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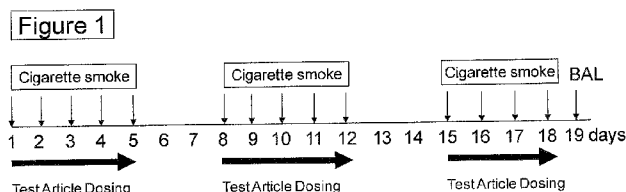
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(54) Title: METHODS AND COMPOSITIONS FOR DISEASE TREATMENT USING INHALATION



(57) Abstract: Methods and compositions for the treatment of pulmonary disease using inhalation are provided. In particular, the present disclosure provides novel methods and compositions for treating pulmonary diseases such as asthma, bronchitis, COPD, emphysema, lung cancer, pneumonia and pulmonary edema. In addition, the present disclosure provides novel methods and compositions for treating complications associated with pulmonary disease such as corticosteroid resistance and pulmonary tissue destruction. The compositions of the present disclosure comprise corticosteroid resistance agents including but not limited to vitamin D, calcitriol and equivalents thereof. The compositions of the present disclosure also comprise alveolar development and maintenance agents including but not limited to vitamin A, ATRA and equivalents thereof. The present invention provides effective administration of therapeutic agents to specific airways of the lungs by utilizing controlled site delivery.



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1                                   **METHODS AND COMPOSITIONS FOR**  
2                                   **DISEASE TREATMENT USING INHALATION**

3             The present invention relates generally to the field of treating pulmonary diseases  
4 comprising the administration of therapeutic agents using inhalation devices. The  
5 disclosure has particular utility in connection with the delivery of powdered medications  
6 to a patient, and will be described in connection with such utility, although other utilities  
7 are contemplated. More specifically, the present invention relates to novel dosage forms  
8 and compositions for treating pulmonary diseases, including but not limited to,  
9 complications such as corticosteroid resistance. In certain embodiments, the present  
10 invention is also related to improving underlying physiological dysfunction contributing  
11 to pulmonary disease. The present invention provides effective administration of  
12 therapeutic agents to specific airways of the lungs by utilizing controlled site delivery.

13            There exists a significant need for efficient inhalation devices that deliver  
14 medicaments for individuals suffering from pulmonary disease. Patients inflicted with  
15 pulmonary problems such as asthma, emphysema or chronic obstructive pulmonary  
16 disorder, are often faced with challenges in administering therapeutic agents sometimes  
17 resulting in life-threatening complications. An individual suffering from difficulties  
18 associated with breathing may be further stressed by having to receive his or her  
19 medication via inhalation due to blocked airway passages. Optimal delivery via  
20 inhalation nevertheless remains the preferred mechanism of treatment for such patients  
21 as controlled site delivery, i.e. delivery of therapeutic agents to the lungs, airway  
22 passages, bronchioles, and alveoli, is the most efficient way in which to deliver  
23 medication and alleviate symptoms.

24            Pulmonary disease, or lung disease, is any disease or disorder that causes the  
25 lungs not to function properly. There are three main types of pulmonary/lung diseases  
26 and they are generally categorized as airway diseases, lung tissue diseases, and lung  
27 circulation diseases.

28            Airway diseases affect the tubes (airways) that carry oxygen and other gases into  
29 and out of the lungs. These diseases usually cause a narrowing or blockage of the  
30 airways. They include asthma, emphysema, and chronic bronchitis. People with airway  
31 diseases sometimes describe the feeling as "trying to breathe out through a straw." Lung  
32 tissue diseases affect the structure of the lung tissue. Scarring or inflammation of the  
33 tissue makes the lungs unable to expand fully ("restrictive lung disease"). This makes it

1 hard for the lungs to breathe in oxygen and release carbon dioxide. Pulmonary fibrosis  
2 and sarcoidosis are examples of lung tissue diseases. People sometimes describe the  
3 feeling as "wearing a sweater or vest that is too-tight" that won't allow them to take a  
4 deep breath. Lung circulation diseases affect the blood vessels in the lungs and they are  
5 caused by clotting, scarring, or inflammation of the blood vessels. Lung circulation  
6 diseases consequently affect the ability of the lungs to take up oxygen and to release  
7 carbon dioxide and may also affect heart function.

8 Pulmonary disease includes, but is not limited to, acute bronchitis, acute  
9 respiratory distress syndrome (ARDS), asbestosis, asthma, atelectasis, aspergilliosis,  
10 bronchiectasis, bronchiolitis, bronchopulmonary dysplasia, byssinosis, chronic  
11 bronchitis, coccidiomycosis, chronic obstructive pulmonary disease (COPD), cystic  
12 fibrosis, emphysema, eosinophilic pneumonia, hantavirus pulmonary syndrome,  
13 histoplasmosis, human metapneumovirus, hypersensitivity pneumonitis, influenza, lung  
14 cancer, lymphangiomatosis, mesothelioma, necrotizing pneumonia, nontuberculosis  
15 Mycobacterium, pertussis, pleural effusion, pneumoconiosis, pneumonia, primary ciliary  
16 dyskinesia, primary pulmonary hypertension, pulmonary arterial hypertension,  
17 pulmonary fibrosis, pulmonary vascular disease, respiratory syncytial virus, sarcoidosis,  
18 severe acute respiratory syndrome, silicosis, sleep apnea, sudden infant death syndrome,  
19 and tuberculosis. The most common lung diseases generally comprise asthma,  
20 bronchitis, COPD, emphysema, lung cancer, pneumonia and pulmonary edema.

21 Of all pulmonary diseases, the most prevalent appears to be COPD. According to  
22 the World Health Organization estimates in the year 2004, 64 million people had COPD  
23 and 3 million people died of COPD. WHO predicts that COPD will become the third  
24 leading cause of death worldwide by 2030. The Merck Manual (2011) provides that an  
25 estimated 12 million people in the US have COPD and describes COPD as the 4th  
26 leading cause of death, resulting in 122,000 deaths in 2003 compared with 52,193 deaths  
27 in 1980. From 1980 to 2000, the COPD mortality rate increased 64% (from 40.7 to  
28 66.9/100,000). Prevalence, incidence, and mortality rates increase with age and though  
29 prevalence is higher in men, total mortality is similar in both sexes. Incidence and  
30 mortality are generally higher in caucasians, blue-collar workers, and people with fewer  
31 years of formal education, probably because these groups have a higher prevalence of  
32 smoking. COPD is increasing worldwide because of the increase in smoking in  
33 developing countries, the reduction in mortality due to infectious diseases, and the

1 widespread use of biomass fuels.

2 COPD is partially reversible airflow limitation caused by an inflammatory  
3 response to inhaled toxins, often cigarette smoke,  $\alpha_1$ -Antitrypsin deficiency and various  
4 occupational exposures. Symptoms are productive cough and dyspnea that develop over  
5 years; common signs include decreased breath sounds, prolonged expiratory phase of  
6 respiration, and wheezing. Severe cases may be complicated by weight loss,  
7 pneumothorax, frequent acute decompensation episodes, right heart failure, and acute or  
8 chronic respiratory failure. Diagnosis is based on history, physical examination, chest x-  
9 ray, and pulmonary function tests. Treatment is with bronchodilators, corticosteroids,  
10 and, when necessary, O<sub>2</sub> and antibiotics. About 50% of patients die within 10 years of  
11 diagnosis.

12 COPD is also manifested outside of the airways by extra-pulmonary  
13 inflammation and muscular atrophy. COPD is a heterogeneous disease encompassing  
14 inflammation and excessive mucus secretion in the large and small airway as well as  
15 destruction of the alveolar sacs. Airway remodeling occurs as a result of inflammation  
16 associated with emphysema, leading to disruption in the alveolar attachment of the small  
17 airways and subsequent airway closure during exhalation (as alveolar attachments are no  
18 longer able to hold the airway open). Disease progression leads to air trapping,  
19 hyperinflation and reduced inspiratory capacity.

20 COPD comprises chronic obstructive bronchitis (clinically defined) and  
21 emphysema (pathologically or radiologically defined), and many patients have features  
22 of both.

23 Chronic obstructive bronchitis is chronic bronchitis with airflow obstruction.  
24 Chronic bronchitis is defined as productive cough on most days of the week for at least  
25 three months total duration in two successive years. Chronic bronchitis becomes chronic  
26 obstructive bronchitis if spirometric evidence of airflow obstruction develops. Chronic  
27 asthmatic bronchitis is a similar, overlapping condition characterized by chronic  
28 productive cough, wheezing, and partially reversible airflow obstruction; it occurs  
29 predominantly in smokers with a history of asthma. In some cases, the distinction  
30 between chronic obstructive bronchitis and chronic asthmatic bronchitis is unclear.

31 Emphysema is destruction of lung parenchyma leading to loss of elastic recoil  
32 and loss of alveolar septa and radial airway traction, which increases the tendency for  
33 airway collapse. Lung hyperinflation, airflow limitation, and air trapping follow.

1   Airsaces enlarge and may eventually develop bullae.

2           Current therapeutic agents for COPD predominately comprise bronchodilators  
3 administered via inhalation, including inhaled long-acting beta<sub>2</sub>-agonists (LABA) or long  
4 acting muscarinic antagonists (LAMA). Although corticosteroids have been proven  
5 effective in other inflammatory diseases such as asthma, rheumatoid arthritis, and  
6 ulcerative colitis, their use is often ineffective in COPD outside of exacerbation  
7 reduction, leading some to question their importance as a therapeutic in the disease.  
8 Conversely, combinations of bronchodilators with long acting corticosteroids have  
9 found utility in preventing COPD exacerbations and treating contaminant asthma, but the  
10 utility of corticosteroids alone have not been demonstrated. Despite being unable to  
11 fully address the inflammation and destructive process associated with the progression of  
12 COPD, various double and triple combination products using corticosteroids are in  
13 development.

14

#### 15   *Corticosteroid Resistance*

16           There has been much investigation into the mechanisms of corticosteroid  
17 resistance, many of which are based on an underexpression of chemical mediators  
18 involved in the regulation of inflammation in COPD. It has also been suggested that the  
19 seemingly “resistant” nature of COPD toward inhaled corticosteroid therapy (ICS) may  
20 not only be due to a physiological resistance, but may reflect the lack of drug deposition  
21 in the small airways. In a study investigating the efficacy of extrafine beclomethasone  
22 dipropionate (1.1 microns in diameter using a HFA pMDI) in patients with COPD, a  
23 significant reduction in air trapping was measured, suggesting a reduction in small  
24 airway inflammation. No prior art dry powder inhalation devices have the ability to  
25 deliver extrafine particles in patients with COPD. What is needed is a method of drug  
26 delivery that effectively targets the small airways and lung parenchyma, which are the  
27 sites of inflammation for pulmonary disease such as COPD. Current therapies lack the  
28 capability to achieve high levels of small airway deposition due to a number of issues:

29

30           (1) The mass median aerodynamic diameter (MMAD) is too large and geometric  
31 standard deviation (GSD) is too broad to effectively target the small airway.

32           (2) Delivery devices require minimal flow rates for optimal operation that are  
33 often beyond the capability of severely flow-restricted subjects.

1 (3) Delivery devices require patient coordination which proves difficult for  
2 elderly patients, or patients having compromised physical abilities.

3 (4) Aerosols are partially blocked or blocked by collapsed airways.

4 (5) Aerosols produced near the end of the inspiratory breath will not have  
5 sufficient time to deposit in the small airways before exhalation.

6  
7 Regardless of whether ICS is effective or ineffective, it is clear that the nature of  
8 the inflammation in COPD is less responsive to the current ICS therapies than other  
9 inflammatory diseases such as asthma, rheumatoid arthritis, and ulcerative colitis, and  
10 requires a different approach to immunomodulatory therapy. Corticosteroid resistance  
11 may be due in part to the limitation of effective therapeutic delivery mechanisms  
12 involving the ability (or lack thereof) to deposit medicaments within the small airway  
13 passages of the lungs, however evidence is also emerging supporting the contention that  
14 metabolic and physiological malfunction may manifest in conditions that prevent COPD  
15 patients from responding to corticosteroid therapy.

16 One mechanism thought to lead to corticoidsteroid resistance (CR) in patients  
17 with COPD pertains to the reduced expression of histone deacetylase (HDAC) within an  
18 inflammatory cell. HDAC is normally recruited by activated glucocorticoid receptors  
19 and results in deacetylation and “switching off” of genes transcribing for inflammatory  
20 cytokines and chemokines. Most COPD patients, being unresponsive to corticosteroids,  
21 possess lower levels of HDAC, and thus are more prone to severe inflammation. It is  
22 suspected that oxidative and nitrative stresses, which are commonly found in cigarette  
23 smoke, are the primary reasons for inhibition of HDAC in COPD. In a study  
24 investigating the influence of HDAC on corticosteroid-resistant bronchoalveolar  
25 macrophages, it was found that corticosteroid sensitivity could be increased when HDAC  
26 was overexpressed.

27 CR is also thought to occur when there is a lack of IL-10 secretion from  
28 regulatory T cells. IL-10 plays an important role in the downregulation of Th1  
29 inflammatory cytokines and promotion of regulatory T cells which help to control the  
30 inflammatory response. In a study investigating the response of CR CD4+ T cells to  
31 calcitriol and dexamethasone, it was found that co-administration of these agents to cell  
32 lines increased IL-10 levels to those seen in normal, corticosteroid-sensitive cell lines.  
33 Accordingly, recent studies support the theory that CR may be the result of physiological

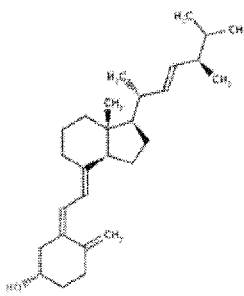
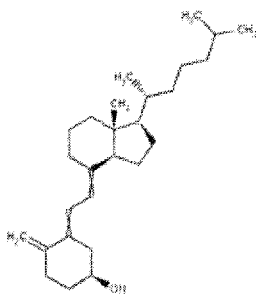
1 changes manifested at the molecular level and likely induced by pulmonary trauma such  
 2 as that caused by cigarette smoking or other oxidative stress. Nevertheless, though the  
 3 role of CR resistance has been identified, no effective therapeutic means or strategies are  
 4 available for reducing or reversing COPD-related consequences of CR resistance.

5

#### 6 *Vitamin D and Pulmonary Disease*

7 Vitamin D is a lipophilic small molecule responsible for maintaining normal  
 8 calcium metabolism in the body. It encompasses several vitamers including vitamin D<sub>1</sub>,  
 9 vitamin D<sub>2</sub>, vitamin D<sub>3</sub>, vitamin D<sub>4</sub>, and vitamin D<sub>5</sub>. Cholecalciferol (vitamin D<sub>3</sub>) is the  
 10 animal-derived form of vitamin D and is produced in the skin when ultraviolet radiation  
 11 cleaves the steroidal ring of 7-dehydrocholesterol. In humans, the majority of  
 12 cholecalciferol is maintained by sun light exposure; however, it may also be  
 13 supplemented to some extent by dietary consumption. Hepatic metabolism of  
 14 cholecalciferol gives rise to the most prevalent circulating metabolite, calcidiol (25-  
 15 hydroxyvitamin D<sub>3</sub>), which is in turn metabolized by the kidney to form the most  
 16 physiologically active vitamin D metabolite, calcitriol (1,25-dihydroxyvitamin D<sub>3</sub>).  
 17 Synthetic versions of calcitriol have been produced by the pharmaceutical industry, as  
 18 well as other synthetic activators of the vitamin D receptor, doxercalciferol and  
 19 paricalcitol.

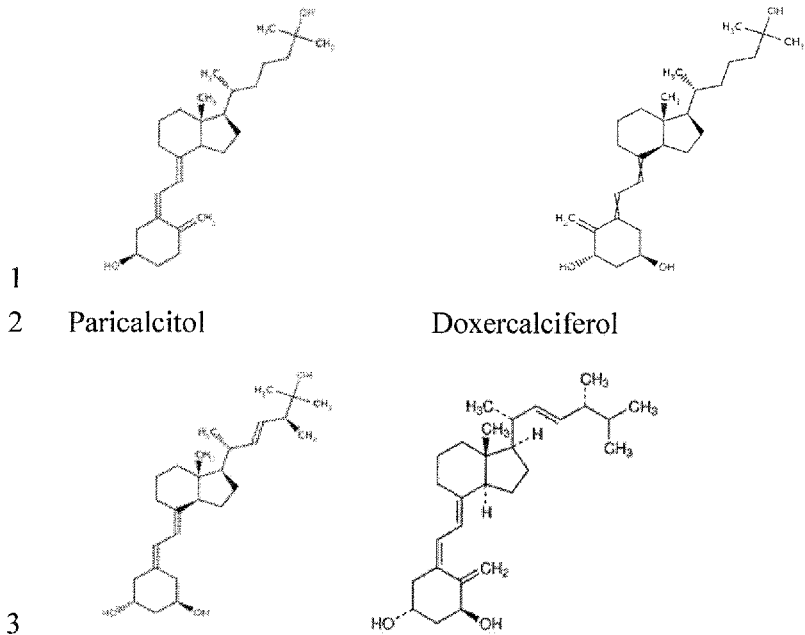
20

21 Cholecalciferol (vitamin D<sub>3</sub>)Ergocalciferol (vitamin D<sub>2</sub>)

22

23 Calcidiol (25-hydroxyvitamin D)

Calcitriol (1,25-dihydroxyvitamin D)



5 The immunomodulatory effects of vitamin D have been well described in the  
6 literature and are predominantly due to its most active metabolite, calcitriol. Calcitriol  
7 acts on a variety of inflammatory cells including monocytes, macrophages, dendritic  
8 cells, effector T cells, and B cells and in turn affects the expression genes encoding for  
9 chemical mediators of inflammation.  $T_H1$  associated cytokines, such as IL-2, IL-6, IL-8,  
10 IL-12, and  $IFN\gamma$ , are generally downregulated by calcitriol and may lead to a more  $T_H2$   
11 mediated inflammation through the upregulation of IL-4 (*Mora et al. Nat. Rev. Immunol.*  
12 *8(9) (2008) 685-698*). However, there is evidence showing that  $T_H2$ -associated  
13 pulmonary inflammation may also be reduced (as measured through a reduction in IL-5  
14 and eosinophils in bronchioalveolar lavage fluid), despite the apparent shift toward  $T_H2$   
15 cytokine expression systemically (*Sandhu et al. American College of Allergy, Asthma, &*  
16 *Immunology 105(3) 191-199*). While the anti-inflammatory mechanisms behind these  
17 seemingly contradictory findings remain unclear, the upregulation of IL-10, an anti-  
18 inflammatory cytokine inhibiting  $T_H1$  and  $T_H2$  responses, could be attributed to  
19 calcitriol's broad inflammation reduction effects. Calcitriol has been shown to promote  
20 IL-10 secreting regulatory T cells as well as IL-10 expression by dendritic cells in  
21 preclinical models. An *in vitro* study of a cell line cultured from patients with  
22 corticosteroid resistant asthma, promotion of regulatory T cells after addition of vitamin  
23 D resulted in increased steroid sensitivity, suggesting that vitamin D may be able to  
reverse corticosteroid resistance (*Xystrakis et al. The Journal of Clinical Investigation*



1 116(1) (2006) 146-155). Despite studies by Xystrakis et al. and others, effective vitamin  
2 D therapy resulting in the reversal of corticosteroid resistance has not been accomplished  
3 or reduced to practice.

4 Vitamin D has been demonstrated to play an important role in improved lung  
5 function. A trial in asthmatic adults with varying levels of vitamin D has shown that a  
6 22.7 mL mean increase in FEV<sub>1</sub> can be expected for every 1 ng/mL increase in systemic  
7 vitamin (D Sutherland et al. *Am. J. Respir. Crit. Care Med.* 181(7) (2010) 699-704). In a  
8 study enrolling 100 asthmatic children, steroid dose used for asthma maintenance  
9 therapy was inversely proportional to systemic vitamin D levels. It was also found that  
10 vitamin D levels were directly proportional to FEV<sub>1</sub> and inversely proportional of  
11 circulating IgE concentrations (*The Journal of Allergy and Clinical Immunology* 125(5)  
12 (2010) 995-1000).

13 Chronic asthma and COPD often result in airway remodeling which is  
14 detrimental to lung function and limits a patient's quality of life. This aspect of airway  
15 disease has also been shown responsive to vitamin D therapy. Airway smooth muscle  
16 proliferation, a contributing factor in airway remodeling seen in severe asthma and  
17 COPD, has been shown to slow due to the anti-proliferative effects of vitamin D Damera  
18 et al. *Am. J. Respir. Crit. Care Med.* 179 (2009) A5606. Currently, several clinical trials  
19 are underway to investigate the effect of oral supplementation of vitamin D on asthma  
20 and COPD, however no such trials or studies have been successfully accomplished for  
21 inhaled supplementation of vitamin D.

22 In addition to its immunomodulating and pulmonary effects, there is evidence  
23 that vitamin D may also function as an anti-proliferative, effective against cancer. The  
24 anti-tumor effects of vitamin D are multifaceted and most likely due to the arrest of G<sub>0</sub>/  
25 G<sub>1</sub> phase of the cell cycle, induction of apoptosis, inhibition of cell growth, and induction  
26 of cell differentiation in malignant cells. The activity of vitamin D toward a variety of  
27 cancer lines (prostate, breast, colorectal, head/neck, lung) is attributed to the presence of  
28 the vitamin D receptor (VDR) in the cell membranes of these malignant cell types. In  
29 situations of vitamin D deficiency, generally due to reduction in sunlight exposure and  
30 genetic factors, incidence rate of some cancers have been shown to increase, further  
31 implicating the role of vitamin D in normal physiological anti-cancer functions.

32 In clinical trials investigating the use of calcitriol as an anti-cancer therapy, very  
33 high doses of calcitriol are required to impart a therapeutic effect, leading to concern

1 over toxicity due to hypercalcemia *Urologic Oncology* 21(5) (2003) 399-405. There is  
2 evidence that dose limitation may not be solely attributed to toxicity, but may be a result  
3 of limited absorption or orally dosed calcitriol. Alternative methods of delivery are  
4 necessary to achieve greater bioavailability through the avoidance of intestinal  
5 absorption and first pass metabolism, thus limiting or eliminating potential toxicity  
6 problems resulting from high doses of calcitriol.

7 Not only does vitamin D have a potential therapeutic role in pulmonary diseases  
8 including asthma, COPD, pulmonary infection and lung cancer, vitamin D therapy is  
9 important for osteoporosis, hypocalcemia, hyperparathyroidism and cancer.  
10 Accordingly, there exists a need for effective dosing and administration of vitamin D  
11 wherein toxic side effects are reduced and preferably eliminated. Preferably, such  
12 dosing and administrative means should be easy to handle and safe for the user to receive  
13 the prescribed amount of vitamin D in a form that is metabolically and physiologically  
14 appropriate.

15

#### 16 *Vitamin A and Alveolar Development*

17 Vitamin A is important for lung development and lung function through  
18 generating alveolar septa which are capable of gas exchange. These effects are mediated  
19 by the Retinoic Acid Receptor [RAR] gamma subtype in alveolar walls, and are  
20 triggered by All Trans Retinoic Acid (ATRA), which is the active metabolite of Vitamin  
21 A. Exogenous ATRA can influence the formation of alveoli in newborn and adult  
22 rodents *Am J Physiol: Lung Cell and Mol. Physiol* 2004 286;2: ppL249-256.  
23 Furthermore, ATRA treatment of adult rats with preexisting elastase-induced  
24 emphysema induces alveolus formation returning the size, number, and surface area of  
25 alveoli, and tissue elastic recoil, to values present in same-aged rats not treated with  
26 elastase (*Nat Med* 1997 3: pp675-677). These effects are governed by the effects of the  
27 RAR on gene expression. ATRA diminishes the formation of pulmonary emphysema in  
28 mice exposed to cigarette smoke and decreases the distance between alveolar walls in  
29 mice with emphysema produced by cigarette smoke. It therefore follows that ATRA  
30 therapy, or therapy with RAR specific agents has the possibility to treat COPD, COPDe  
31 and emphysema by generating new alveoli for greater gas exchange, however no such  
32 therapies are currently available.

1           None of the above models, however accurately represent human emphysema. In  
2 fact, higher order species have shown less clear results with the use of ATRA on  
3 alveologenesis (*Am J Respir Cell Mol Biol* 2002 26: pp52–57) and recent trials in adults  
4 with hereditary emphysema with ATRA (*Chest* 2006 130;5: pp1334-1345) and RAR-  
5 gamma selective agents have not been successful. Elsewhere in the body, ATRA is  
6 known to induce matrix-metalloproteinase-9 (MMP-9) and Interleukin-8 which are likely  
7 additive to the inflammatory cascade in COPD and emphysema and cause progressive  
8 loss of pulmonary function and likely destruction of newly formed alveoli (*Br J*  
9 *Haematol.* 2002 118;2: pp419-25). Accordingly, though studies have investigated the  
10 effects of ATRA, the active metabolite of vitamin A, on pulmonary function and alveolar  
11 formation, the findings are inconsistent and currently no therapeutic formulations or  
12 mechanisms are available that effectively deliver vitamin A with the ultimate goal of  
13 improving lung function and decreasing COPD or other pulmonary malfunction.

#### 14 15 *Treatment of Respiratory Disease using Inhaled Therapeutics*

16           Many diseases of the respiratory tract are known to respond to treatment by the  
17 direct application of therapeutic agents. As these agents are most readily available in dry  
18 powdered form, their application is most conveniently accomplished by inhaling the  
19 powdered material through the nose or mouth. This powdered form can result in the  
20 better utilization of the medicament in that the drug is deposited exactly at the site  
21 desired and where its action may be required; hence, very minute doses of the drug are  
22 often equally as efficacious as larger doses administered by other means, with a  
23 consequent marked reduction in the incidence of undesired side effects and medicament  
24 cost. In addition, a drug in dry powder form may be used for treatment of diseases other  
25 than those of the respiratory or pulmonary system. When the drug is deposited on the  
26 very large surface areas of the lungs, it may be very rapidly absorbed into the blood  
27 stream; hence, this method of application may take the place of administration by  
28 injection, tablet, or other conventional means.

29           It is the opinion of the pharmaceutical industry that the bioavailability of the drug  
30 is optimum when the drug particles delivered to the respiratory tract are between 1 to 5  
31 microns in size. When drug particles need to be in this size range, dry powder delivery  
32 systems need to address a number of issues:

33           (1) Small size particles may develop an electrostatic charge on themselves during

1 manufacturing and storage. This may cause the particles to agglomerate or  
2 aggregate, resulting in clusters of particles which have an effective size greater  
3 than 5 microns. The probability of these large clusters navigating to the deep  
4 lungs then decreases. This in turn results in a lower percentage of the packaged  
5 drug being available to the patient for absorption.

6 (2) The amount of active drug that needs to be delivered to the patient may be of  
7 the order of 10s of micrograms. For example, in the case of albuterol, a drug  
8 used in asthma, this is usually 25 to 100 micrograms. Current manufacturing  
9 equipment cannot effectively deliver aliquots of drugs in milligram dose range  
10 with acceptable accuracy. So the standard practice is to mix the active drug with  
11 a filler or bulking agent such as lactose. This additive also makes the drug "easy  
12 to flow". This filler is also called a carrier since the drug particles also stick to  
13 these particles through electrostatic or chemical bonds. These carrier particles  
14 are very much larger than the drug particles in size. The ability of an inhaler to  
15 separate drug from the carrier is an important performance parameter in the  
16 effectiveness of the design.

17 (3) Active drug particles with sizes greater than 5 microns will be deposited  
18 either in the mouth or throat. This introduces another level of uncertainty since  
19 the bioavailability and absorption of the drug in these locations is different from  
20 the lungs. Inhalers need to minimize the drug deposited in these locations to  
21 reduce the uncertainty associated with the bioavailability of the drug.

22  
23 Three types of inhaler devices have been traditionally used to create the aerosol  
24 needed for pulmonary delivery: dry powder inhalers (DPIs), metered dose inhalers  
25 (MDIs), and aqueous nebulizers.

### 26 27 *Dry Powder Inhalers*

28 Prior art dry powder inhalers (DPIs) usually have a means for introducing the  
29 drug (active drug plus carrier) into a high velocity air stream. The high velocity air  
30 stream is used as the primary mechanism for breaking up the cluster of micronized  
31 particles or separating the drug particles from the carrier. Several inhalation devices  
32 useful for dispensing powder forms of medicament are known in the prior art. For  
33 example, in U.S. Pat. Nos. 3,507,277; 3,518,992; 3,635,219; 3,795,244; and 3,807,400,

1 inhalation devices are disclosed having means for piercing of a capsule containing a  
2 powdered medicament, which upon inhalation is drawn out of the pierced capsule and  
3 into the user's mouth. Several of these patents disclose propeller means, which upon  
4 inhalation aid in dispensing the powder out of the capsule, so that it is not necessary to  
5 rely solely on the inhaled air to suction powder from the capsule. For example, in U.S.  
6 Pat. No. 2,517,482, a device is disclosed having a powder containing capsule placed in a  
7 lower chamber before inhalation, where it is pierced by manual depression of a piercing  
8 pin by the user. After piercing, inhalation is begun and the capsule is drawn into an  
9 upper chamber of the device where it moves about in all directions to cause a dispensing  
10 of powder through the pierced holes and into the inhaled air stream. U.S. Pat. No.  
11 3,831,606 discloses an inhalation device having multiple piercing pins, propeller means,  
12 and a self-contained power source for operating the propeller means via external manual  
13 manipulation, so that upon inhalation the propeller means aids in dispensing the powder  
14 into the stream of inhaled air. See also U.S. Pat. Nos. 3,948,264 and 5,458,135.

15 In prior U.S. Patent Nos. 7,318,434 and 7,334,577 incorporated herein by  
16 reference, and assigned to the common assignee MicroDose Technologies, Inc., there is  
17 provided an improvement over prior art inhalers that utilize vibration to facilitate  
18 suspension of powder into an inhaled gas stream and which utilizes synthetic jetting to  
19 aerosolize drug powder from a blister pack or the like. As taught in the aforesaid U.S.  
20 Patent No. 7,318,434 and 7,334,577 there is provided a dry powder inhaler having a first  
21 chamber such as a blister pack or other container, for and holding a dry powder, and a  
22 second chamber connected to the first chamber via a passageway for receiving an  
23 aerosolized form of the dry powder from the first chamber and for delivering the  
24 aerosolized dry powder to a user. A vibrator is coupled to the dry powder in the first  
25 chamber. The vibrator is energized and coupled to the first chamber and drives the  
26 powder from the chamber by synthetic jetting.

27 As described in U.S. Patent No. 7,080,644 also incorporated herein by reference,  
28 and also assigned to common assignee MicroDose Technologies, Inc., controlled aliquots  
29 or doses of a medication or drug are pre-packaged in a blister pack, which includes a  
30 frangible crowned top element which may be conical, conical with a rounded point,  
31 rounded, or other raised shape configuration, and a bottom element which may be a flat  
32 web or membrane, or which itself may be of shaped configuration, e.g. conical, round,  
33 dish shaped, etc. for closely engaging with an underlying vibrating element, the shape

1 and size of which is chosen to provide optimum controlled delivery of a given  
2 medication or drug. The top element of the blister pack is pierced with a piercing device  
3 such as a sharp needle to form one or more apertures for delivery of the medication or  
4 drug contained within the blister pack. The hole pattern and hole size is selected to  
5 provide optimization of delivery of the particular medication or drug packaged therein.

#### 6 7 *Metered Dose Inhalers*

8 Metered dose inhalers (MDIs) have a pressurized canister filled with a liquid  
9 propellant. The drug is either suspended or dissolved in the propellant. The MDIs have a  
10 metering valve for metering out a known quantity of the propellant and hence the drug.  
11 When the canister is depressed against the MDI housing a known quantity of the  
12 propellant is discharged. The propellant evaporates leaving behind a fine aerosol of the  
13 drug suitable for inhalation by the patient. For effective delivery of the drug to the lungs  
14 the patient needs to coordinate breath inhalation with the discharge of the drug from the  
15 canister. Patients are not always effective in achieving this coordination leading to dose  
16 variability. Incorporation of a breath actuation mechanism addresses this concern but the  
17 variability still exists because of the "cold" freon effect where the patient stops breathing  
18 when the cold aerosol hits the back of the throat. This is especially true of the pediatric  
19 patients where co-ordination is of major concern. To overcome these limitations and to  
20 minimize the variability of the dose delivered, the MDI is normally recommended to be  
21 used with a spacer especially for children. The primary function of the spacer is to slow  
22 down the MDI discharge and function as a holding chamber for the aerosol plume. A  
23 face mask may be attached to the end of the spacer. These spacers normally are made of  
24 plastic and therefore tend to build up electrostatic charge on the inside surface of the  
25 spacer. The large dead space between the inlet and outlet of the spacer coupled with the  
26 electrostatic charge has the effect of lowering the amount of dose delivered and the  
27 amount of drug that is in the respirable range. It is estimated that MDIs deliver about  
28 10% to 20% of the dose to lungs in adults with good coordination. Studies have shown  
29 that for pediatric patients between the ages of 3 years to 5 years using an MDI with a  
30 spacer and face mask, the lung delivery is less than 10% of the dose. Accordingly, drug  
31 delivery using current MDIs is ineffective, especially among pediatric patients.

#### 32 33 *Nebulizers*

1 Nebulizers, such as the jet nebulizers, produce a fine aerosol mist/droplets which  
2 carry the drug either as a suspension or dissolved in the aqueous medium. The jet  
3 nebulizers use compressed air to atomize the aqueous solution. The flow rate of the  
4 compressed air should be matched to the inhalation flow rate of the patient for optimum  
5 delivery of the drug. A drug can be administered to a patient with repetitive non-forced  
6 inhalation over a prolonged period of time. The amount of drug delivered is influenced  
7 by a large number of factors such as viscosity, volume of drug fill, surface tension,  
8 inhalation flow, etc. The amount of drug delivered ranges from 3% to 6% for pediatric  
9 patients and 3% to 13% for adults. Pediatric delivery nebulizers are normally coupled to  
10 a face mask. Since the nebulizer continues to produce the aerosol during the exhale  
11 cycle of the breath this leads to drug wastage, increased exposure of the drug to the  
12 patient's face and eyes and also to the caregiver. The disadvantages of nebulizers in  
13 general are their poor efficiency of delivery to the patient, a requirement for a  
14 compressor or compressed air and long delivery times, on the order of 5 to 20 minutes.

15 Thus there is a need for a delivery mechanism for infants and young children, and  
16 also for respiratory compromised patients that overcomes the aforesaid and other  
17 disadvantages of the prior art, in a manner that delivers the drug efficiently, does not  
18 require inhalation coordination, operates under low inhalation volume, minimizes the  
19 exposure of the caregiver to the drug, delivers the drug in a short time (preferably less  
20 than a minute), and is low cost and portable.

21 What is needed therefore, is an improved and efficient method and delivery  
22 device for depositing therapeutic agents within the pulmonary cavities of affected  
23 subjects, wherein in such therapeutic agents include those suited to address  
24 complications associated with corticosteroid resistance. More specifically, methods and  
25 delivery devices that successfully result in the deposition of therapeutic agents within the  
26 small airways and lung parenchyma are particularly desirable. Such methods and  
27 devices should be easy to administer and facilitate therapeutic compliance. In addition,  
28 such methods and devices should preferably be available for all relevant indications and  
29 not be limited to those related to pulmonary disease and malfunction.

30 The present disclosure provides an improvement over prior art devices such as  
31 discussed above by providing methods for treating pulmonary disease comprising the use  
32 of improved inhaler devices for the delivery of therapeutic compositions via inhalation.  
33 The improved methods of the present invention satisfy the heretofore unmet need in the

1 art for methods and devices that enable the efficient deposition of therapeutic and  
2 pharmaceutical agents to the small airways and parenchyma of the lungs. The inhalers  
3 combine the properties of controlling the drug particle size as well as the dosing  
4 mechanism by which the drug is delivered to the subject.

5 In addition, the methods of the present invention are particularly useful for  
6 addressing complications associated with pulmonary disease including, but not limited  
7 to, corticosteroid resistance (CR), as the devices used herein have the functionality to  
8 deliver drugs (such as CR reversal agents) deep into the lung tissues, and may also be  
9 configured to deliver more than one therapeutic agent (i.e. CR reversal agent and  
10 corticosteroid). The methods and compositions of the present invention may be further  
11 utilized for addressing physiological and anatomical destruction associated with  
12 pulmonary malfunction; for example, in certain embodiments, the methods and  
13 compositions of the present invention may be targeted to improving alveolar function  
14 and development via the administration of alveolar regrowth and/or maintenance agents

15 The methods and compositions described herein are particularly suited for  
16 depositing therapeutic agents necessary for alleviating symptoms associated with  
17 pulmonary disease and malfunction, however, as would be evident to one skilled in the  
18 art, they may also be utilized for additional indications.

19 Accordingly, it is an object of the present invention to provide improved methods  
20 and devices for the delivery of therapeutic and pharmaceutical agents to the small  
21 airways and parenchyma of the lungs.

22 Another object of the present invention is to provide improved methods and  
23 devices for the delivery of therapeutic and pharmaceutical agents to the small airways  
24 and parenchyma of the lungs, wherein such devices combine controlling drug particle  
25 size and delivery mechanism to optimize delivery.

26 Another object of the present invention is to provide improved methods and  
27 devices for the delivery of therapeutic and pharmaceutical agents to the small airways  
28 and parenchyma of the lungs, wherein such devices are self-contained, easy to use, and  
29 improve therapeutic compliance.

30 Yet another object of the present invention is to provide improved methods and  
31 devices for the delivery of therapeutic and pharmaceutical agents to the small airways  
32 and parenchyma of the lungs, wherein such devices overcome the limitations of patients  
33 having restricted inspiratory flow.



1           Yet another object of the present invention is to provide improved methods and  
2 devices for the delivery of therapeutic and pharmaceutical agents to the small airways  
3 and parenchyma of the lungs, wherein the therapeutic and pharmaceutical agents  
4 alleviate symptoms associated with pulmonary disease and malfunction.

5           A further object of the present invention is to provide improved methods and  
6 devices for the delivery of therapeutic and pharmaceutical agents to the small airways  
7 and parenchyma of the lungs, wherein the therapeutic and pharmaceutical agents  
8 alleviate and prevent symptoms associated with asthma, atelectasis, bronchitis, COPD,  
9 emphysema, lung cancer, pneumonia and pulmonary edema.

10          Another object of the present invention is to provide improved methods and  
11 devices for the delivery of therapeutic and pharmaceutical agents to the small airways  
12 and parenchyma of the lungs, wherein the therapeutic and pharmaceutical agents  
13 alleviate and prevent symptoms associated with corticosteroid resistance (CR).

14          Another object of the present invention is to provide improved methods and  
15 devices for the delivery of therapeutic and pharmaceutical agents to the small airways  
16 and parenchyma of the lungs, wherein the therapeutic and pharmaceutical agents  
17 improve the development and regrowth of lung tissue.

18          A further object of the present invention is to provide improved methods and  
19 devices for the delivery of therapeutic and pharmaceutical agents to the small airways  
20 and parenchyma of the lungs, wherein the therapeutic and pharmaceutical agents  
21 improve the development, and regrowth of alveoli, and subsequent maintenance of the  
22 regrown alveoli.

23          Yet another object of the present invention is to provide improved methods and  
24 devices for the delivery of therapeutic and pharmaceutical agents to the small airways  
25 and parenchyma of the lungs, wherein the devices may be configured to deliver more  
26 than one therapeutic or pharmaceutical agent.

27          A further object of the present invention is to provide improved methods and  
28 devices for the delivery of therapeutic and pharmaceutical agents to the small airways  
29 and parenchyma of the lungs, wherein the devices may be configured to deliver more  
30 than one therapeutic or pharmaceutical agent such as those comprising, but not limited  
31 to, CR reversal agents, corticosteroids, bronchodilators, vitamin D (and active  
32 metabolites, vitamin D receptor agonists/partial agonists and equivalents thereof), and  
33 vitamin A (and active metabolites, vitamin A receptor agonists/partial agonists and

1 equivalents thereof).

2 Another object of the present invention is to provide improved methods and  
3 devices for the delivery of therapeutic and pharmaceutical agents, which are targeted to  
4 be delivered to the small airways and parenchyma of the lungs, wherein the therapeutic  
5 and pharmaceutical agents comprise corticosteroids, muscarinic antagonists, macrolides,  
6 non-steroidal anti-inflammatory drugs (NSAIDs), bronchodilators and CR reversal  
7 agents.

8 Another object of the present invention is to provide improved methods and  
9 devices for the delivery of therapeutic and pharmaceutical agents to the small airways  
10 and parenchyma of the lungs, wherein the CR reversal agents comprise antioxidants,  
11 iNOS inhibitors, Phosphoinositide-3-kinase- $\delta$  inhibitors, p38 MAP kinase inhibitors,  
12 JNK inhibitors, MIF inhibitors, p-glycoprotein inhibitors, macrolides, calcineurin  
13 inhibitors, and vitamin D, synthetic vitamin D, vitamin D analogs, calcitriol and  
14 equivalents thereof.

15 Another object of the present invention is to provide improved methods and  
16 devices for the delivery of therapeutic and pharmaceutical agents to the small airways  
17 and parenchyma of the lungs, wherein the agents for improving pulmonary tissue growth  
18 and development comprise vitamin A, All Trans Retinoic Acid (ATRA), retinoic acid  
19 receptor (RAR) agonists and RAR selective alveolar growth agents and equivalents  
20 thereof.

21 Another object of the present invention is to provide improved methods and  
22 devices for the delivery of therapeutic and pharmaceutical agents to the small airways  
23 and parenchyma of the lungs, wherein the therapeutic and pharmaceutical agents  
24 comprise CR reversal agents and corticosteroids.

25 Another object of the present invention is to provide improved methods and  
26 devices for the delivery of therapeutic and pharmaceutical agents to the small airways  
27 and parenchyma of the lungs, wherein the therapeutic and pharmaceutical agents  
28 comprise budesonide, fluticasone, beclomethasone, flunisolide, triamcinolone,  
29 mometasone, any derivative or pharmaceutically acceptable salt thereof, or any other  
30 corticosteroid suitable for inhalation such as prodrugs (i.e. ciclesonide) or "soft" steroids  
31 which offer milder immunosuppression and fewer steroid side effects (i.e. loteprednol,  
32 fluorometholone).

33 Another object of the present invention is to provide improved methods and

1 devices for the delivery of therapeutic and pharmaceutical agents to the small airways  
2 and parenchyma of the lungs, wherein the therapeutic and pharmaceutical agents  
3 comprise a combination of therapeutic agents selected from the group consisting of  
4 bronchodilators, CR reversal agent, a corticosteroid and pulmonary tissue growth and  
5 development agents such as vitamin A. Another object of the present invention is to  
6 provide improved methods and devices for the delivery of therapeutic and  
7 pharmaceutical agents to the small airways and parenchyma of the lungs, wherein the  
8 therapeutic and pharmaceutical agents comprise calcitriol, fluticasone and a  
9 bronchodilator.

10 A further object of the present invention is to provide improved methods and  
11 devices for the delivery of therapeutic and pharmaceutical agents to the small airways  
12 and parenchyma of the lungs, wherein the therapeutic and pharmaceutical agents  
13 alleviate and prevent symptoms associated with non-pulmonary diseases and  
14 malfunctions.

15 These and other objects, features and advantages of the present invention will  
16 become apparent after a review of the following detailed description of the disclosed  
17 embodiments and the appended claims.

18 Figure 1 provides a schematic summarizing the experimental design of the effect  
19 of treatment of therapeutic compositions as described in Example 7 on smoke-exposed  
20 female mice.

21 The present invention may be understood more readily by reference to the  
22 following detailed description of the specific embodiments included herein. Reference is  
23 made to the accompanying drawings, which form a part hereof, and in which is shown,  
24 by way of illustration, various embodiments of the present disclosure. Although the  
25 present invention has been described with reference to specific details of certain  
26 embodiments thereof, it is not intended that such details should be regarded as  
27 limitations upon the scope of the invention. The entire text of the references mentioned  
28 herein are hereby incorporated in their entireties by reference including United States  
29 Provisional Patent Application Serial No. 61/386,733 filed on September 27, 2010,  
30 United States Provisional Patent Application Serial No. 61/386,767 filed on September  
31 27, 2010, United States Provisional Patent Application Serial No. 61/386,771 filed on  
32 September 27, 2010, United States Provisional Patent Application Serial No. 61/386,776  
33 filed on September 27, 2010. Also incorporated by reference are the following co-

1 pending patent applications: United States Patent Application Serial No. 12/785,082  
2 filed on May 21, 2010, United States Patent Application Serial No. 12/828,133 filed on  
3 June 30, 2010 and United States Patent Application Serial No. 12/985,158 filed on  
4 January 5, 2011.

5 The methods and compositions of the present invention are particularly suited for  
6 the delivery of therapeutic and pharmaceutical agents to the lung. More specifically the  
7 methods and compositions of the present invention are particularly suited for the delivery  
8 of therapeutic and pharmaceutical agents to all the airway passages within the lung,  
9 including but not limited to, the bronchioles, the respiratory bronchioles, the alveolar  
10 ducts, the atria, the alveolar sacs, the alveoli (air sacs or clusters of cells). The present  
11 invention is further suited for the delivery of therapeutic and pharmaceutical agents to  
12 the circulatory system of the lung, including but not limited to, the pulmonary artery,  
13 pulmonary capillaries, pulmonary veins, bronchial arteries, and bronchial veins.

14 As discussed above, the unique features of the present invention enable the user  
15 of the inhaler to receive an effective dose of the desired pharmaceutical or therapeutic  
16 agent in an optimal manner. The inhalers used herein enable site-specific delivery of  
17 micronized dry powder or liquid medicaments in optimal fashion as a result of novel  
18 mechanical features that combine the dynamic properties of flow and inspiration, such  
19 that the user receives an appropriate therapeutic amount of the medicament.

20 The present invention satisfies the long felt need in the market for a device that  
21 has the capability to deliver medicaments in micronized form. The invention enables the  
22 delivery of medicaments having a particle size that is sufficiently small per mass median  
23 aerodynamic diameter (MMAD), and has the appropriate geometric standard deviation  
24 (GSD) to effectively target the airways of the lung, in particular the small airways of the  
25 lung. In addition, the internal mechanical features as described above enable the use of  
26 the device even by flow-restricted subjects for whom minimal flow rates are often  
27 problematic. The combination of features with the ergonomic design of the inhaler result  
28 in an easy to use device which is necessary for subjects having limited or restricted  
29 physical abilities (such as the elderly, very young, or infirm).

30 In one embodiment of the present invention the methods taught herein are  
31 directed to the treatment of pulmonary disease. The incidence of pulmonary diseases  
32 such as asthma, atelectasis, bronchitis, COPD, emphysema, lung cancer, pneumonia and  
33 pulmonary edema is steadily increasing and there exists a need for improved methods for

1 delivering therapeutic agents to subjects suffering from such disease so that treatment  
2 and recovery is facilitated.

3 A complication of pulmonary diseases, especially COPD, is a condition often  
4 referred to as corticoidsteroid resistance (CR) wherein patients become poorly  
5 responsive to the anti-inflammatory actions of corticosteroids and consequently minimal  
6 clinical benefit is derived from such drugs. In some cases, it is thought that CR  
7 manifests when the administered corticosteroid agent does not reach the target areas of  
8 the lungs. Though not wishing to be bound by the following theory, additional  
9 contributing factors of CR are thought to include the impairment of histone deacetylase 2  
10 (HDAC2) and/or the lack of IL-10 secretion from regulatory T-cells. In normal  
11 subjects, HDAC2 is involved in the switching off of inflammatory gene transcription.  
12 As a result of impairment, most likely resulting from cigarette smoking and oxidative  
13 stress, the function of HDAC2 is significantly reduced, gene transcription regulation is  
14 diminished, and ultimately synthesis of inflammatory proteins may proceed unchecked.  
15 IL-10 is known to play an important role in the downregulation of Th1 inflammatory  
16 cytokines and the promotion of regulatory T cells which help to control the inflammatory  
17 response. Certain studies have demonstrated that increasing IL-10 levels to normal  
18 levels, alleviates some of the problems associated with CR resistance.

19 There exists a crucial need in the art for an efficient method of delivering  
20 therapeutic agents to patients suffering from COPD, especially those who also have  
21 complications resulting from CR. Although practitioners skilled in the art recognize the  
22 possible causes of CR (i.e. inability to deliver therapeutic agents in deep lung tissue,  
23 impairment of HDAC function, disruption of IL-10 production), until the development of  
24 the present invention, no effective method or device had been created to meet the needs  
25 of such patients. The novel methods and devices of the present invention enable a  
26 patient for the first time to receive, via inhalation, an agent for CR reversal concurrently  
27 (or sequentially) with a corticosteroid. Although it has been established in the literature  
28 that certain agents possess the ability to improve the efficacy of corticosteroids in CR  
29 patients, an effective method to deliver and achieve beneficial levels in humans without  
30 inducing untoward side effects has not been devised until now.

31 The methods and devices of the present invention overcome problems associated  
32 with prior art methods such as those that result in undesirable side effects including  
33 diminished drug responsiveness due to non-targeted methods drug administration. In

1 contrast, the novel features of the present invention enable controlled site delivery,  
2 namely the deposition of CR reversal agents in proximity to, or at the location of,  
3 corticosteroid deposition. Furthermore, the present invention addresses the  
4 complications that may arise from delivering more than one therapeutic agent wherein  
5 each agent displays dissimilar aerosol characteristics and deposition patterns. The  
6 invention satisfies the need for delivery of corticosteroids and agents for reversal of CR  
7 to the lungs where heightened local concentrations are obtained, systemic levels are  
8 minimized, and synergistic immunomodulating aspects of the two moieties are realized.  
9 In summary, the present invention provides novel methods and devices for pulmonary  
10 delivery of corticosteroids with agents for reversal of CR to a mammalian host,  
11 particularly a human patient, whereby a more significant and/or prolonged  
12 immunomodulatory response greater than that achieved by the corticosteroid alone is  
13 achieved.

14 It has been discovered that pulmonary co-administration of a corticosteroid with  
15 an agent for reversal of CR allows for lower dosage levels than would be necessary to  
16 achieve a similar pulmonary therapeutic response by other methods of delivery (i.e. oral  
17 delivery, intravenous delivery). This allows for reduction of systemic side effects of  
18 either or both agents. Using the inhalers of the present invention, co-administration  
19 allows direct targeting of the agent for reversal of CR to the site of action, since aerosol  
20 deposition of both agents occurs at the same region of the lung and throughout the lung  
21 compartments. Precise targeting of CR reversal agents allows for high local  
22 concentrations in the region of corticosteroid deposition, creating a microenvironment  
23 where corticosteroid activity is increased. Co-administration as described above offers a  
24 more patient compliant alternative to multiple-dosage medicaments and also provides  
25 greater therapeutic efficacy by supplying therapeutic levels of drug at the same tissue  
26 targets (particularly important for CR reversal). The unique features of this invention  
27 resulting in the direct administration of CR reversal agents to the lungs, enhance overall  
28 therapeutic effectiveness. For example, targeted drug delivery according to the methods  
29 herein result in advantages including, but not limited to, prolonged release resulting from  
30 slow dissolution, preferential lung tissue residence resulting from lipophilic  
31 interactions/cellular retention mechanisms, enhancement of pulmonary bioavailability  
32 resulting from avoidance of intestinal and hepatic metabolism, and enhancement of  
33 pulmonary bioavailability resulting from avoidance of poor absorption through the

1 gastrointestinal wall.

2 In certain embodiments, the CR reversal agent comprises vitamin D, vitamin D  
3 analogs, synthetic vitamin D, vitamin D receptor agonists and antagonists, calcitriol,  
4 calcitol and equivalents thereof. Also included are CR reversal agents known to those  
5 skilled in the art, including, but not limited to, antioxidants, iNOS inhibitors,  
6 Phosphoinositide-3-kinase- $\delta$  inhibitors, theophylline, p38 MAP kinase inhibitors, JNK  
7 inhibitors, MIF inhibitors, p-glycoprotein inhibitors, macrolides, and calcineurin  
8 inhibitors.

9 The term "vitamin D" is intended to encompass not only vitamin D2 and vitamin  
10 D3, but any salt, metabolite, or derivative of vitamin D having immunoregulatory  
11 activity like vitamin D, and which is non-toxic and pharmacologically acceptable, for  
12 example, calcitriol.

13 One embodiment of the present invention comprises the administration of dry  
14 powder calcitriol via inhalation. Dosing ranges for such therapeutic administration may  
15 range from 0.0025  $\mu\text{g}$  to 10  $\mu\text{g}$ , from 0.05 $\mu\text{g}$  to 5 $\mu\text{g}$ , or from 0.1  $\mu\text{g}$  to 2.5 $\mu\text{g}$ . In addition,  
16 the mass median particle size of the calcitriol dry powder may range from 0.1  $\mu\text{m}$  to 10  
17  $\mu\text{m}$ , from 0.25 $\mu\text{m}$  to 5 $\mu\text{m}$ , or from 0.5 $\mu\text{m}$  to 4 $\mu\text{m}$ . As would be evident to one skilled  
18 the art, appropriate dosing levels are ultimately determined by the size, weight, and age  
19 of the patient, as well as severity of symptoms to be treated. Nevertheless, one unique  
20 aspect of the present invention comprises low effective dosaging ranges. The unique  
21 methodology of the present invention enables the patients with pulmonary problems to  
22 receive compositions comprising vitamin D, including calcitriol, in low but highly  
23 effective doses. High vitamin D dosing levels can cause toxicity, however the effective  
24 delivery of low dosages of enables the patient to receive the beneficial effects of the  
25 therapeutic composition without potential toxicity. Until now, delivery of vitamin D  
26 compositions via inhalation has been discussed, but not actually reduced to practice. The  
27 inventors of the present invention have overcome problems such as toxicity and inability  
28 to achieve an effective concentration at the site of action, by developing stable,  
29 consistent dry powder formulations and effectively delivering them to the target lung  
30 region even for patients with compromised pulmonary function. Accordingly, though  
31 prior art studies and discussions make reference to vitamin D inhalation, successful  
32 therapeutic intervention comprising vitamin D inhalation was not accomplished until the  
33 present inventors demonstrated the delivery of vitamin D dry powder compositions by

1 coupling suitable formulations with delivery via inhalation.

2 Pulmonary delivery of vitamin D via inhalation as described herein, to a patient,  
3 particularly a human patient, provides heightened and less variable pulmonary or  
4 systemic concentrations compared to those that could be achieved by other methods of  
5 administration. In addition, the direct administration of vitamin D to the lungs as  
6 described herein include but are not limited to prolonged release resulting from dose  
7 reduction, slow dissolution, preferential lung tissue residence resulting from lipophilic  
8 interactions, preferential lung tissue residence resulting from large molecular size,  
9 enhancement of bioavailability (as compared to oral administration) resulting from  
10 avoidance of absorption variability in the gut and reduction of intestinal and hepatic  
11 metabolism.

12 As referenced earlier, therapeutic effects of calcitriol have been documented in  
13 scientific studies for both pulmonary disease and for cancer. However, in such studies,  
14 calcitriol is utilized in very high doses in order for a positive effect to be attained. High  
15 dosing of calcitriol poses significant problems associated with toxicity due to  
16 hypercalcemia. Nevertheless calcitriol has the potential to function as an important and  
17 effective anti-inflammatory pharmaceutical, especially in the area of pulmonary disease  
18 such as COPD where there is no currently available effective anti-inflammatory  
19 therapeutic.

20 The present invention overcomes prior art problems by providing novel methods  
21 and compositions of calcitriol that are suitable for achieving therapeutic concentrations  
22 in the lung following low dose delivery via inhalation as opposed to oral intake which  
23 requires very extremely high doses to achieve the same lung concentrations and therefore  
24 risk significant toxicity. The methods and compositions of the present invention satisfy  
25 the long felt need in the art for a pulmonary disease therapeutic that not only results in  
26 the reduction inflammation and corticosteroid resistance, but also significantly  
27 minimizes toxicity.

28 In certain embodiments, dry powder calcitriol comprises a crystalline anhydrous  
29 form that is micronized to a particle size less than volume median particle size of  
30 approximately 2-8 microns and most preferably approximately 1-4 microns and is  
31 formulated with anhydrous lactose. In certain other dry powder embodiments, calcitriol  
32 may be prepared into a liquid calcitriol/lactose feedstock and processed using spray  
33 drying and/or ultrasonic evaporation processes to yield calcitriol-lactose fused crystals



1 with a particle size less than volume median particle size of approximately 5 microns at a  
2 ratio of 1:10-1:1000, such fused crystals may be further formulated with anhydrous  
3 carrier lactose. In preferred embodiments, the formulations of calcitriol contain no  
4 triazoline adduct of pre-calcitriol and methylene calcitriol.

5 The dry powder calcitriol compositions as described above may be administered  
6 to patients via the use of an inhalation device. In one embodiment, such calcitriol  
7 compositions are administered using proprietary technology developed by MicroDose  
8 Therapeutx, Inc. (Monmouth Junction, New Jersey). The compositions are packaged for  
9 unit dose delivery of 0.25-10.0 micrograms, 0.5-5.0 micrograms or 0.1-2.5 micrograms  
10 (or varying ranges thereof) in a dry powder inhaler (DPI) available from MicroDose  
11 Therapeutx, Inc. The combination of the unique formulation, particle size and delivery  
12 methodology results in effective therapeutic consequence: a reduction in corticosteroid  
13 resistance, and improvement in steroid therapy.

14 Delivery of the dry powder calcitriol compositions described herein via the  
15 inhalers developed by MicroDose Therapeutx, Inc. (as described in United States Patent  
16 Application Serial Nos. 12/785,082, 12/828,133 and 12/985,158) accomplishes  
17 successful administration of appropriate doses to desired sites within the lung and  
18 pulmonary tissue. More specifically, calcitriol compositions may be delivered to small  
19 airways and parenchyma of the lungs for optimal results, namely reduction in  
20 corticosteroid resistance. Patients having compromised lung function benefit from the  
21 methods described herein as administration of therapeutic compositions are  
22 accomplished at a low flow rate. Patients having a breathing flow rate of even a minimal  
23 10 L/min may utilize the inhalers described herein and dosing may be accomplished via  
24 tidal breathing irrespective of any specifically required breathing pattern. Moreover, the  
25 inhaler is designed to deliver drug in a single breathing maneuver at flow rates up to 30  
26 L/min or over a series of tidal inhalations at peak flow rates less than 25 L/min.

27 In certain other embodiments, the administration of calcitriol may be optionally  
28 coupled with a pulmonary tissue growth or repair agent to take advantage of the anti-  
29 inflammatory action of calcitriol in offsetting selective pro-inflammatory action of the  
30 pulmonary tissue growth or repair agent.

31 In some embodiments, the administration of the calcitriol compositions as  
32 described above may be preceded by the administration of bronchodilator. In certain  
33 embodiments therapeutic intervention may involve the preliminary administration of a

1 bronchodilator, followed by the administration of calcitriol optionally combined with a  
2 steroid such as fluticasone.

3 In some embodiments, the therapeutic regimen recommends implementation of  
4 the methods described herein at specific times of the day in order to optimize  
5 effectiveness based on natural biological variation in calcitriol metabolism. For  
6 example, since calcitriol exhibits diurnal variation with the low at around 0400 hr and a  
7 peak at 1600 hr followed by a decline in the evening, in a preferred embodiment,  
8 calcitriol dosing is recommended at night (preferably between 1800hr and 2000hr) to  
9 maximize local supplementation of calcitriol.

10 As mentioned above, in addition to corticosteroid resistance, another obstacle in  
11 pulmonary disease involves the destruction of pulmonary tissue. More specifically, the  
12 destruction of alveoli in COPD patients typically results in significant airspace  
13 enlargement with reduction of alveolar capillary exchange area. The alveoli become  
14 weakened and ruptured air sacs are unable to efficiently move oxygen from the air to the  
15 blood. Previous studies have demonstrated beneficial effects of agents that interact with  
16 the Retinoic Acid Receptor (RAR) on alveoli growth and regeneration, however, until  
17 the disclosure of the present invention herein, no effective therapeutic or administrative  
18 methods for inhalation of vitamin A (or related compounds thereof) were available. In  
19 contrast to currently available therapeutic methods, the methods herein involve  
20 administration of vitamin A via inhalation for controlled site delivery. As a result,  
21 vitamin A therapeutic compositions are delivered in close proximity to damaged alveoli  
22 for direct effect. More specifically, the delivery methods of the present invention  
23 achieve optimal delivery of vitamin A compositions at low doses thereby reducing  
24 unnecessary side effects such as skin reactions (for instance, mucocutaneous eruptions),  
25 and headache. The unique aspects of vitamin A composition delivery as claimed herein,  
26 comprise stable formulations and delivery systems optimized to administer less than 500  
27  $\mu\text{g}$  of active vitamin A compositions to patients with compromised lung function; such  
28 delivery systems coincide with tidal breathing and unlike currently available commercial  
29 devices, do not require coordination with a predetermined breathing patterns by a patient.  
30 One embodiment of the present invention comprises the administration of dry  
31 powder vitamin A compositions via inhalation. Dosing ranges for such therapeutic  
32 administration may range from 0.05  $\mu\text{g}$  to 10  $\mu\text{g}$ , from 0.1  $\mu\text{g}$  to 5  $\mu\text{g}$ , or from 1  $\mu\text{g}$  to 4  $\mu\text{g}$ .  
33 In addition, the mass median particle size of the vitamin A dry powder may range from

1 0.1  $\mu\text{m}$  to 10  $\mu\text{m}$ , from 0.25 $\mu\text{m}$  to 5 $\mu\text{m}$ , or from 0.5 $\mu\text{m}$  to 4 $\mu\text{m}$ . As would be evident to  
2 one skilled the art, appropriate dosing levels are ultimately determined by the size,  
3 weight, and age of the patient, as well as severity of symptoms to be treated.  
4 Nevertheless, one unique aspect of the present invention comprises low effective dosing  
5 ranges. The unique methodology of the present invention enables the patients with  
6 pulmonary problems to receive compositions comprising vitamin A, including ATRA, in  
7 low but highly effective doses.

8 The vitamin A compositions of the present invention include 'alveolar growth  
9 agents' that promote the generation of new alveoli and are selected from agents that  
10 interact with the Retinoic Acid Receptor (RAR). Also included are 'alveolar  
11 maintenance' agents used in combination to maintain newly generated alveoli from being  
12 attacked by the progressive nature of COPD and to minimize unexpected deleterious  
13 effects of the aforementioned RAR therapy.

14 Various alveolar growth agents have been considered in clinical studies, however  
15 all such studies have been limited to methods of administration that do not include  
16 inhalation. These agents include but are not limited to ATRA, ATRA derivatives, RAR  
17 agonists, 13-cis Retinoic acid and RAR selective agonists i.e. palovarotene. In contrast,  
18 the methods of the present invention comprise compositions for inhalation with the goal  
19 of maximizing drug concentrations in the target (lung) and minimizing systemic  
20 exposure to the rest of the body.

21 The present invention further comprises alveolar maintenance agents including  
22 but not limited to: macrolides (Cyclosporine, Tacrolimus, Sirolimus, Clarithromycin,  
23 erythromycin, telithromycin, azithromycin), immunosuppressants (Mycophenolate  
24 sodium), anti-malarials (Hydroxychloroquine, mefloquine), NSAIDS (fenspiride), anti-  
25 oxidants (quercetin, curcumin compounds) and other vitamins/vitamin derivatives  
26 (vitamin D, C, E). The novel methods and compositions of the present invention  
27 comprise vitamin A formulations for inhalation which serve to minimize systemic  
28 exposure, provide effective amounts of both agents to the target organ (the lung) and  
29 avoid the complex systemic metabolism and bioavailability issues of ATRA and RAR  
30 agents.

31 The novel methods and compositions of the present invention overcome current  
32 problems in the prior art by achieving the effective delivery of therapeutic compositions  
33 via inhalation for alleviating and reducing symptoms associated with pulmonary disease.

1 The compositions of the present invention comprise agents for reversing corticosteroid  
2 resistance such as vitamin D, calcitriol and equivalents thereof. In addition, the  
3 compositions of the present invention comprise alveolar growth and maintenance agents  
4 such as ATRA and erythromycin. Furthermore, the present invention may comprise a  
5 combination of therapeutics: certain embodiments may comprise agents for reversing  
6 corticosteroid resistance as well as agents for alveolar regrowth. Certain other  
7 embodiments may further comprise an alveolar maintenance agent. Additional  
8 embodiments may optionally comprise bronchodilating substances.

9 Certain preferred embodiments of the present invention comprise methods for the  
10 treatment of pulmonary disease comprising the administration of compositions  
11 comprising vitamin D and vitamin A via inhalation. More specifically, certain preferred  
12 embodiments comprise methods for the treatment of pulmonary disease, such as COPD,  
13 comprising the administration of compositions comprising calcitriol and ATRA via  
14 inhalation. Such embodiments overcome prior art problems associated with toxicity and  
15 achieve optimal therapeutic effect as a result of controlled site delivery.

16 In addition, certain preferred embodiments comprise methods of delivering  
17 calcitriol and ATRA in ratios from 1:50 to 1:500000 and more preferably from 1:500 to  
18 1:50000. Also, plasma levels of calcitriol do not exceed 30 pg/mL above baseline levels  
19 in serum 4 hours following administration.

20

### 21 *Inhalers*

22 Prior art inhalers are unable to deliver sufficiently micronized medicaments and  
23 as such, therapeutic intervention using such inhalers is not efficient or completely  
24 effective. In contrast, the inhalers of the present invention have the unique ability to  
25 deliver micronized medicaments to the lung airways, and more particularly to the small  
26 lung airways such that uptake of the medicament is accelerated and optimized. The  
27 specific embodiments and details of inhalers contemplated for use herein are described in  
28 detail in United States Patent Application 12,785,082 (United States Published  
29 Application No. 20100294287) filed on May 21, 2010, United States Patent Application  
30 12,828,133 (United States Published Application No. 20110000481) filed on June 1,  
31 2010 and United States Patent Application 12,985,158 (United States Published  
32 Application No. 20110162642) filed on January 5, 2011 and incorporated herein in its  
33 entirety.

1           In some embodiments, the methods of the present invention comprise devices  
2 wherein the improvements pertain to the internal dosing mechanics of the devices, the  
3 administration of individual doses, and also to the general delivery of the medicament.  
4 For example, one improvement pertains to the embodiment of an inhaler having a  
5 vibration element for aerosolizing medicament contained in a blister pack, wherein the  
6 inhaler is adapted to hold a plurality of individual blister packs which can be individually  
7 accessed and moved into an operative or dispensing position between the vibration  
8 element and a piercing element. The advantages of this construction include: simpler,  
9 more compact assembly for an inhaler containing a plurality of blister packs; and the  
10 ability to isolate and shield individual blister packs from the piercing element prior to  
11 use.

12           An additional improvement pertains to an inhaler comprising a compact size  
13 pharmaceutical delivery package including a unique dose drum formed into a cylinder  
14 and containing a plurality of dose compartments for containing individual doses. This  
15 improvement results in better therapeutic compliance by ensuring that the appropriate  
16 dose is delivered to a patient.

17           Another improvement involves the use of a specialized nebulizer that is  
18 particularly useful for pediatric patients and other patients with compromised physical  
19 abilities. The nebulizer contemplated herein utilizes a powder plume, that enables the  
20 delivery of aerosolized dry powders in much higher dose concentrations than are  
21 possible with liquid carried drugs. In addition, the generation of powder plume is  
22 independent of inhalation rate and inhalation timing and the use of the nebulizer results  
23 in reproducible and recordable pulmonary doses from pre-measured blister packs.

24           In accordance with the specific features described above, the inhaler of the  
25 present invention results in improved delivery of therapeutic or pharmaceutical agents by  
26 active device aerosol generation. The mechanism of delivery further utilizes pulmonary  
27 fluid as a delivery medium in order to deliver "through" airflow limited airways and  
28 delivery is accomplished while maintaining positive pressure within the lung. Such  
29 features overcome limitations that may have resulted because of airflow limitation  
30 caused by disease progression. Accordingly, efficient and effective drug delivery is  
31 accomplished regardless of narrowed, collapsed or otherwise compromised airway  
32 passages. For subjects such as those suffering from COPD with reduced inspiratory  
33 capacity and compromised lung function, therapeutic intervention using the presently

1 described inhalers results in expedited relief and reduction of symptoms.

2 An additional advantage of the present invention the ability to deliver more than  
3 one therapeutic agent via inhalation without complications arising from disparate  
4 aerosolization profiles. The present inhalers overcome problems that result from  
5 dissimilar aerosol characteristics and deposition patterns. Accordingly, the present  
6 invention enables the delivery of more than one therapeutic agent, i.e. CR reversal agent,  
7 corticosteroid, pulmonary/alveolar growth agent, bronchodilator. In one embodiment of  
8 the present invention the option of administering a bronchodilating substance prior to the  
9 delivery of the therapeutic agent intended for deep lung delivery is provided. The  
10 bronchodilating substance may be delivered via the same inhaler device thereby  
11 increasing the subject's convenience, and ultimately improving therapeutic compliance.  
12 Also in accordance with the features described above, the methods and device of the  
13 present invention are particularly desirable because a concentrated plume of drug is  
14 delivered within the small volume of inhaled air at the onset of inspiration.

15

#### 16 *Terms and Definitions*

17 The terms "fine drug particles," and "aerodynamic particle size" as used herein,  
18 mean particles having a size sufficiently small so as to be delivered to the airways of the  
19 lungs, and especially to the small airways. For optimal delivery to the lungs, the dry  
20 powder form of the therapeutic agents described herein preferably should be micronized,  
21 spray dried, or engineered to a maximum aerodynamic particle size in the range of 0.1  
22  $\mu\text{m}$  to 10  $\mu\text{m}$ , from 0.25  $\mu\text{m}$  to 5  $\mu\text{m}$ , or from 0.5  $\mu\text{m}$  to 4  $\mu\text{m}$ .

23

24 As used herein, the term "agent for reversal of CR" is intended to encompass any  
25 agent that when administered at an effective level will increase the anti-inflammatory  
26 response induced by a corticosteroid. This term applies not only agents for reversal of  
27 CR, but any salt or derivative of said agent having activity to reverse CR, and which is  
28 non-toxic and pharmacologically acceptable.

29 As used herein, CR reversal agents, include but are not limited to, vitamin D,  
30 vitamin D analogs, synthetic vitamin D, vitamin D receptor agonists and antagonists,  
31 calcitrol and equivalents thereof. Also included are CR reversal agents known to those  
32 skilled in the art. Including, but not limited to, antioxidants, iNOS inhibitors,  
33 Phosphoinositide-3-kinase- $\delta$  inhibitors, theophylline, p38 MAP kinase inhibitors, JNK

1 inhibitors, MIF inhibitors, p-glycoprotein inhibitors, macrolides, and calcineurin  
2 inhibitors.

3 As used herein, the term “vitamin D” is intended to encompass vitamin D,  
4 vitamin D2, vitamin D3, vitamin D analogs, synthetic vitamin D, vitamin D receptor  
5 agonists and antagonists, calcitriol, calcitol and equivalents thereof

6 As used herein, the term “vitamin A” is intended to encompass those agents that  
7 interact with Retinoic Acid Receptor (RAR) including but not limited ATRA, ATRA  
8 derivatives, RAR agonists, 13-cis Retinoic acid and RAR selective agonists for example,  
9 palovarotene.

10 As used herein, the term “alveolar growth agent” is intended to encompass any  
11 agent that promotes the growth of new alveoli via the retinoic acid receptor, and includes  
12 ATRA or RAR selective agent therapy.

13 As used herein, the term “alveolar maintenance agent” is intended to encompass  
14 any agent that when administered at an effective level will increase the anti-  
15 inflammatory response induced by COPD, COPDe and Emphysema and any undesirable  
16 effects of ATRA or RAR selective agent therapy. This term applies not only agents for  
17 alveolar maintenance, but any salt, hydrate, prodrug or derivative of said agent having  
18 similar activity, and which is non-toxic and pharmacologically acceptable.

19 As used herein, bronchodilating substances include, but are not limited to, beta2-  
20 agonists (short and long acting, LABA), long acting muscarinic antagonists (LAMA),  
21 anticholinergics (short acting), and theophylline (long acting). “Co-administered,” as  
22 used herein, means to deliver more than one pharmaceutical or therapeutic agent, for  
23 example, both corticosteroid and agent for reversal of CR as an aerosol within the same  
24 breath via the pulmonary route.

25 “An effective amount,” as used herein, is an amount of the pharmaceutical  
26 composition that is effective for achieving a desired therapeutic effect, including but not  
27 limited to bronchodilation, CR reversal, anti-inflammation, alveolar regrowth. For  
28 example,

29 an effective amount of an agent for reversal of CR may comprise the specified amount  
30 of calcitriol, within a defined aerodynamic particle size range suitable for absorption in  
31 the lungs, that is able to reduce or eliminate the resistance to corticosteroids.

32 As used herein, “pharmaceutical” and “therapeutic” agents include but are not  
33 limited to any and all medicaments and pharmaceutical agents and formulations that may

1 be administered for the treatment of pulmonary disease, including agents for preventing  
2 disease and including agents for maintaining improvement of disease condition. As used  
3 herein, such therapeutic and pharmaceutical agents include, but are not limited to,  
4 corticosteroids, muscarinic antagonists, macrolides, and non-steroidal anti-inflammatory  
5 drugs (NSAIDs), antioxidants, iNOS inhibitors, phosphoinositide-3-kinase- $\delta$  inhibitors,  
6 p38 MAP kinase inhibitors, JNK inhibitors, MIF inhibitors, p-glycoprotein inhibitors,  
7 macrolides, calcineurin inhibitors, and vitamin D, synthetic vitamin D, vitamin D  
8 analogs, calcitriol, vitamin A, All Trans Retinoic Acid (ATRA), retinoic acid receptor  
9 (RAR) agonists, RAR selective alveolar growth agents, budesonide, fluticasone,  
10 beclomethasone, flunisolide, triamcinolone, mometasone, ciclesonide, loteprednol,  
11 fluorometholone as well as any derivative, equivalent or pharmaceutically acceptable salt  
12 thereof.

13 A “pharmaceutical” or “therapeutic” composition as used herein, means a  
14 medicament for use in treating a patient, for example, an agent for reversal of CR in a  
15 dry powder form of a defined aerodynamic particle size prepared in a manner that is  
16 suitable for pulmonary administration to a patient. A pharmaceutical composition  
17 according to the invention may optionally, include a non-toxic pharmaceutically  
18 acceptable carrier. In certain embodiments “pharmaceutical” or “therapeutic”  
19 composition may comprise a singular entity (i.e. calcitriol alone), or a combination of  
20 compositions selected from the group consisting of CR reversal agents, anti-  
21 inflammatory agents, bronchodilators, alveolar growth agents, and others.

22 Other agents that may be delivered via the methods and inhaler described herein  
23 include, but are not limited to chemotherapeutics, angiogenesis inhibitors, kinase  
24 inhibitors, histone deacetylase inhibitors as well as other modifiers of epigenetic  
25 phenomena and proteasome inhibitors. Representative agents that may be used in the  
26 instant invention include, but are not limited to, the following; Aldeskeukin,  
27 Alemtuzumab, alitretinoin, allopurinol, altretamine, amifostine, anastrozole, arsenic  
28 trioxide, asparaginase, BCG Live, bexarotene capsules, bexarotene gel, bleomycin,  
29 busulfan intravenous, busulfan oral, calusterone, capecitabine, carboplatin, carmustine,  
30 carmustine with Polifeprosan 20 implant, celecoxib, chlorambucil, cisplatin, cladribine,  
31 cyclophosphamide, cytarabine, cytarabine liposomal, dacarbazine, dactinomycin  
32 actinomycin D, Darbepoetin alfa, daunorubicin liposomal, daunorubicin, daunomycin,  
33 Denileukin difitox, dexrazoxane, docetaxel, doxorubicin, doxorubicin liposomal,



1 Dromostanolone propionate, Elliot's B solution® (Orphan Medical Inc. Minnetonka,  
2 MN), epirubicin, Epoetin alfa, estramustine, etoposide phosphate, etoposide VP-16,  
3 exemestane, Filgrastim, floxuridine, fludarabine, fluorouracil, fulvestrant, gemcitabine,  
4 bemtuzumab ozogamicin, goserelin acetate, hydroxyurea, Ibritumomab Tiuxetan,  
5 idarubicin, ifosfamide, imatinib mesylate, Interferon alfa-2a, Interferon alfa-2b,  
6 irinotecan, letrozole, leucovorin, levamisole, lomustine CCNU, mecllorethamine  
7 (nitrogen mustard), megestrol acetate, melphalan (L-PAM), mercaptopurine (6-MP),  
8 mesna, methotrexate, methoxsalen, mitomycin C, mitotane, mitoxantrone, MKC-1  
9 nadrolone phenpropionate, Nofetumomab, Oprelvekin, oxaliplatin, paclitaxel,  
10 pamidronate, pegademase, Pegaspargase, Pegfilgrastim, pnetostatin, pipobroman,  
11 plicamycin (mithramycin), porfimer sodium, quinacrine Rasburicase, Rituximab,  
12 Sargramotim, streptozocin, talc, tamoxifen, temozolomide, teniposide (VM-26),  
13 testolactone, thioguanine (6-TG), thiotepa, topotecan, toremifene, Tositumomab,  
14 Trastuzumab, tretinoin (ATRA), Uracil Mustard, valrubicin, vinblastine, vincristine,  
15 vinorelbine and zoledronate.

16 It should be emphasized that the above-described embodiments of the present  
17 device and process, particularly, and "preferred" embodiments, are merely possible  
18 examples of implementations and merely set forth for a clear understanding of the  
19 principles of the disclosure. All these and other such modifications and variations are  
20 intended to be included herein within the scope of this disclosure and protected by the  
21 following claims. Therefore the scope of the disclosure is not intended to be limited  
22 except as indicated in the appended claims.

23 The following specific examples will illustrate the invention as it applies to the methods  
24 of treatment using the inhaler. It will be appreciated that other examples, including  
25 minor variations in procedures will be apparent to those skilled in the art, and that the  
26 invention is not limited to these specific illustrated examples.

27

#### 28 Example 1

#### 29 *Controlled Site Delivery of Corticosteroid and* 30 *Corticosteroid Resistant Agents via Inhalation*

31 Inhaled corticosteroids (ICS) mometasone furoate or fluticasone furoate are  
32 prepared with volume median particle size of less than 5 microns. Calcitriol (1, 25-  
33 Dihydroxycholecalciferol) is also prepared in crystalline form and subsequently

1 micronized to a volume median particle size of less than 5 microns. The ICS's are  
2 incorporated at appropriately 30-50% of the commercial ICS dose when administered via  
3 a passive dry powder inhaler, due to the efficiency of the invention delivered by a dry  
4 powder inhaler (DPI) available from MicroDose Therapeutx, Inc. One preferred  
5 embodiment utilizes an ICS dosed once daily, i.e. mometasone furoate or fluticasone  
6 furoate, to coincide with a once daily dose of the vitamin D receptor agonist. This  
7 combination product is designed to reverse corticoidsteroid resistance (CR) by adding  
8 the protective anti-inflammatory effects of calcitriol with the local anti-inflammatory  
9 effects of these ICS's. The inhaler is operated at 15 L/min and for both medicaments,  
10 the aerosol performance with a fine particle fraction (% of particles exiting the inhaler  
11 that are less than 5.8 microns) is less than or equal to 45% with at least 10% of particles  
12 in the less than 2.1 micron size range when tested with a next generation Impactor.

13

## 14 Example 2

15

16 *Controlled Site Delivery of Corticosteroid and  
Corticosteroid Resistant Agents via Inhalation*

17

18 The ICS of Example 1, in crystalline form, are micronized to a maximum particle  
19 size of about 5 microns. A dry powder unit dose containing clinically effective doses of  
20 either ICS is blended with 1000 micrograms lecithin and packaged for delivery in a dry  
21 powder inhaler (DPI) available from MicroDose Therapeutx, Inc. This combination is  
22 designed to spread into alveolar fluid and treat lung parenchyma through partially  
occluded small airways.

23

24

## Example 3

25

26 *Controlled Site Delivery of Corticosteroid and  
Corticosteroid Resistant Agents via Inhalation*

27

28 The ICS formulation from Example 1 or 2 is combined with albuterol sulfate in  
29 crystalline form separately micronized to a maximum particle size of about 5 microns.  
30 Delivery from a multiple dose dry powder inhaler (DPI) available from MicroDose  
31 Therapeutx, Inc. (Monmouth, New Jersey) leverages the short acting bronchodilation of  
albuterol to allow deeper penetration of the ICS into the lung parenchyma.

32

33

## Example 4

1 *Calcitriol Compositions for Inhalation*

2 Calcitriol is a synthetic vitamin D analog and has been used as a pharmaceutical  
3 as well as a nutraceutical. It is the synthetic version of a vitamin D metabolite that  
4 naturally occurs in the body. Calcitriol in the crystalline anhydrous form is micronized  
5 to a particle size less than volume median particle size of 4 microns and is formulated  
6 with anhydrous lactose. The resulting formulation has a residual moisture of less than  
7 1% and loss of drying of less than 1.5%. The powder is packaged for unit dose delivery  
8 of 0.5-2.5 micrograms in a dry powder inhaler (DPI) available from MicroDose  
9 Therapeutx, Inc. (Monmouth, New Jersey). The formulation is contained within a blister  
10 packaged under inert gas blanket (e.g. Nitrogen) within an aluminum-polymer laminate  
11 heat sealed blister to protect the formulation from moisture, light and oxygen. The  
12 inhaler is operated at 15 L/min and yields an aerosol performance with a fine particle  
13 fraction (% of particles exiting the inhaler that are less than 5.8 microns) of at least 50%  
14 with at least 10% of particles in the less than 2.1 micron size range when tested with a  
15 next generation Impactor. The formulation of calcitriol contains no triazoline adduct of  
16 pre-calcitriol and methylene calcitriol.

17 Use of the aforementioned calcitriol composition and administration via the  
18 MicroDose Therapeutx, Inc. DPI results in optimal delivery of the composition to the  
19 affected areas of the lung and enables reduced corticosteroid resistance.

20

21 Example 5

22 *Calcitriol-Lactose Compositions for Inhalation*

23 Calcitriol is prepared into a liquid calcitriol/lactose feedstock and processed using  
24 spray drying and/or ultrasonic evaporation processes to yield calcitriol-lactose fused  
25 crystals with a particle size less than volume median particle size of 5 microns at a ratio  
26 of 1:10-1:1:1000. The aforementioned fused crystals can be further formulated with  
27 anhydrous carrier lactose. The resulting formulation has a residual moisture of less than  
28 1 % and loss of drying of less than 1.5%. The powder is packaged for unit dose delivery  
29 of 0.5-2.5 micrograms in a dry powder inhaler (DPI) available from MicroDose  
30 Therapeutx, Inc. (Monmouth, New Jersey).

31 Use of the aforementioned calcitriol composition and administration via the  
32 MicroDose Therapeutx, Inc. DPI results in optimal delivery of the composition to the  
33 affected areas of the lung and enables reduced corticosteroid resistance.

1

2

## Example 6

3

*ATRA and Calcitriol Compositions for Inhalation*

4

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6

7

All Trans Retinoic Acid (ATRA) is prepared in crystalline form and subsequently micronized to a volume median particle size of less than 5 microns. Calcitriol (1, 25-Dihydroxycholecalciferol) is also prepared in crystalline form and subsequently micronized to a volume median particle size of less than 5 microns.

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The powder is packaged for unit dose delivery of 10-1000 micrograms of ATRA and 0.5-2.5 micrograms of calcitriol, formulated in an inhalation-grade anhydrous lactose blend in a dry powder inhaler (DPI) available from MicroDose Therapeutx, Inc. This combination product is designed to maximize alveolar regrowth and maintenance potential by adding the protective anti-inflammatory effects of calcitriol with alveolar regrowth induction of ATRA. The inhaler is operated at 15 L/min and for both medicaments, the aerosol performance with a fine particle fraction (% of particles exiting the inhaler that are less than 5.8 microns) is less than or equal to 45% with at least 10% of particles in the less than 2.1 micron size range when tested with a next generation Impactor.

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## Example 7

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Administration of the combination ATRA and calcitriol formulation results in reduced corticosteroid resistance and improved alveolar growth and maintenance.

*Effect of Treatment with Test Articles A, B, C, D, E, F, G, H and I in Cigarette Smoke-Exposed Female C3H/HeN Mice (3 weeks of exposure)*

This study (see Figure 1 and Table 1) will evaluate the efficacy of Test Articles A, B, C, D, E, F, G, H and I on inflammatory endpoints in female C3H/HeN mice (6 – 8 weeks of age on arrival and 8 – 10 weeks of age at start of exposure) exposed to filtered air (FA) or cigarette smoke (CS) for 6 hours per day, 5 days per week for 3 weeks (except for the third week where exposure will be for only 4 days). Mice will be exposed to FA sham (no vehicle), FA plus vehicle, CS plus vehicle, and CS plus intratracheal (IT) delivered Test Articles A, B, C, D, E, F, G, H and I (doses to be determined). Dosing of Test Articles will begin the 1<sup>st</sup> day of CS exposure (see Figure 1)

1 and will be administered q.d. (immediately before CS exposure) for days 1 – 5, 8 – 12,  
 2 and 15 - 18. Some animals may be stagger-started as necessary to accommodate dosing,  
 3 necropsy and sample processing. At the end of the study, mice will be euthanized and  
 4 blood collected for blood gas analysis and plasma isolation. Bronchoalveolar lavage  
 5 (BAL) will be performed on the lungs using three aliquots of PBS. BAL fluid will be  
 6 analyzed at LRRI for total cell counts and differentials (macrophages, neutrophils,  
 7 lymphocytes and eosinophils will be counted on cell differential slides). Lung lobes  
 8 (lavaged) and cell-free BAL supernatant will be snap-frozen and stored at -80°C. Lung  
 9 tissue (lavaged) will be analyzed at LRRI for IL-6, IL-10, IL1- $\alpha$ , IL1- $\beta$ , eotaxin,  
 10 RANTES, MCP-1, MIP-1 $\alpha$ , TNF- $\alpha$ , KC, IL-13, GM-CSF, IP-10, and IFN- $\gamma$  using  
 11 Luminex. Lung tissue will also be analyzed for HDAC2. Plasma and cell-free BAL  
 12 supernatant will be stored at -80°C and sent to the sponsor.

13

14 Table 1. Treatment Groups for Cigarette Smoke-Induced Pulmonary Inflammation

15

Group No. / Descriptor	Animal #	Whole –Body smoke exposure (5 days/week)	Air	Treatment	Delivery Route/Frequency	Tissues Collected/Endpoints
1. Sham	8	-	+	None (IT bolus of air)	IT	Blood collected for blood gas analysis followed by processing to plasma. Plasma sent to sponsor.  Whole lung – BAL (total cells and differentials). Cell-free BAL supernatant collected and sent to sponsor.  Lung lobes – snap frozen individually after lavage – cytokines, chemokines and HDAC2.
2. Vehicle	8	-	+	Vehicle	IT/q.d. (5 days/week)	Blood collected for blood gas analysis followed by processing to plasma. Plasma sent to sponsor.  Whole lung – BAL (total cells and

						<p>differentials). Cell-free BAL supernatant collected and sent to sponsor.</p> <p>Lung lobes – snap frozen individually after lavage – cytokines, chemokines and HDAC2.</p>
3. Vehicle	8	+	-	Vehicle	IT/q.d. (5 days/week)	<p>Blood collected for blood gas analysis followed by processing to plasma. Plasma sent to sponsor.</p> <p>Whole lung – BAL (total cells and differentials). Cell-free BAL supernatant collected and sent to sponsor.</p> <p>Lung lobes – snap frozen individually after lavage – cytokines, chemokines and HDAC2.</p>
4. Test Article A	8	+	-	Calcitriol Low Dose	IT/q.d. (5 days/week)	<p>Blood collected for blood gas analysis followed by processing to plasma. Plasma sent to sponsor.</p> <p>Whole lung – BAL (total cells and differentials). Cell-free BAL supernatant collected and sent to sponsor.</p> <p>Lung lobes – snap frozen individually after lavage – cytokines, chemokines and HDAC2.</p>
5. Test Article B	8	+	-	ATRA	IT/q.d. (5 days/week)	<p>Blood collected for blood gas analysis followed by processing to plasma. Plasma sent to sponsor.</p> <p>Whole lung – BAL (total cells and differentials). Cell-free BAL supernatant collected and sent to sponsor.</p>

						Lung lobes – snap frozen individually after lavage – cytokines, chemokines and HDAC2.
6. Test Article C	8	+	-	Calitriol High Dose	IT/q.d. (5 days/week)	<p>Blood collected for blood gas analysis followed by processing to plasma. Plasma sent to sponsor.</p> <p>Whole lung – BAL (total cells and differentials). Cell-free BAL supernatant collected and sent to sponsor.</p> <p>Lung lobes – snap frozen individually after lavage – cytokines, chemokines and HDAC2.</p>
7. Test Article D	8	+	-	Dexamethasone	IT/q.d. (5 days/week)	<p>Blood collected for blood gas analysis followed by processing to plasma. Plasma sent to sponsor.</p> <p>Whole lung – BAL (total cells and differentials). Cell-free BAL supernatant collected and sent to sponsor.</p> <p>Lung lobes – snap frozen individually after lavage – cytokines, chemokines and HDAC2.</p>
8. Test Article E	8	+	-	Dexamethasone + Calitriol	IT/q.d. (5 days/week)	<p>Blood collected for blood gas analysis followed by processing to plasma. Plasma sent to sponsor.</p> <p>Whole lung – BAL (total cells and differentials). Cell-free BAL supernatant collected and sent to sponsor.</p> <p>Lung lobes – snap frozen individually after lavage –</p>

						cytokines, chemokines and HDAC2.
9. Test Article F	8	+	-	Calcitriol + ATRA	IT/q.d. (5 days/week)	<p>Blood collected for blood gas analysis followed by processing to plasma. Plasma sent to sponsor.</p> <p>Whole lung – BAL (total cells and differentials). Cell-free BAL supernatant collected and sent to sponsor.</p> <p>Lung lobes – snap frozen individually after lavage – cytokines, chemokines and HDAC2.</p>

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1 We claim:

2 1. A method for treating pulmonary disease comprising the use of an inhaler  
3 for administrating pharmaceutical agents.

4 2. The method of claim 1, wherein the pharmaceutical agent comprises  
5 bronchodilators, corticosteroids, corticosteroid reversal agent, and alveolar growth  
6 agents.

7 3. The method of claim 2, wherein the bronchodilators comprise long-acting  
8 beta<sub>2</sub>-agonists or long acting muscarinic antagonists.

9 4. The method of Claim 2, wherein the corticosteroids comprise budesonide,  
10 fluticasone, beclomethasone, flunisolide, triamcinolone, ciclesonide, loteprednol,  
11 fluorometholone, and derivatives or pharmaceutically acceptable salts thereof.

12 5. The method of claim 2, wherein the corticosteroid reversal agent  
13 comprises vitamin D, synthetic vitamin D, vitamin D analogs, vitamin D receptor  
14 agonists, vitamin D receptor partial agonists, calcitriol, calcitriol, antioxidants, iNOS  
15 inhibitors, Phosphoinositide-3-kinase- $\delta$  inhibitors, p38 MAP kinase inhibitors, JNK  
16 inhibitors, MIF inhibitors, p-glycoprotein inhibitors, macrolides, calcineurin inhibitors,  
17 and equivalents thereof.

18 6. The method of claim 2, wherein the alveolar growth agent comprises  
19 vitamin A, All Trans Retinoic Acid (ATRA), retinoic acid receptor (RAR) agonists and  
20 RAR selective alveolar growth agents, RAR selective agonists, palovarotene and  
21 equivalents thereof.

22 7. The method of any of claims 1-6, wherein the pulmonary disease  
23 comprises asthma, atelectasis, bronchitis, COPD, emphysema, lung cancer, pneumonia  
24 and pulmonary edema.

25 8. The method of any of claims 1-6, wherein the pulmonary disease  
26 comprises COPD and the pharmaceutical agents comprise a corticosteroid reversal agent  
27 and a corticosteroid.

28 9. The method of claim 8, wherein the corticosteroid reversal agent  
29 comprises calcitriol, and the corticosteroid comprises fluticasone.

30 10. The method of claim 9, optionally comprising a bronchodilator or an  
31 alveolar growth agent.

32 11. A method for treating COPD comprising the use of an inhaler for  
33 administrating pharmaceutical agents.

1           12. The method of claim 11, wherein the pharmaceutical agents comprise  
2 bronchodilators, corticosteroids, corticosteroid reversal agent, and alveolar growth  
3 agents.

4           13. The method of claim 12, wherein the corticosteroid reversal agent  
5 comprises vitamin D, synthetic vitamin D, vitamin D analogs, vitamin D receptor  
6 agonists, vitamin D receptor partial agonists, calcitriol, calcitriol, antioxidants, iNOS  
7 inhibitors, Phosphoinositide-3-kinase- $\delta$  inhibitors, p38 MAP kinase inhibitors, JNK  
8 inhibitors, MIF inhibitors, p-glycoprotein inhibitors, macrolides, calcineurin inhibitors,  
9 and equivalents thereof.

10          14. The method of claim 13, wherein calcitriol comprises a crystalline  
11 anhydrous form.

12          15. The method of claim 13, wherein calcitriol comprises calcitriol-lactose  
13 fused crystals.

14          16. The method of claim 12, wherein alveolar growth agent comprises  
15 vitamin A, All Trans Retinoic Acid (ATRA), retinoic acid receptor (RAR) agonists and  
16 RAR selective alveolar growth agents, RAR selective agonists, palovarotene and  
17 equivalents thereof.

18          17. The method of claim 12, further comprising alveolar maintenance agents.

19          18. The method of claim 17, wherein the alveolar maintenance agents  
20 comprise macrolide, cyclosporine, tacrolimus, sirolimus, clarithromycin, erythromycin,  
21 telithromycin, azithromycin, immunosuppressants, mycophenolate sodium, anti-  
22 malarials, hydroxychloroquine, mefloquine, NSAIDs, fenspiride, anti-oxidants quercetin,  
23 curcumin compounds, vitamin D, vitamin C, and vitamin E.

24          19. The method of claim 11, wherein the pharmaceutical agents comprise  
25 calcitriol and ATRA.

26          20. The method of claim 19, further comprising alveolar maintenance agents.

Figure 1

