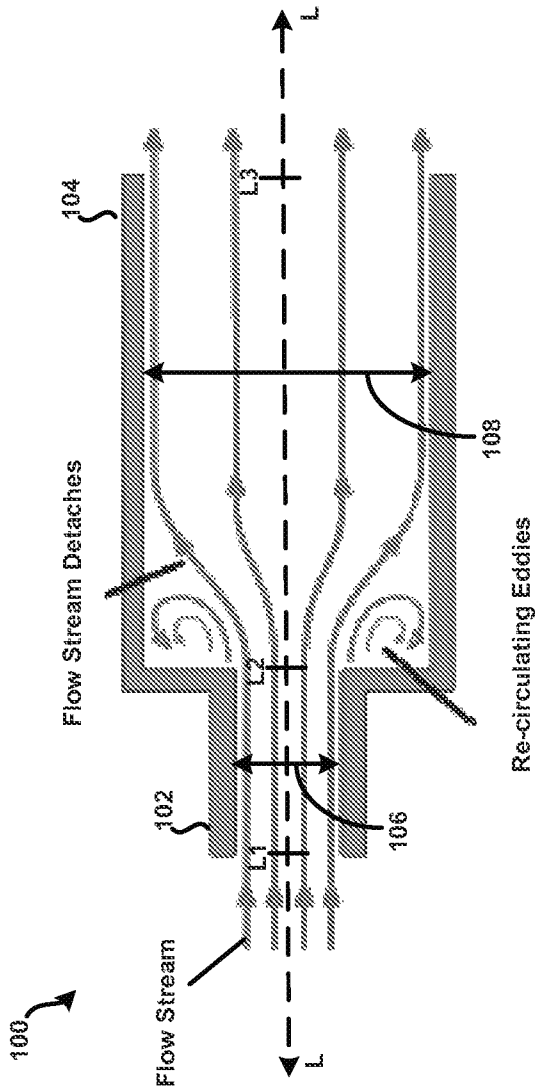
100
Flow Stream
102
104
Flow Stream Detaches
L
L1
L2
L3
106
108
Re-circulating Eddies

FIG. 1

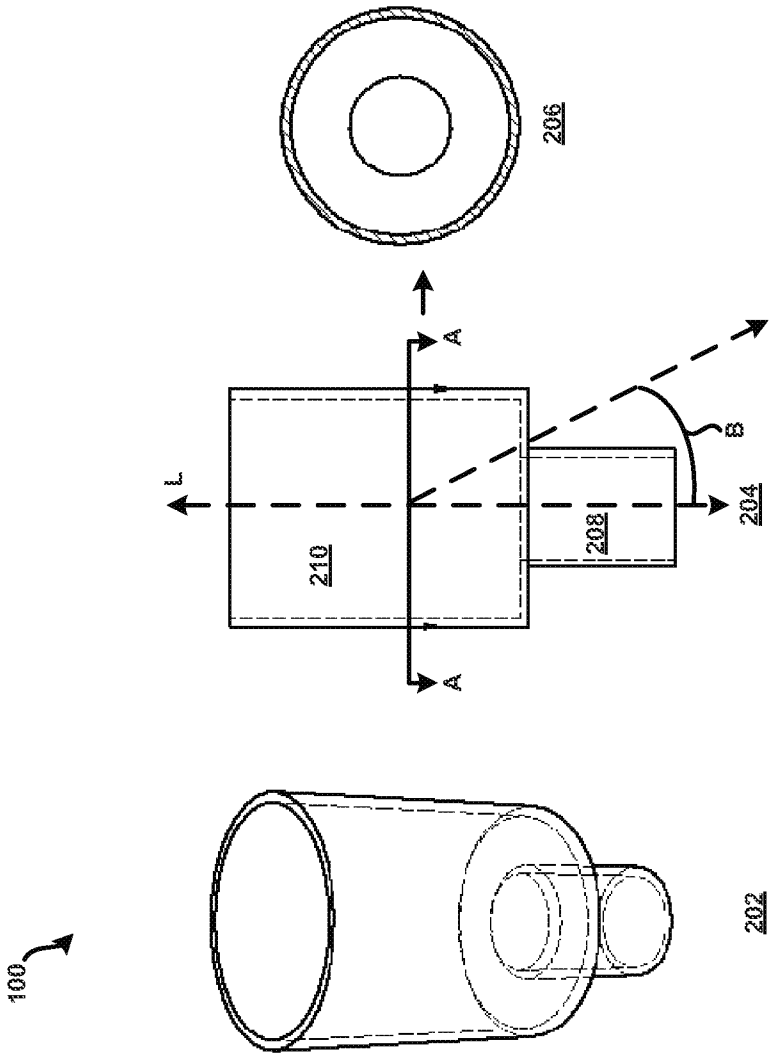

FIG. 2

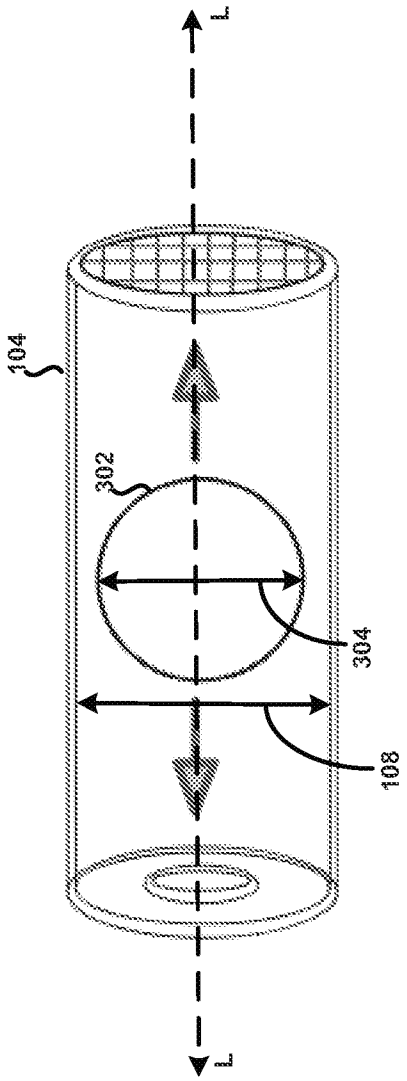

FIG. 3

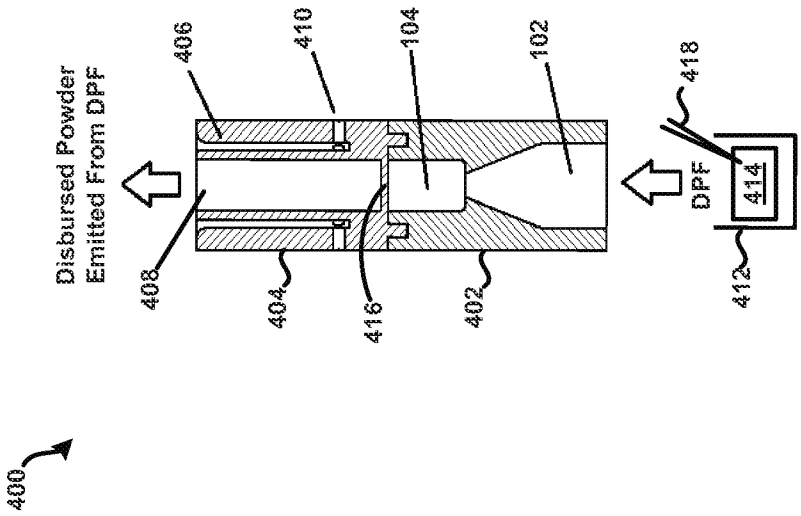
400
Disbursed Powder
Emitted From DPF
406
410
104
102
418
DPF
414
408
404
416
402
412

FIG. 4

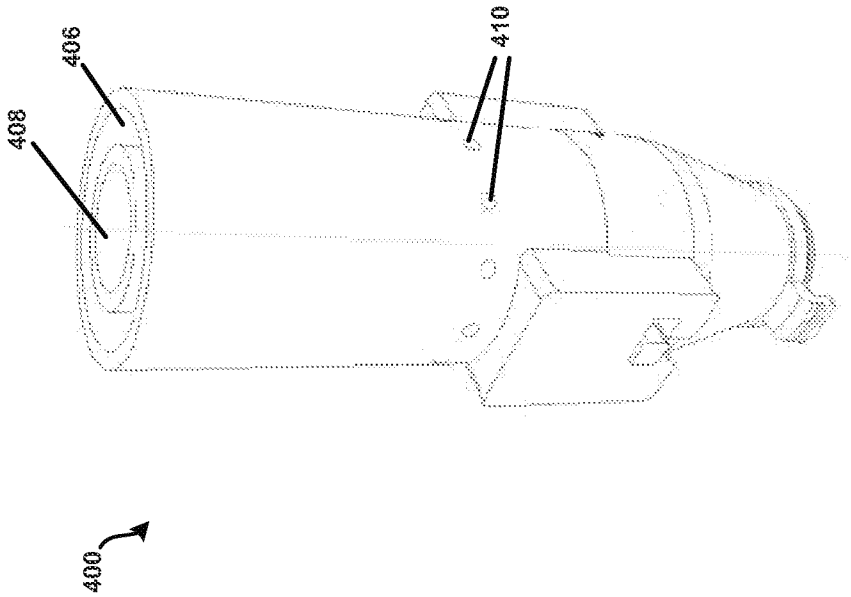

FIG. 5

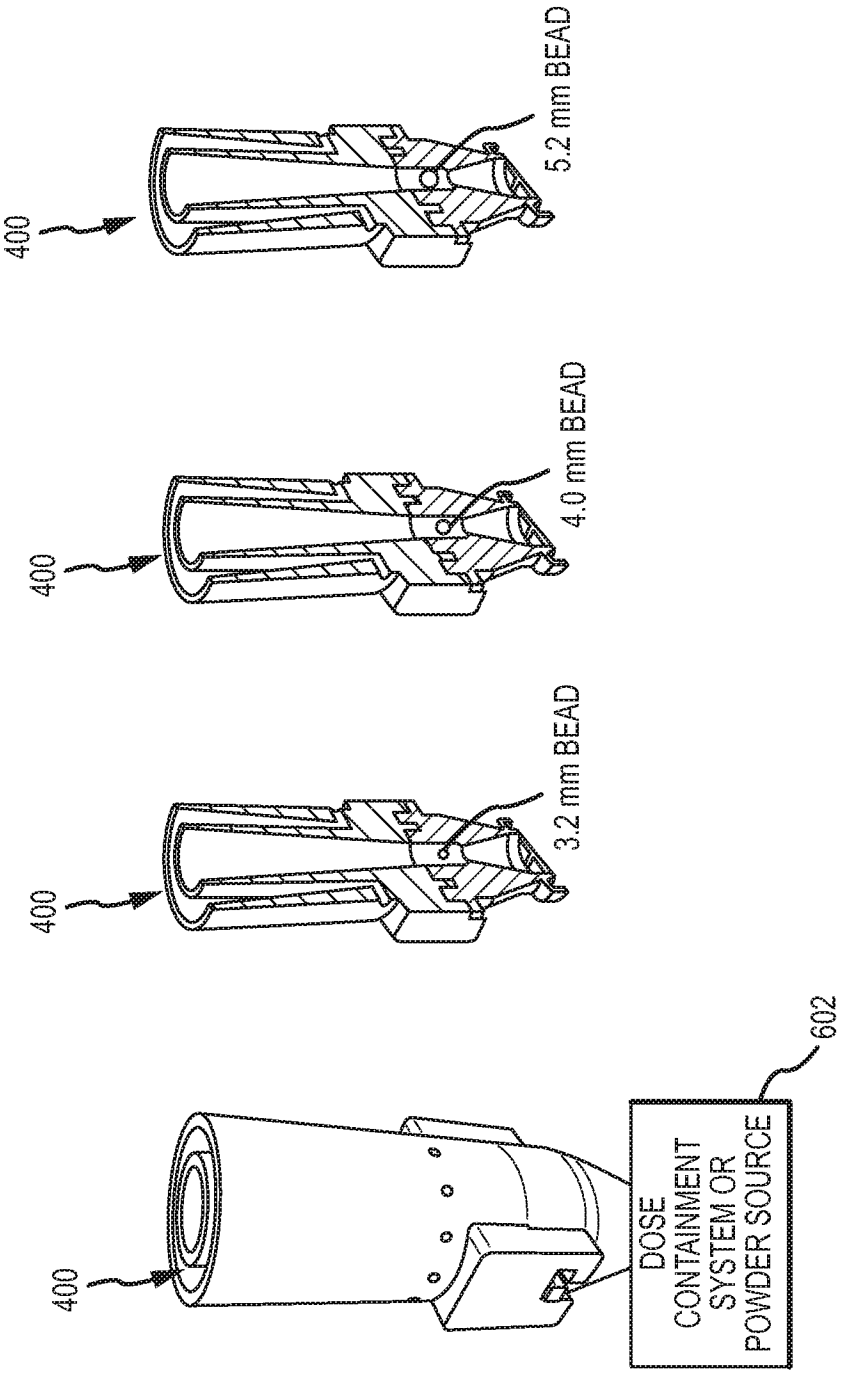
400
5.2 mm BEAD
400
4.0 mm BEAD
400
3.2 mm BEAD
400
DOSE CONTAINMENT SYSTEM OR POWDER SOURCE
602

FIG.6

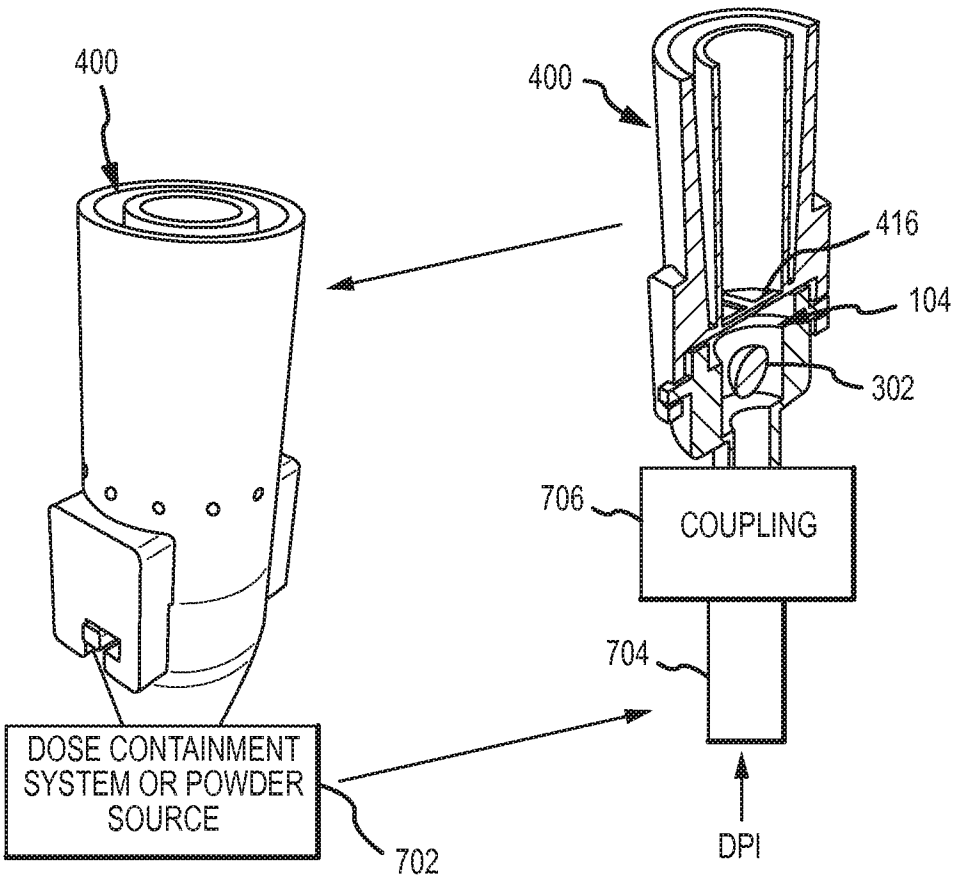
400
400
416
104
302
706
COUPLING
704
DOSE CONTAINMENT SYSTEM OR POWDER SOURCE
702
DPI

FIG.7

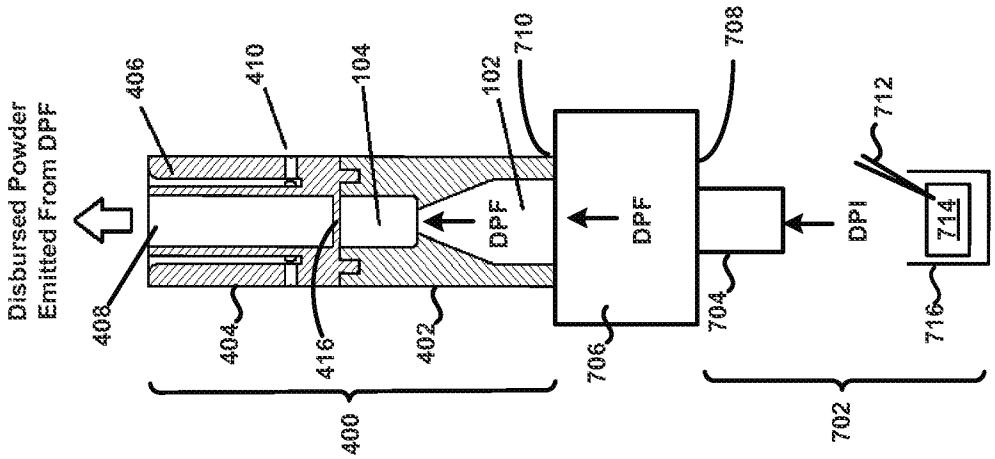
Disbursed Powder
Emitted From DPF
406
410
104
102
710
708
712
408
404
416
402
DPF
DPF
DPI
714
704
706
716
400
702

FIG. 8

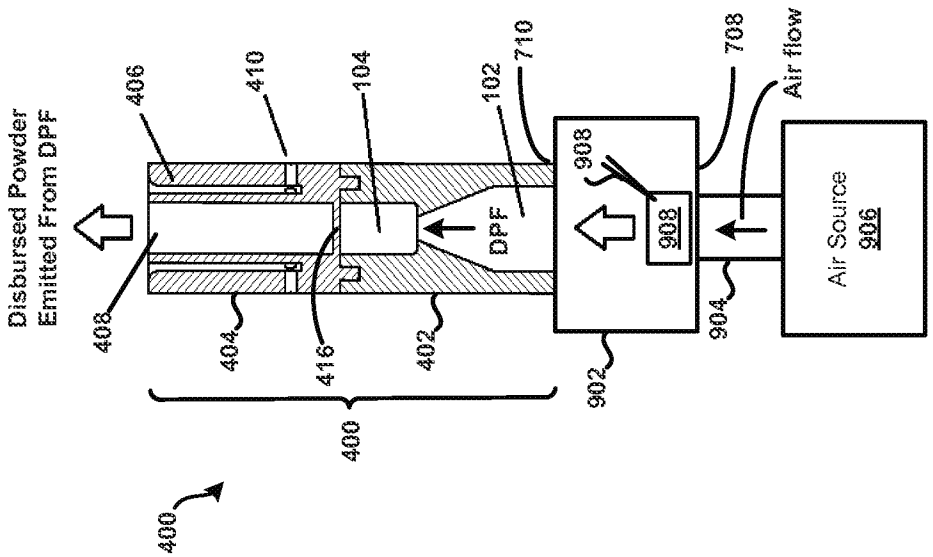
Disbursed Powder
Emitted From DPF
406
410
104
102
710
708
Air flow
908
908
DPF
Air Source
906
408
404
416
402
902
904
400
400

FIG. 9

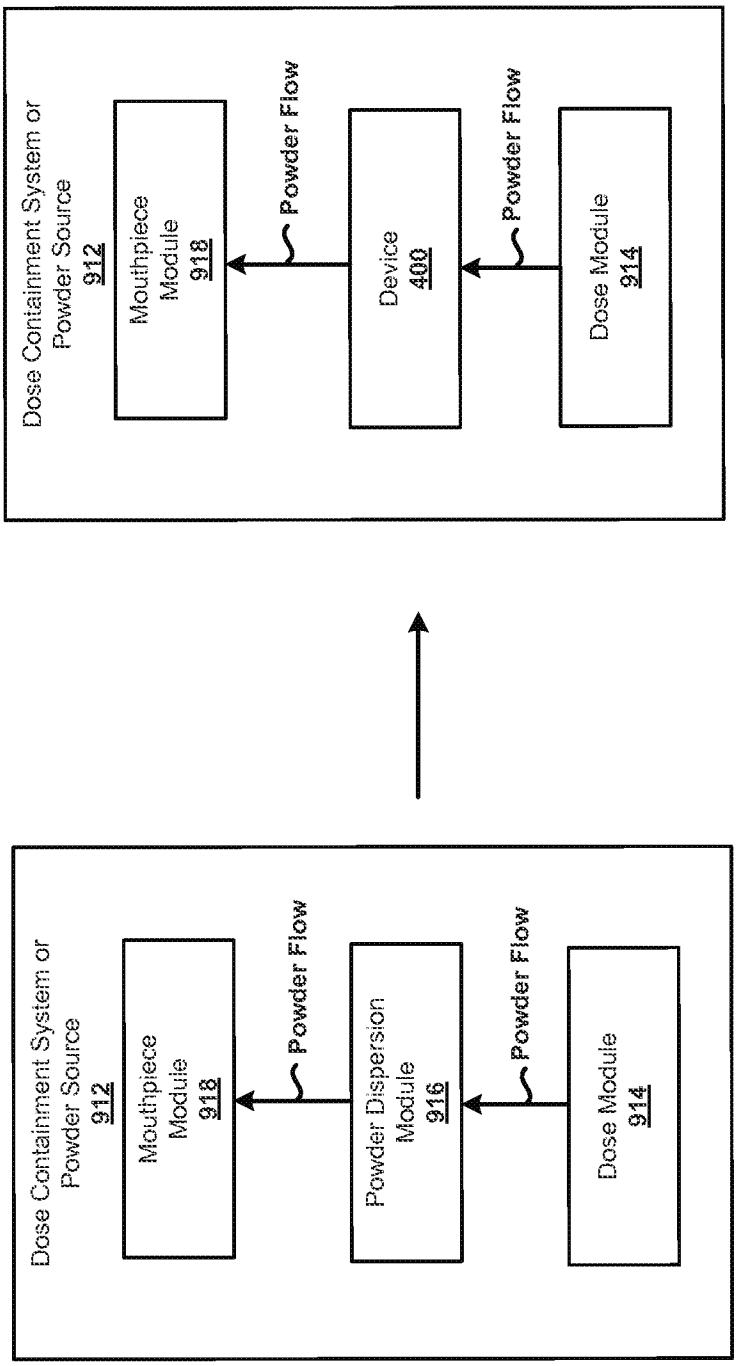
Dose Containment System or Powder Source 912
Mouthpiece Module 918
Powder Flow
Powder Dispersion Module 916
Powder Flow
Dose Module 914
Dose Containment System or Powder Source 912
Mouthpiece Module 918
Powder Flow
Device 400
Powder Flow
Dose Module 914

FIG. 10

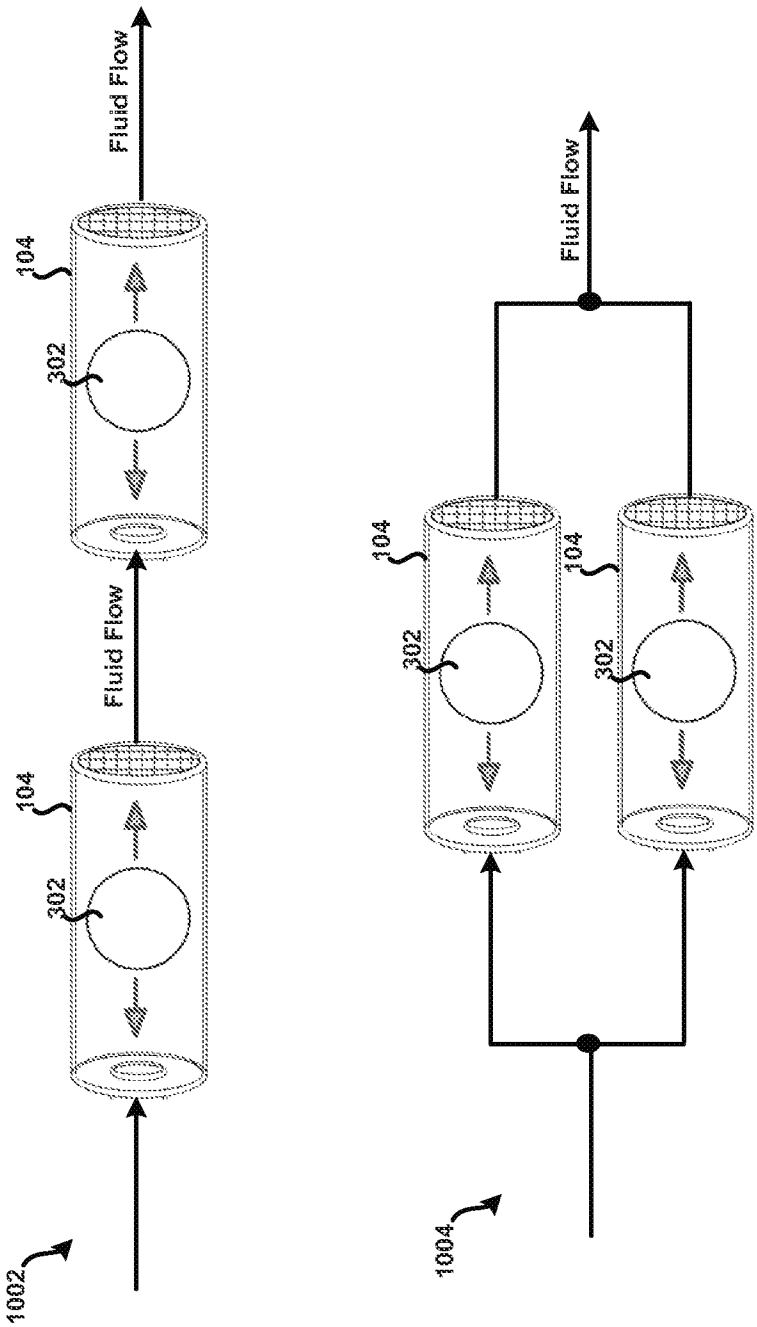
Fluid Flow
104
302
Fluid Flow
104
302
1002
Fluid Flow
104
302
104
302
1004

FIG. 11

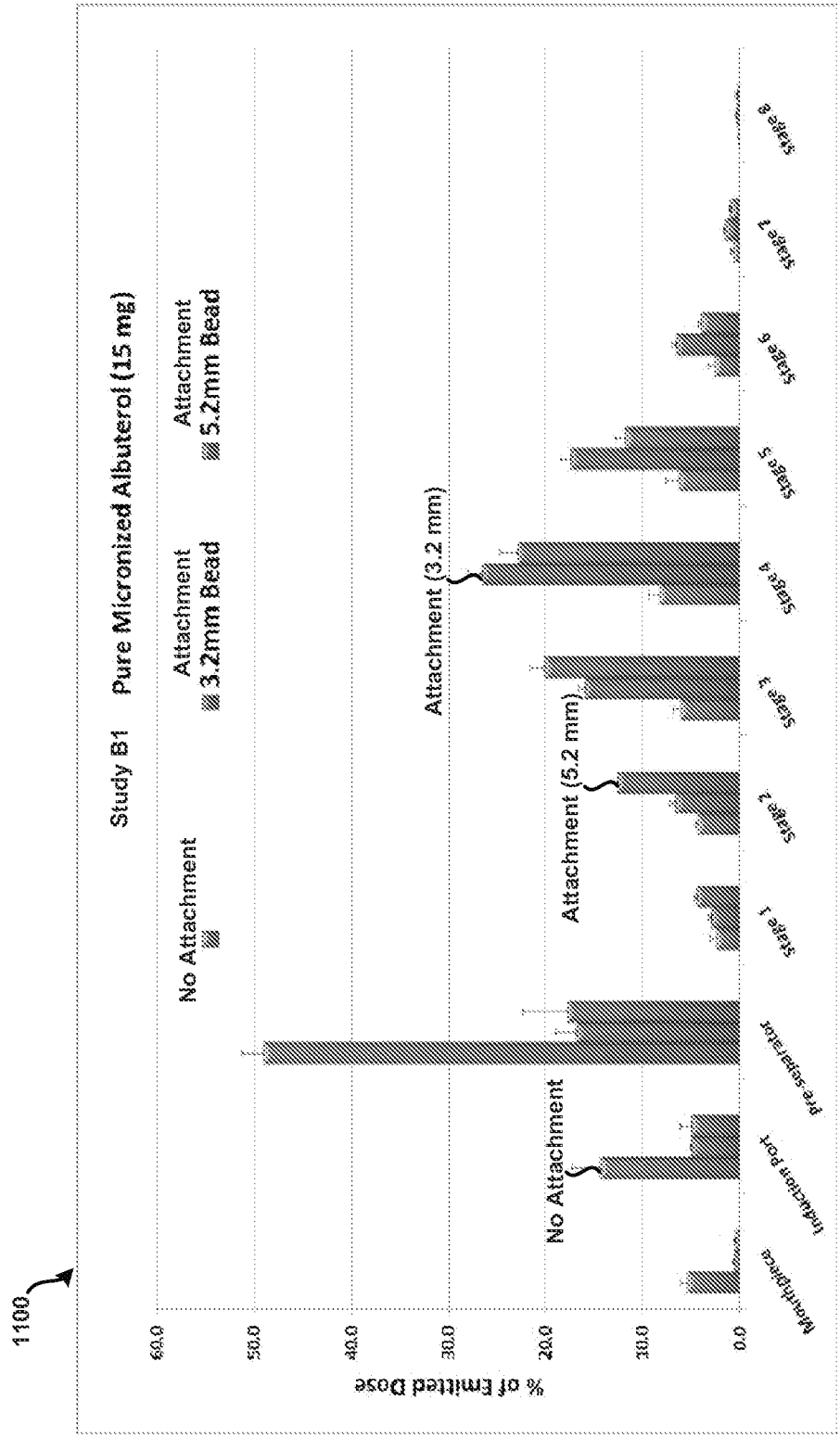
1100
Study B1 Pure Micronized Albuterol (15 mg)
No Attachment
Attachment 3.2mm Bead
Attachment 5.2mm Bead
% of Emitted Dose
60.0
50.0
40.0
30.0
20.0
10.0
0.0
No Attachment
Attachment (5.2 mm)
Attachment (3.2 mm)
Mouthpiece
USP Induction Port
Pre-separator
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Stage 6
Stage 7
Stage 8

FIG. 12

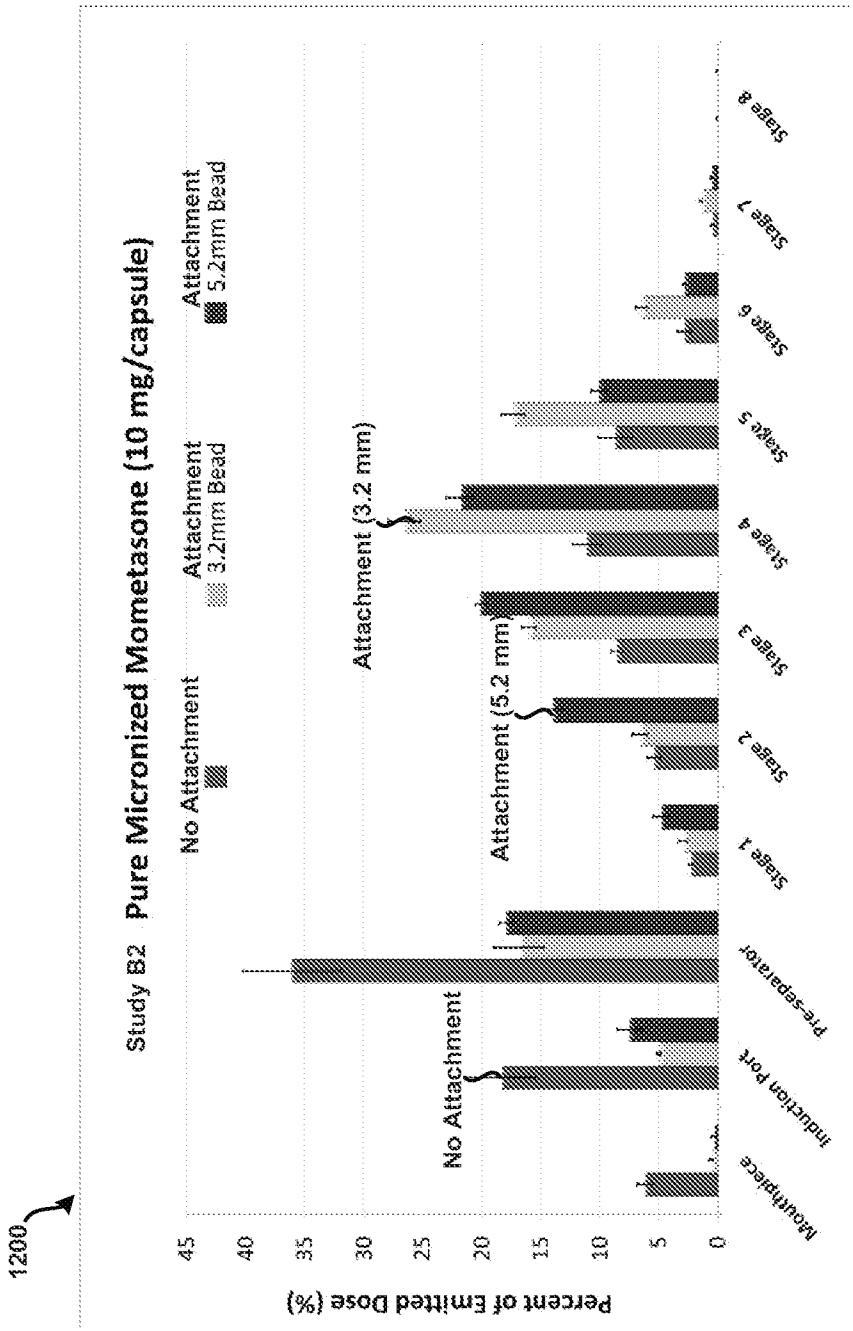
1200
Study B2 Pure Micronized Mometasone (10 mg/capsule)
No Attachment
Attachment 3.2mm Bead
Attachment 5.2mm Bead
Attachment (3.2 mm)
Attachment (5.2 mm)
No Attachment
Percent of Emitted Dose (%)
0
5
10
15
20
25
30
35
40
45
Mouthpiece
Induction Port
Pre-separator
Stage 1
Stage 2
Stage 3
Stage 4
Stage 5
Stage 6
Stage 7
Stage 8

FIG. 13

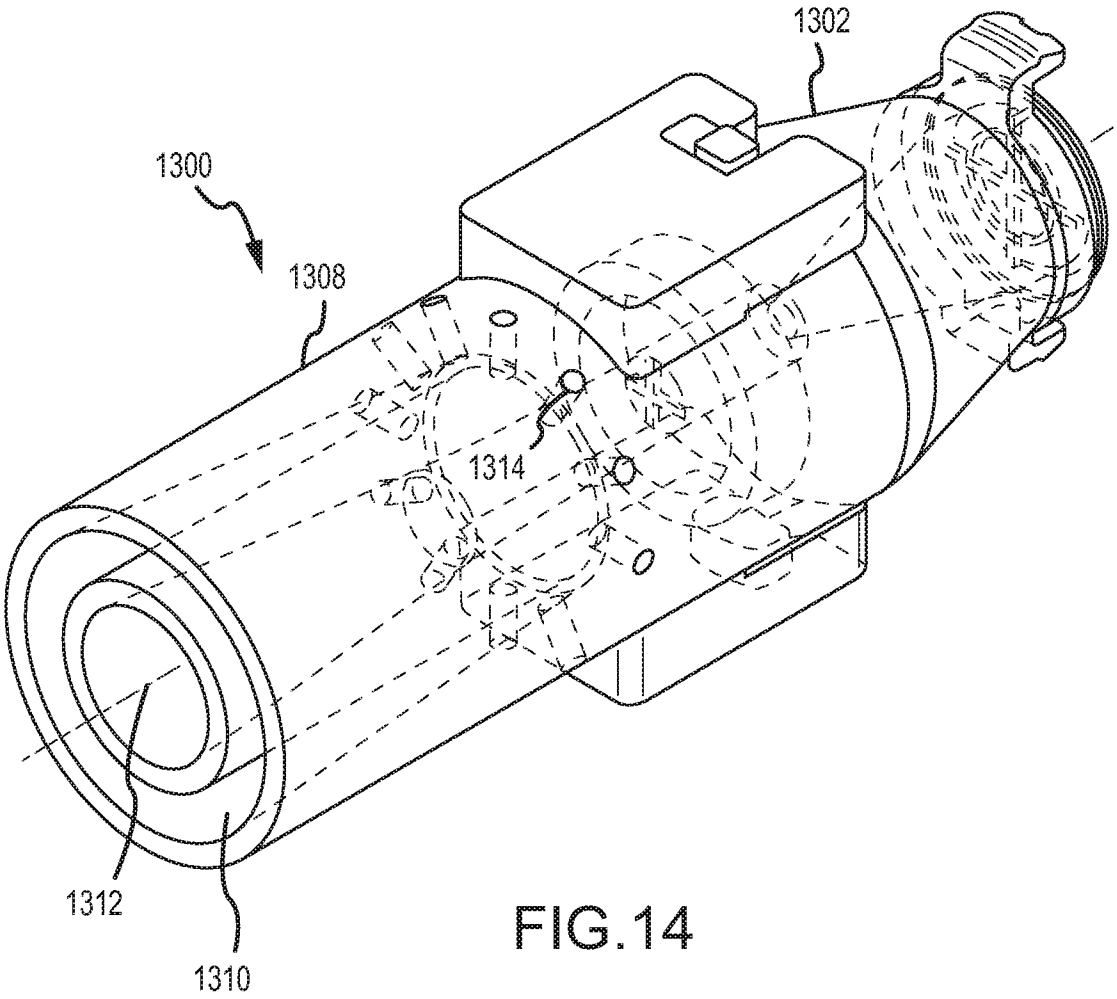

FIG.14

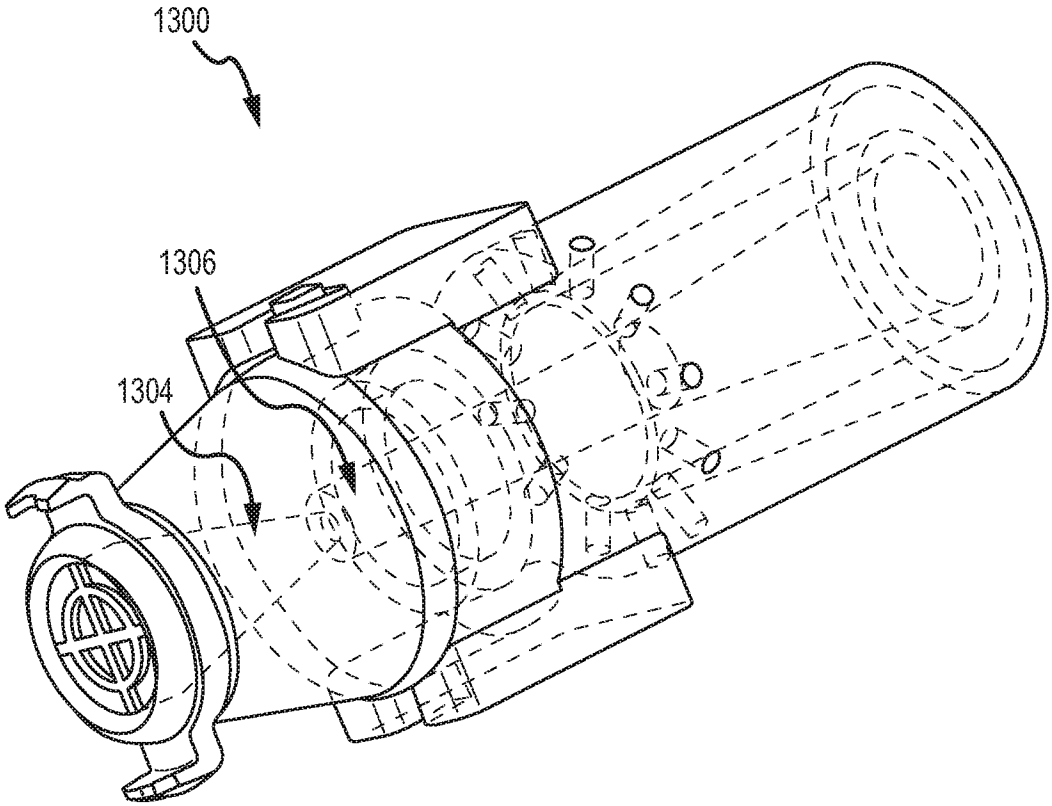

FIG.15

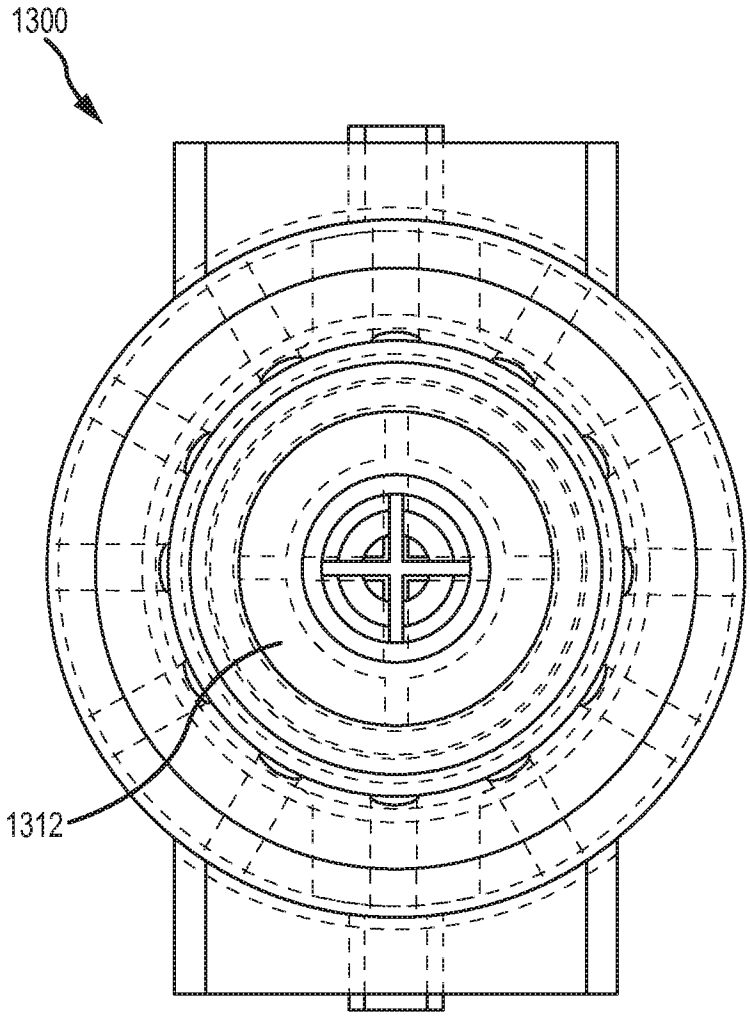

FIG.16

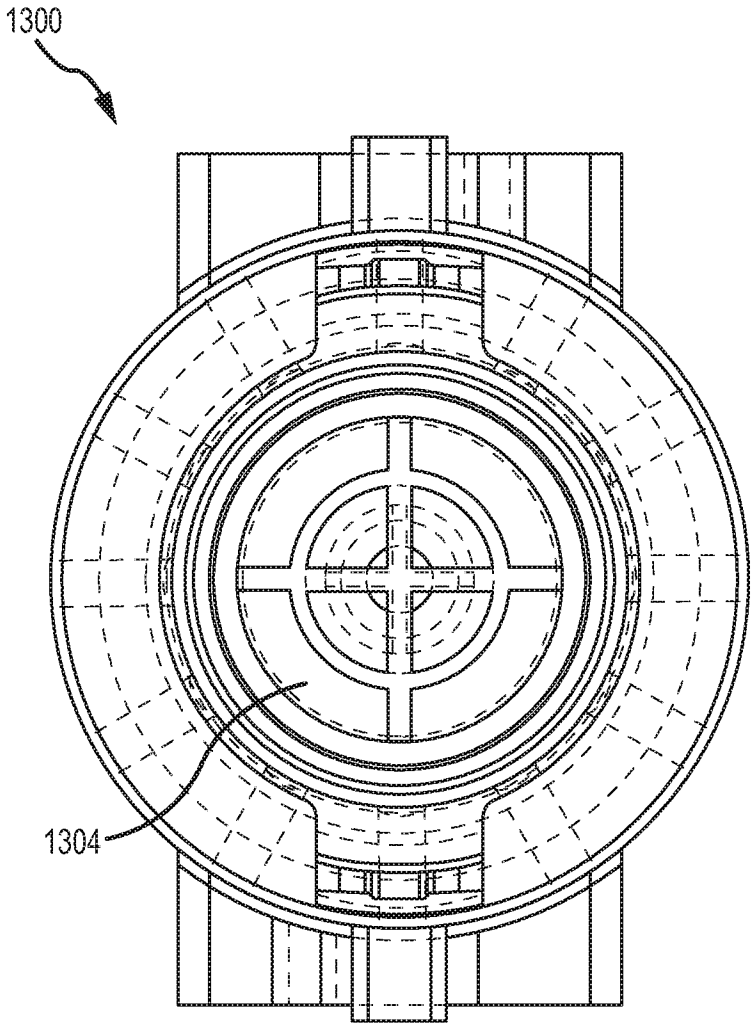

FIG.17

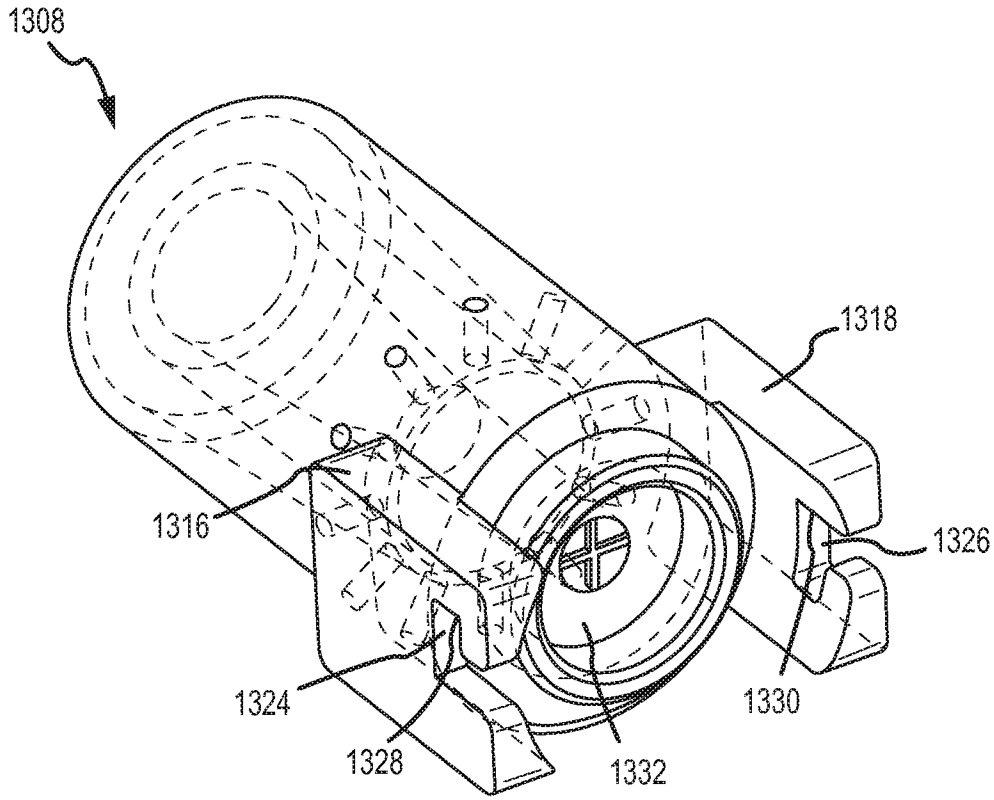

FIG.18

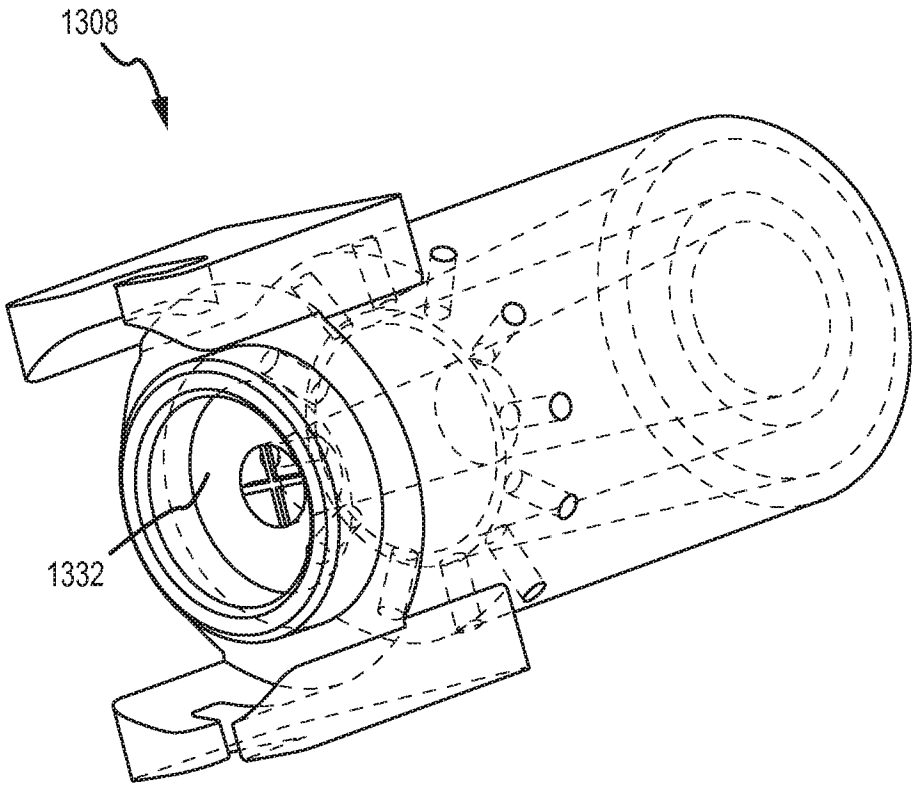

FIG.19

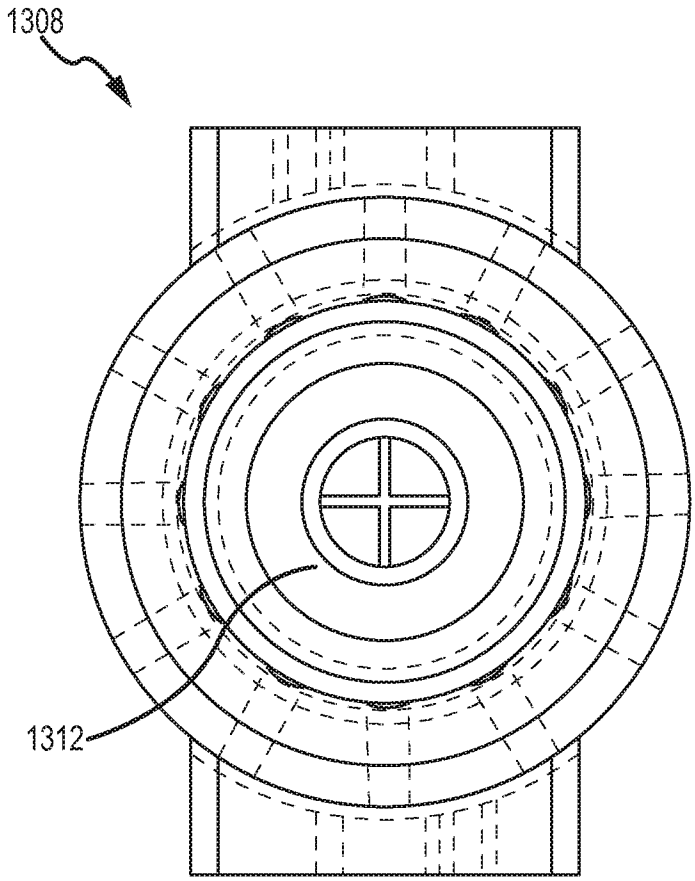

FIG.20

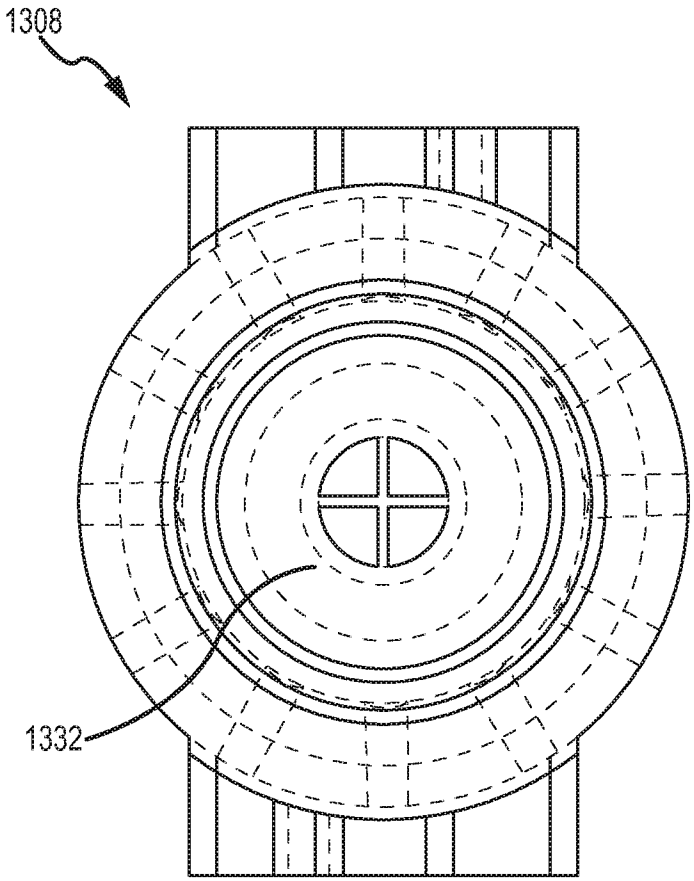

FIG.21

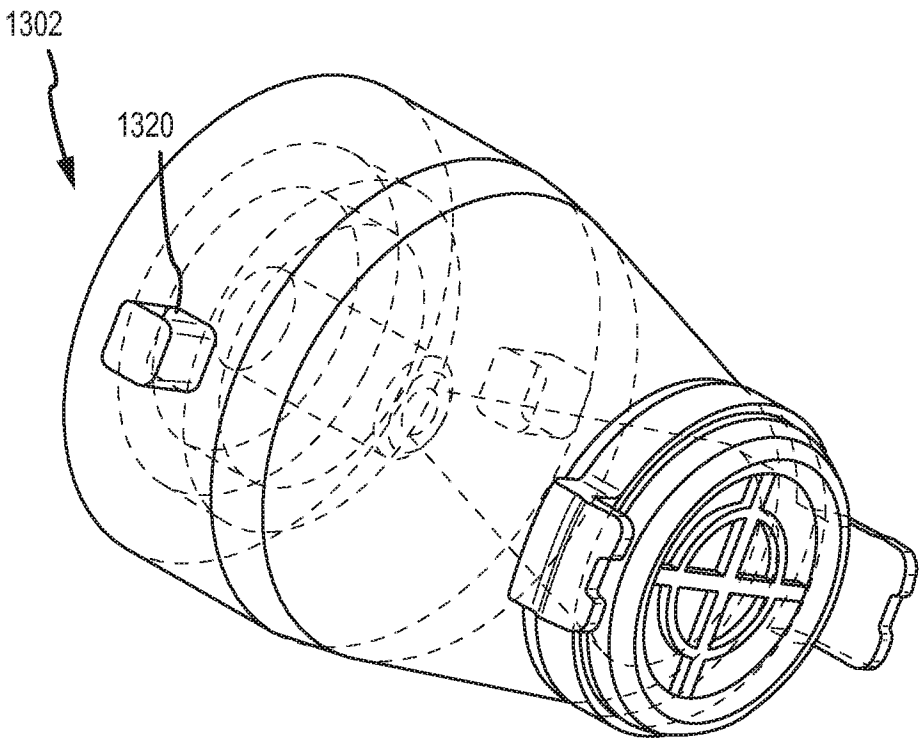

FIG.22

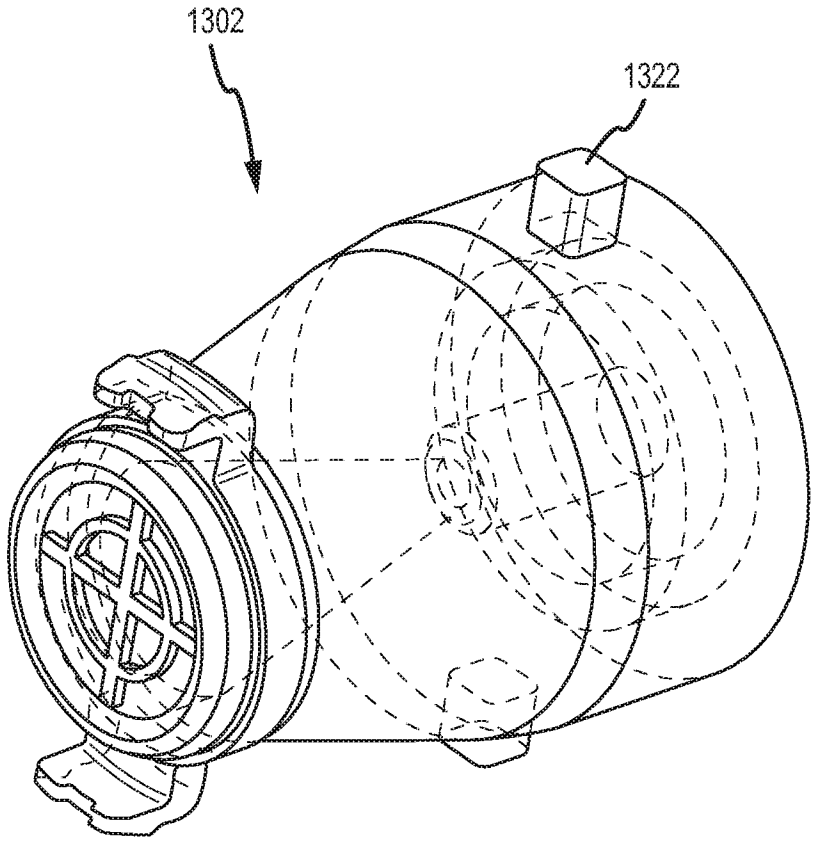

FIG.23

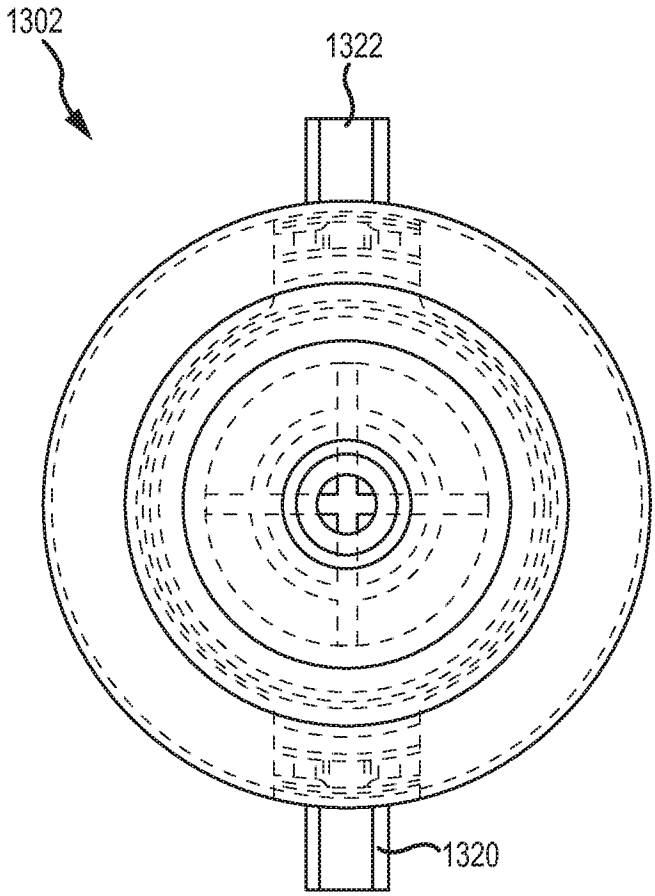

FIG.24

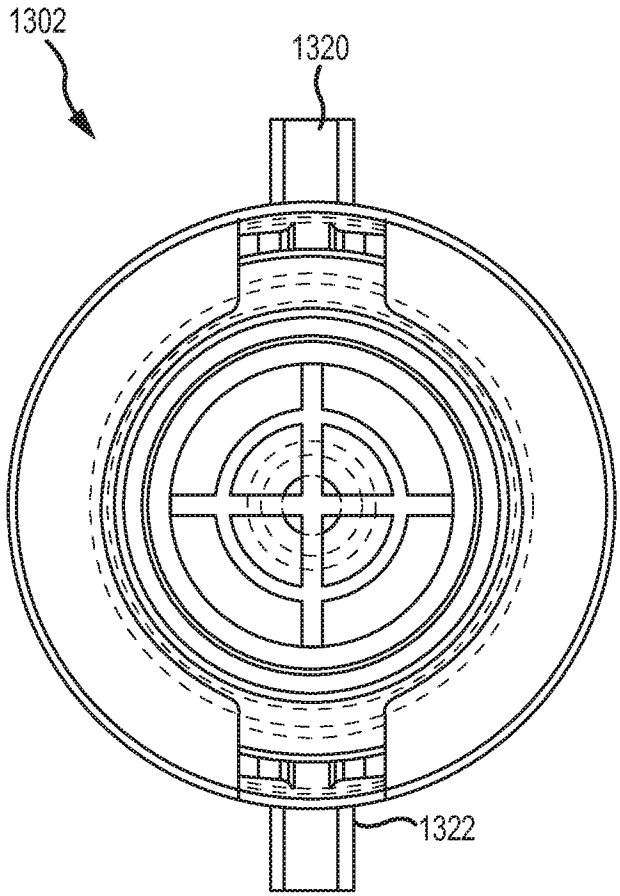

FIG.25

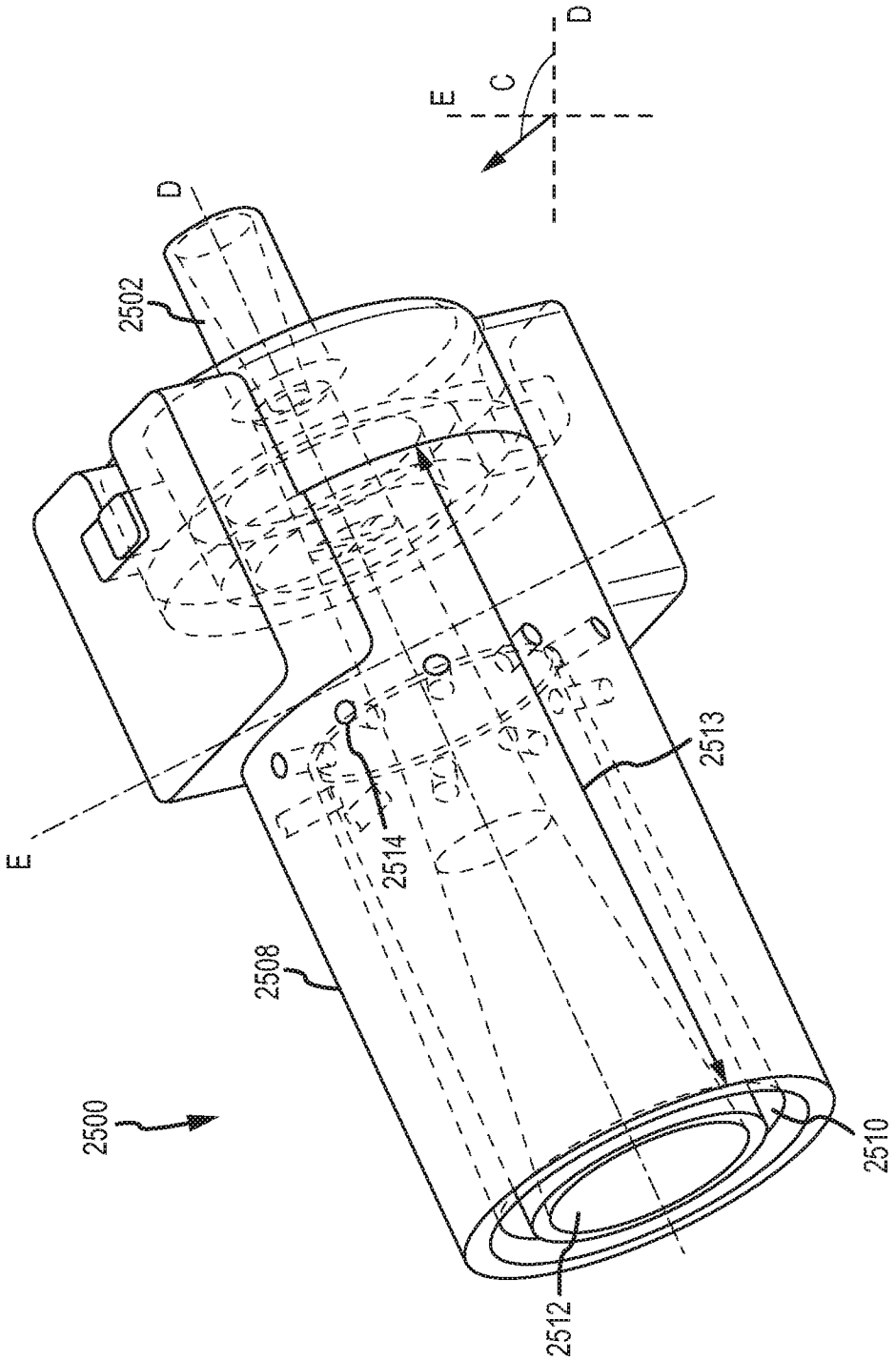

FIG.26

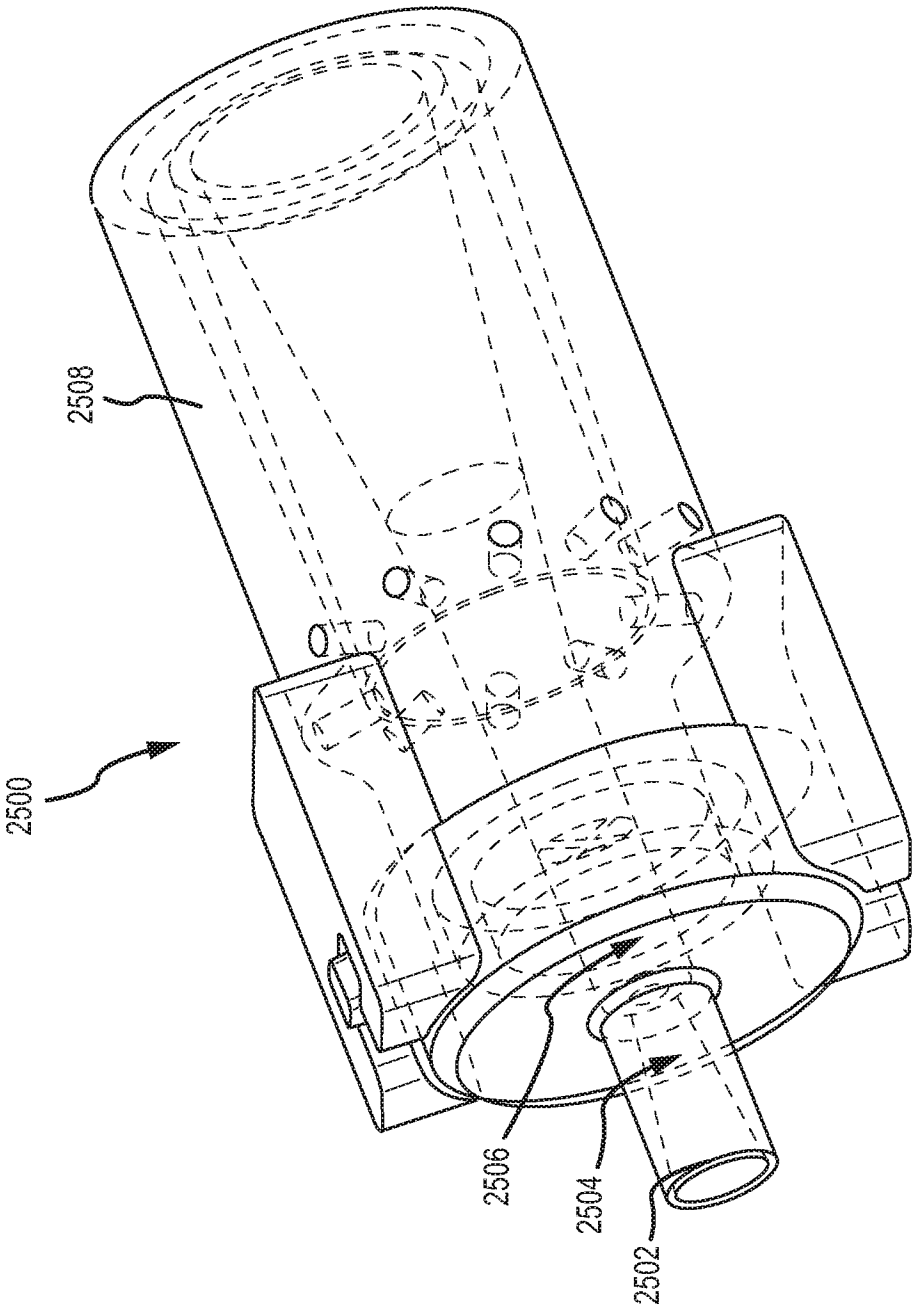

FIG.27

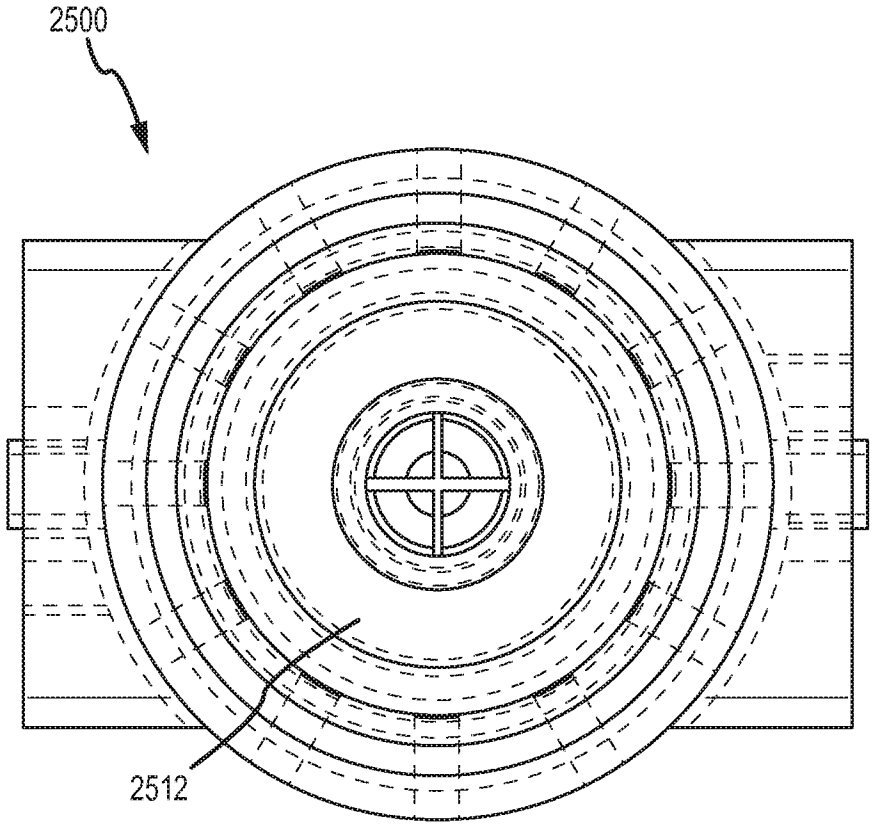

FIG.28

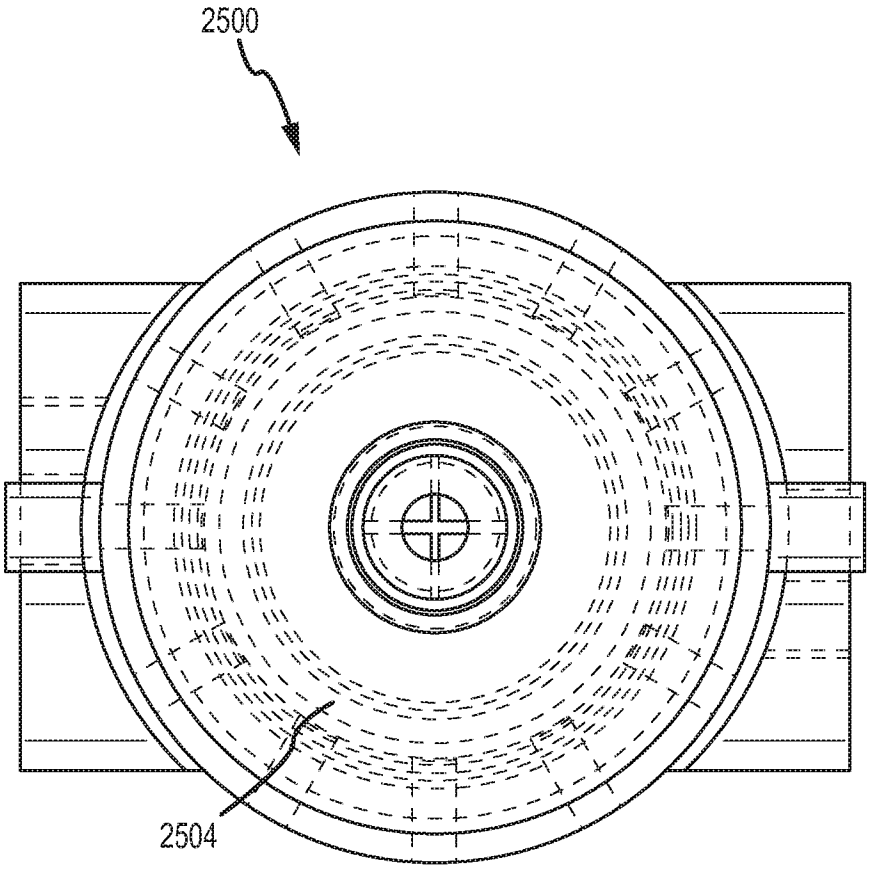

FIG.29

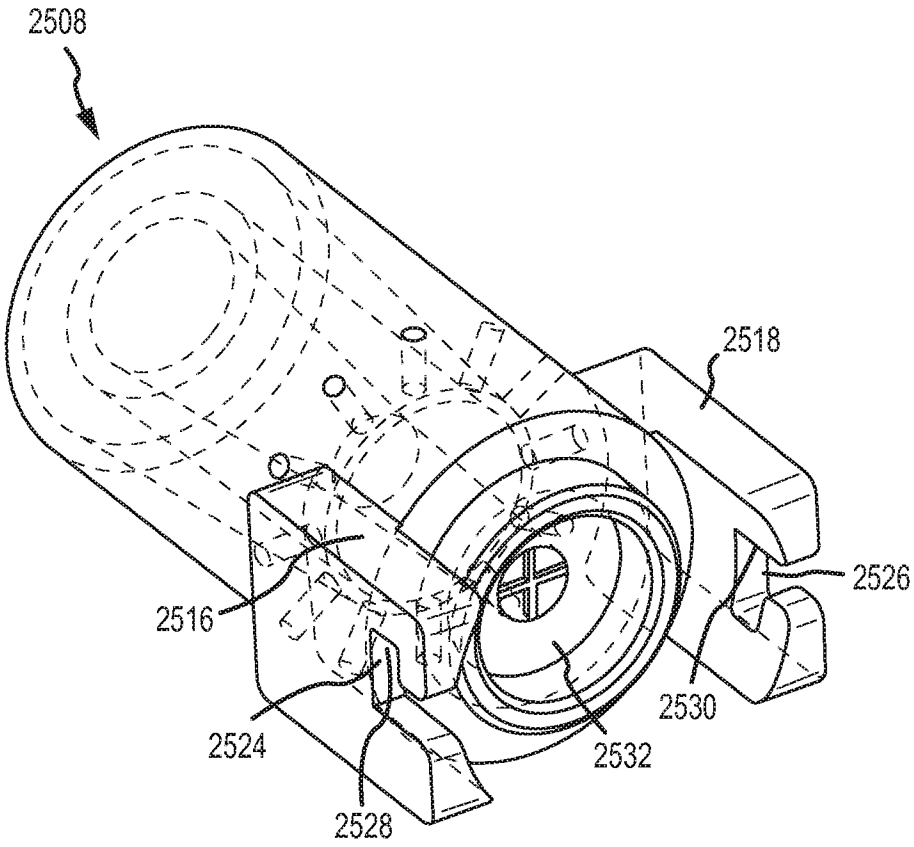

FIG.30

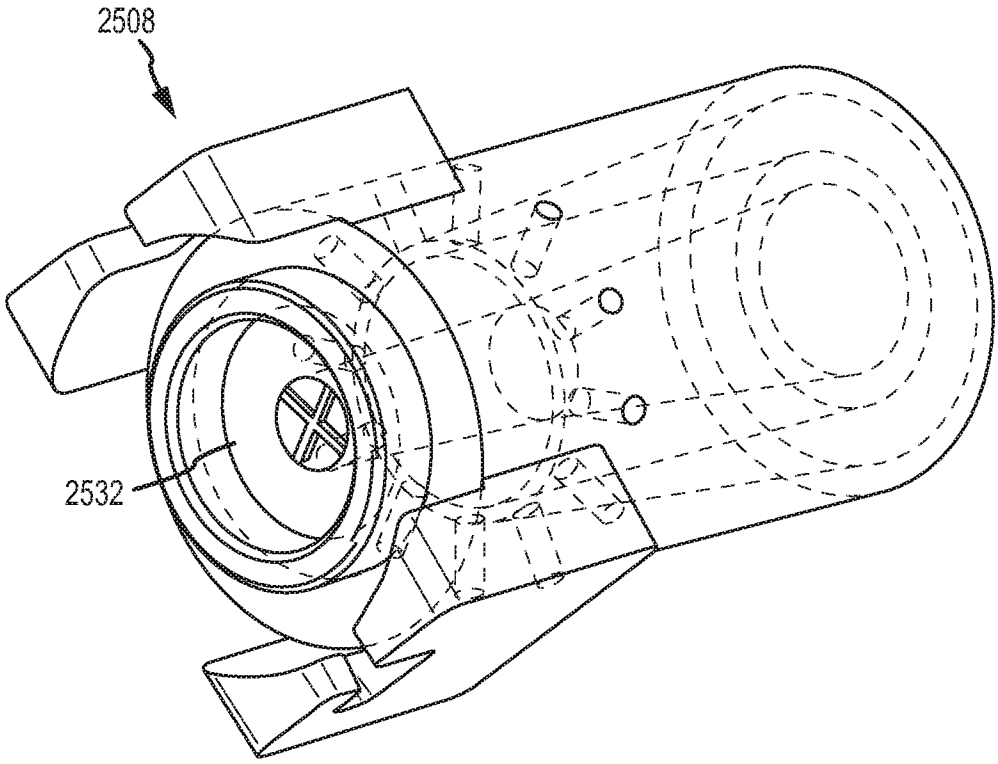

FIG.31

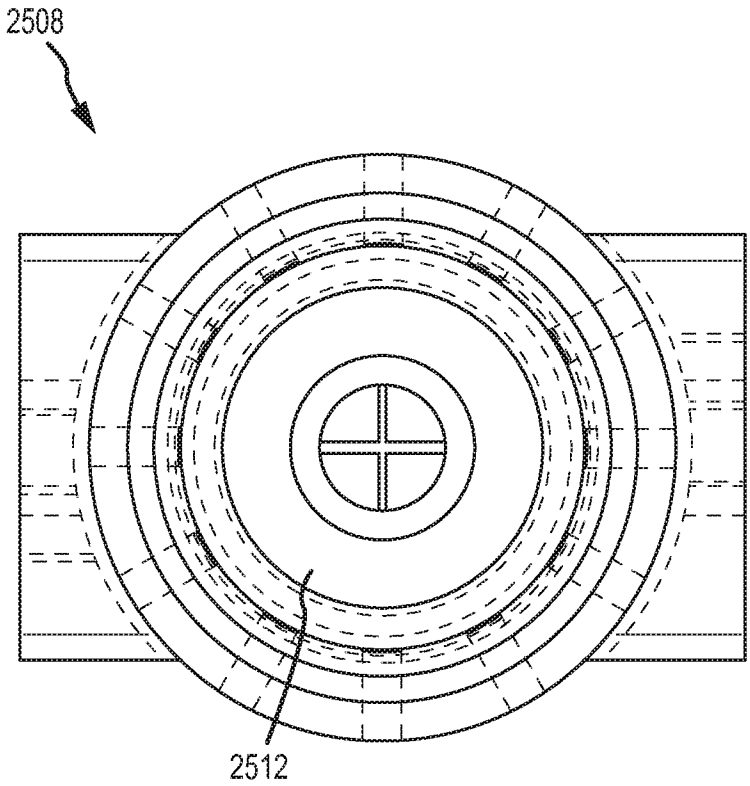

FIG.32

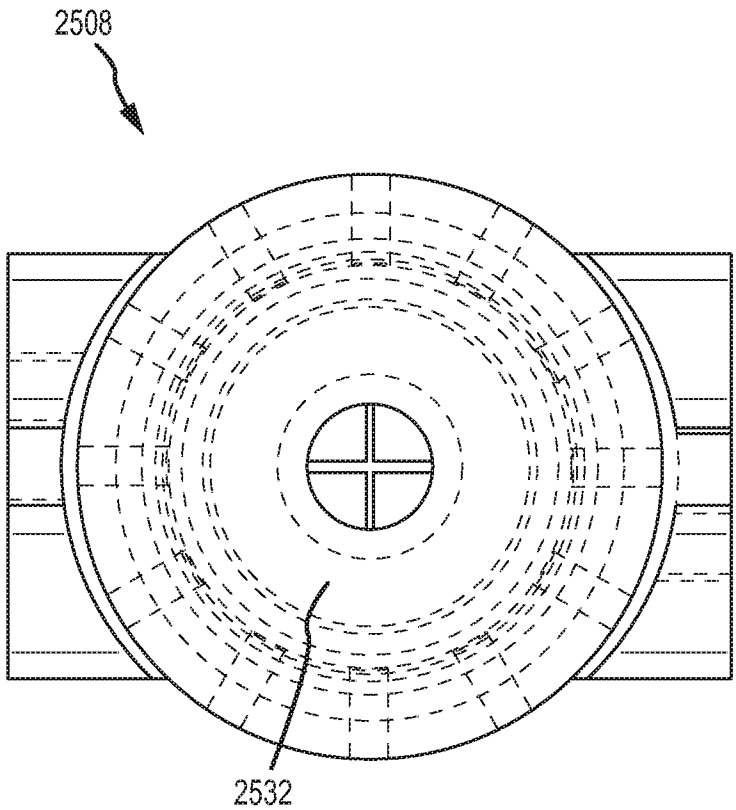

FIG.33

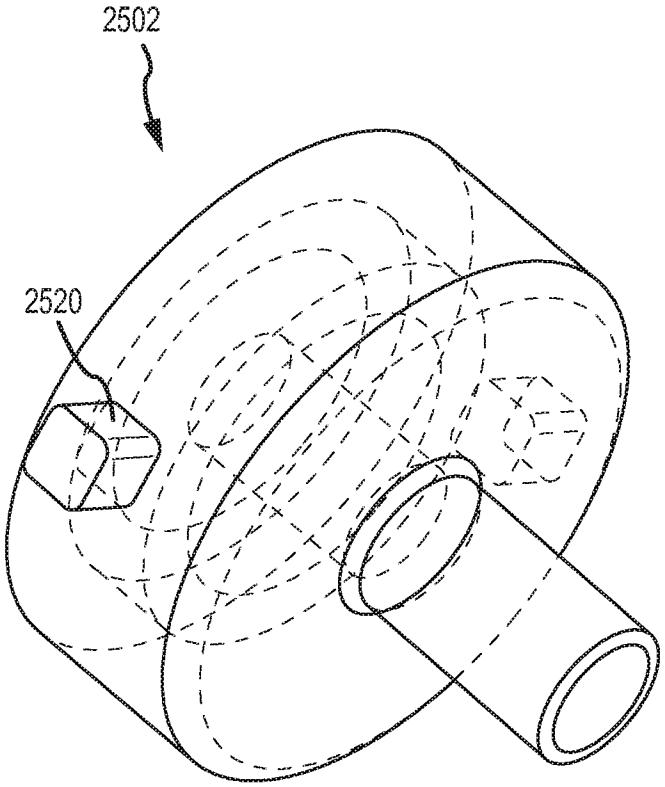

FIG.34

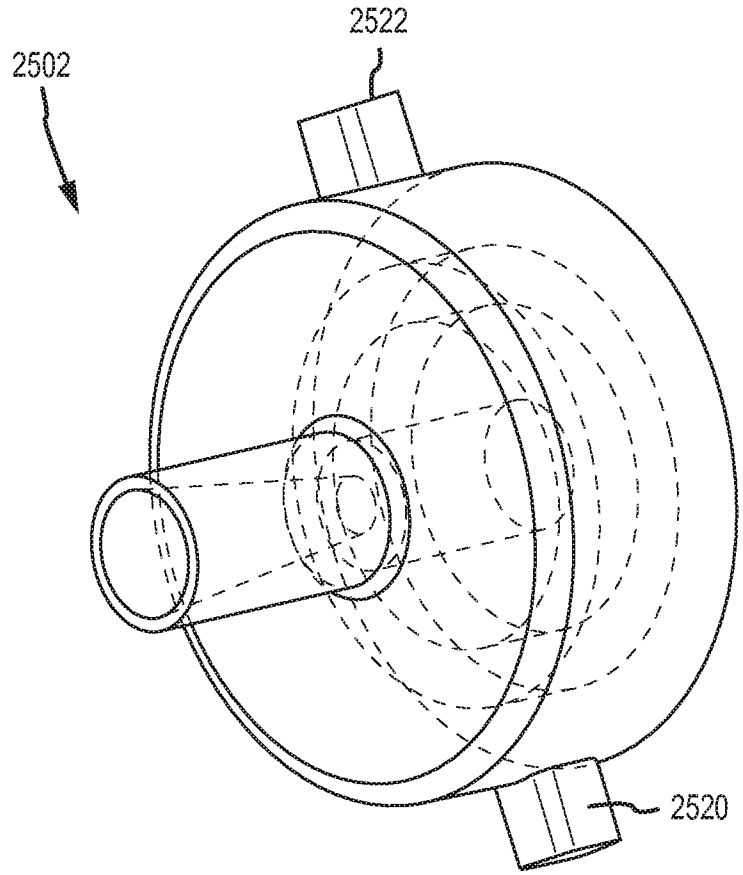

FIG.35

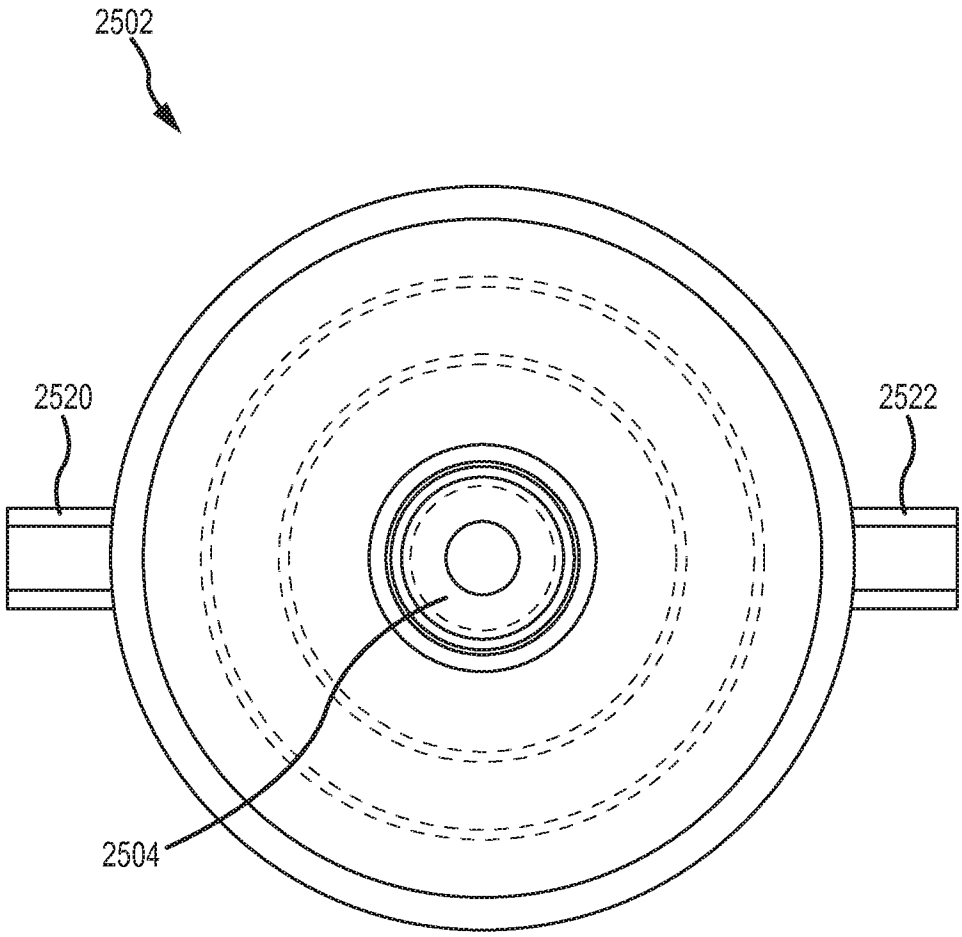

FIG.36

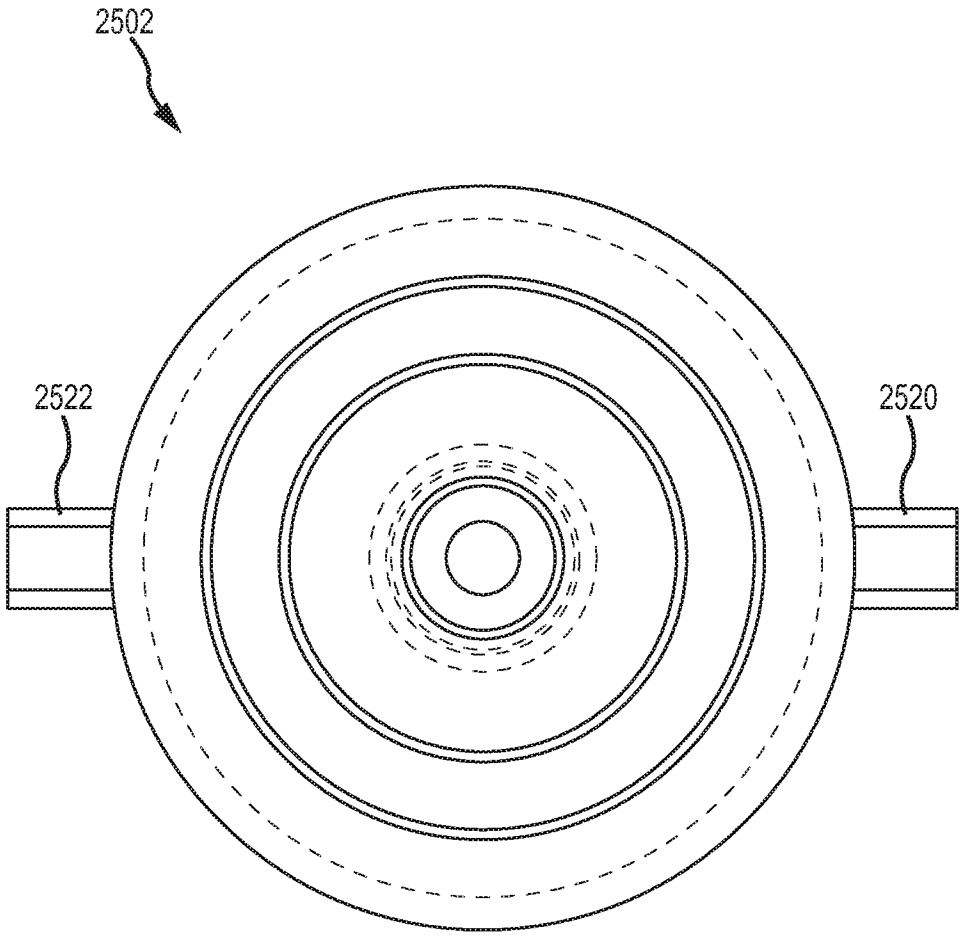

FIG.37

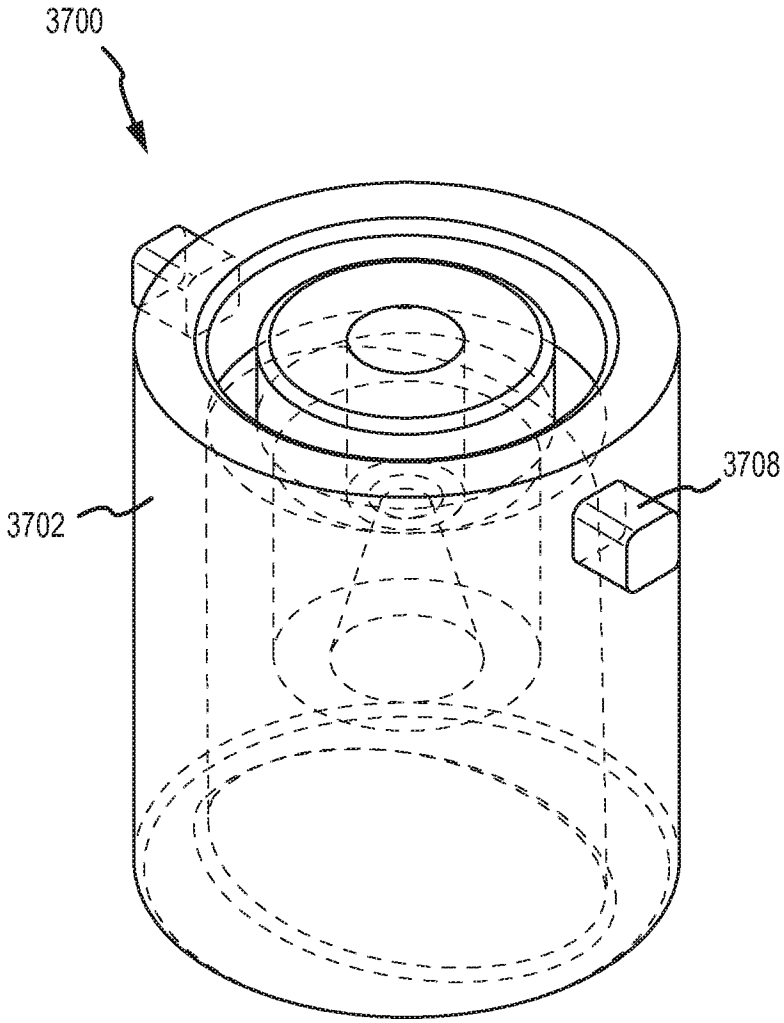

FIG.38

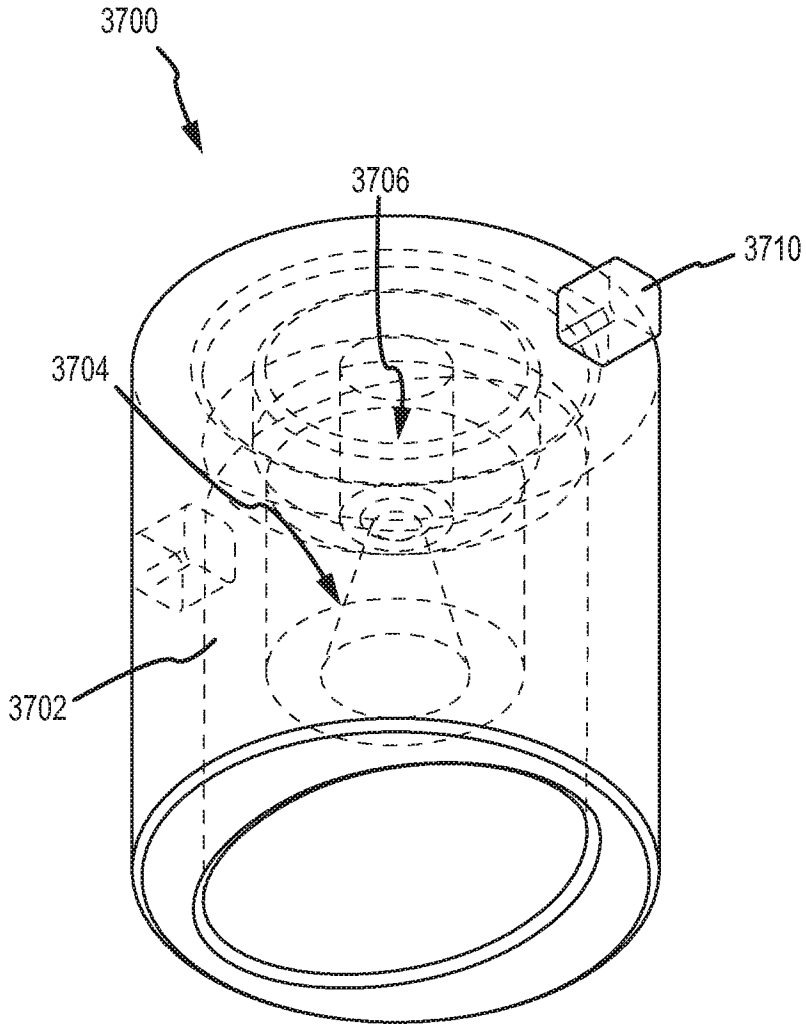

FIG.39

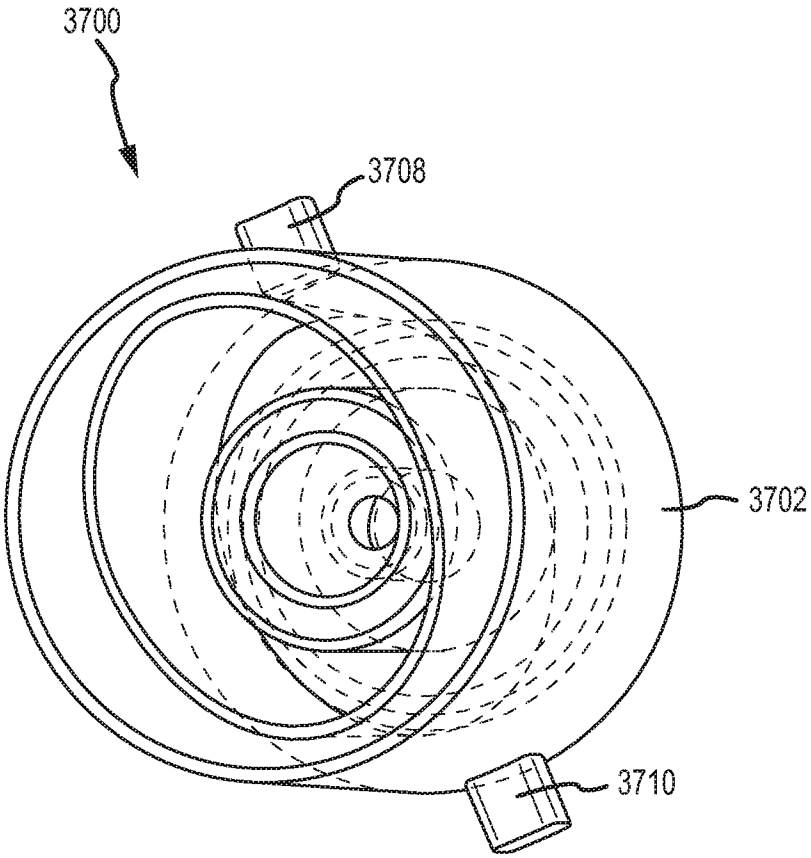

FIG.40

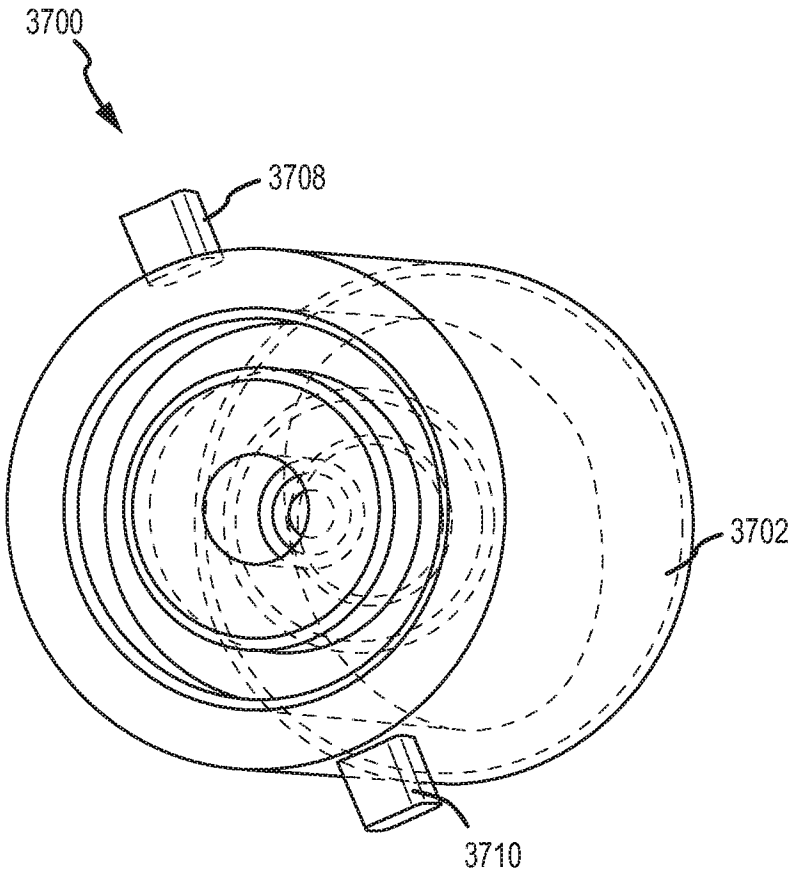

FIG.41

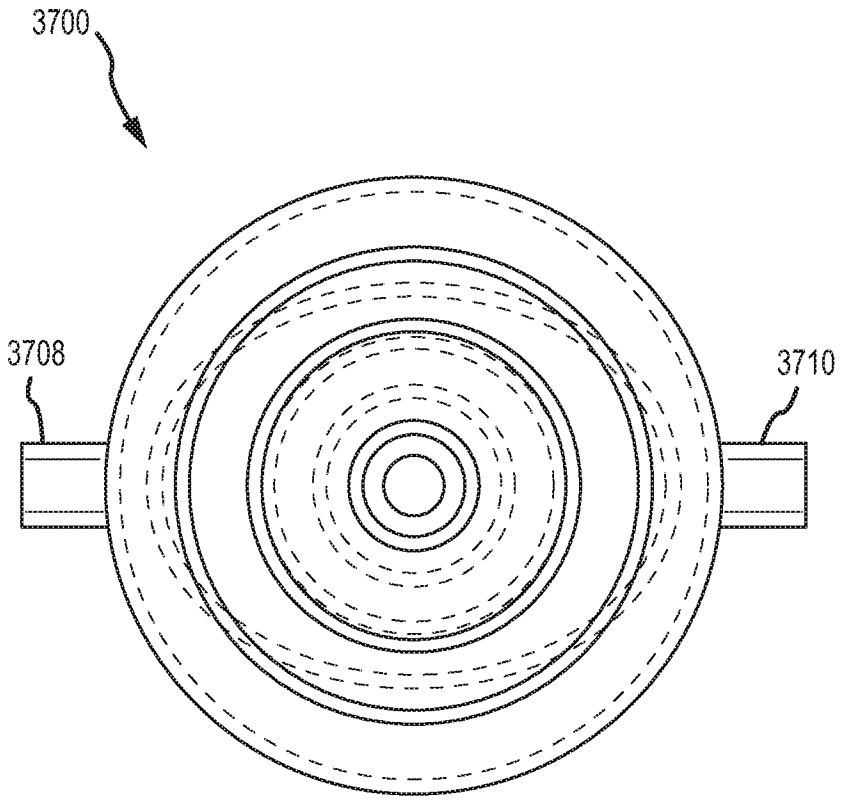

FIG.42

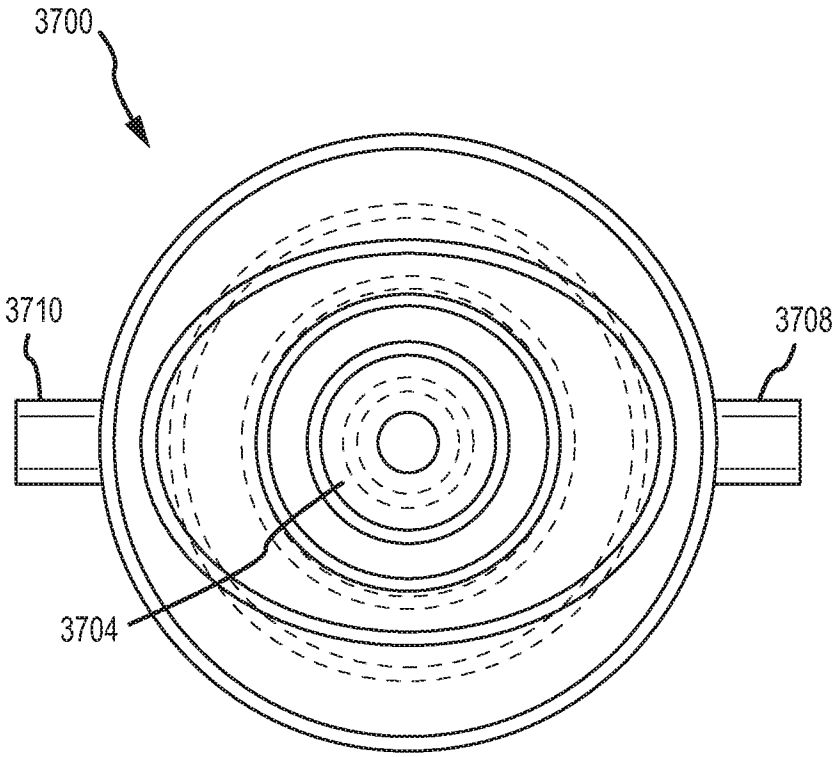

FIG.43

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/046779

A. CLASSIFICATION OF SUBJECT MATTER

A61M 15/06(2006.01)i, B65D 83/06(2006.01)i

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)
A61M 15/06; A61M 15/00; A61M 15/08; A61M 16/00; B65D 83/06

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: dry powder inhaler, dispersion, inlet, outlet, channel, flow profile, flow path, actuator, oscillate, deaggreate, bead

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2012-0145150 A1 (DONOVAN, M. J. et al.) 14 June 2012 See abstract; claims 1-15; paragraphs [0060], [0089], [0091], [0096], [0103], [0105], [0115], [0123]; figures 2A, 4A, 5A, 7, 8A-9C.	1-18,22-28
A	US 6230707 B1 (HORLIN, E.) 15 May 2001 See abstract; claim 1; figure 3.	1-18,22-28
A	US 2011-0120467 A1 (PARDONGE, J. M.) 26 May 2011 See abstract; claim 1; figures 1-2.	1-18,22-28
A	US 2010-0000529 A1 (PRIME, D. et al.) 7 January 2010 See abstract; claim 1; figure 6a.	1-18,22-28
A	US 2009-0320838 A1 (MALHOTRA, G. et al.) 31 December 2009 See abstract; claim 1; figures 11-13.	1-18,22-28

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 August 2013 (27.08.2013)	**02 September 2013 (02.09.2013)**

Name and mailing address of the ISA/KR
Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea
Facsimile No. +82-42-472-7140

Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/046779

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 19-21,29-32
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 19-21,29-32 pertain to methods for treatment of the human and thus relate to a subject-matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2013/046779

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2012-0145150 A1	14/06/2012	US 2012-291780 A1	22/11/2012
		WO 2012-078804 A1	14/06/2012
US 6230707 B1	15/05/2001	AU 682052 B2	18/09/1997
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2013/046779

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		MX 2008016153 A	20/01/2009
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