Oral inhalation: An approach for better therapy

Pooja Chavda and Priya Jinjala

Abstract
Enhanced therapeutics is drug products derived from existing drugs that provide additional benefits to the patients and the healthcare system. Now a day's pulmonary drug delivery gaining substantial interest as an alternative route for administration of systematically acting drugs that are poorly absorbed from the gastrointestinal tract or are pre systemically metabolized molecules. Generally half of all pharmaceuticals are not soluble in water, but are soluble in lipid. As the lung is able to absorb both water and oil into the tissue, solubility is not a constraint for pulmonary delivery. The inhalation route is a fast and effective way of delivering medication locally to the lungs and also for the systemic administration of certain agents. Inhalation therapy has been employed as the mainstay of the treatment in chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). The progress of dry powder inhaler (DPI) technology has created opportunities in other therapeutic areas where systemic exposure is required. Low dosed drugs and large molecules have been successfully delivered via the respiratory tract for the treatment of systemic diseases. The formulation and the container closure systems collectively constitute the drug product. Drug contain in pressurized metered dose inhalers (PMDIS) is suspended or dissolve in a volatile propellant, which is atomized for breath-coordinated inhalation.

Keywords: Inhalation, pressurized metered dose inhalers (PMDI), dry powder inhaler (DPI), chronic obstructive pulmonary disease (COPD)

Introduction
Chronic Respiratory Diseases (CRDs) are one of the major root causes for deaths around the world. CRDs cover a wide range of different diseases like asthma, chronic obstructive pulmonary disease (COPD), rhinitis, sleep-apnea and other CRDs. There are various treatments are available to treat diseases one of this the oral inhalation is most widely used now a days [1].

Drug delivery to the lung is an effective way of targeted drug delivery for the treatment of CRDs, but it is gaining substantial interest as an alternative route for the administration of systemically acting drugs that are poorly absorbed from the gastrointestinal tract or are Presystemically metabolized liked polypeptides, proteins, genes or vaccines and has also been applied successfully for diagnostic purposes [2]. Pulmonary drug delivery offers superior direct targeting to the site of action, higher lung doses, and lower systemic drug concentrations, opening the potential for higher therapeutic index with a higher absorption area and with a lower total body dose and reduced potential for adverse events [3]. Delivery of drug to the deep lung can also offer improved access to the systemic circulation with several advantages, including rapid onset of action, avoidance of first-pass metabolism, and convenience as compared to injection. With the increasing demand from emerging markets and the financial concerns in the mature markets, pharmaco economic aspects and especially the costs of medicine have to be addressed [4]. As the product and process design is crucial for the finished product costs, economic evaluations will increasingly become an integral part of product development [5]. Altogether, this has led to an increasing interest and investment in pulmonary drug delivery throughout the pharmaceutical and medical sciences in academia, industry and regulatory authorities [6].
Inhalation system for pulmonary drug delivery
There are three commonly used inhalation drug delivery systems.
- Dry powder inhaler system (DPIs)
- Pressurized metered dose inhalers (pMDI)
- Nebulizer
  - Jet nebulizer
  - Ultrasonic nebulizer

Dry powder inhalers (DPIs): have traditionally used micronized powdered medication blended with a large quantity of lactose-based carrier, limiting the amount of drug that can be delivered. With no propellant, DPIs generally rely on the force of patient inhalation for delivery, which has limited their use in patient populations with potentially compromised lung capacity, such as children and the elderly [7]. These lactose blends are typically composed of more than 80% to 90% lactose with microgram quantities of drug, resulting in a low drug, mass-to-volume of powder ratio that limits their use primarily to high-potency drugs. These powders are also generally higher flow rate-dependent with respect to their dispersibility, have poor delivery efficiency with typically less than 20% of drug making it to the lung, and have high patient-to-patient variability. Second generation DP delivery based on particle engineering approaches (rather than active devices) have included production of porous particles and coating of particles with hydrophobic force-modifying excipients, such as magnesium stearate. [8] Porous particles allow for aerosolizable powders with good dispersibility over a wide range of expiratory flow rates, however, the inherent low particle density results in a low drug mass-to-volume of powder inhaled. The reduction in the amount of drug per unit volume can make porous particles unsuitable for large molecule drugs or drug combinations that often require higher effective drug mass loadings per dose [9]. Limitations of existing inhaled drug delivery methods have created the opportunity for a new approach to DP inhaled drug delivery technology. Moving forward, trends in the industry indicate that this significant opportunity is growing as more pharmaceutical and biopharmaceutical companies pursue the following product and formulation objectives.
- Using pulmonary delivery for a range of small-to-large drug molecules, spanning both existing and new drug entities; increasing the dosage of active drug molecules in inhaled therapeutics, specifically increasing the drug mass to inhaled volume.
- Seeking to commercialize drug combination formulations, including two, three, and higher numbers of drugs combined into a single inhaled product; and pursuing reproducible delivery across a range of patient populations, including pediatrics, the elderly, and those with generally compromised lung function.
- A new dry powder formulation approach has been developed that overcomes the limitations of traditional inhaled delivery and has the potential to expand therapeutic options, disease targets, and patient populations for pulmonary drug delivery [10, 13].

Pressurized metered dose inhalers (pMDIs): contain drug suspended or dissolved in a volatile propellant that is atomized for inhalation. The propellants that were originally used, chlorofluorocarbons and hydro fluoroalkanes, emit environmentally unfriendly gases. Moving away from these propellants has proven to be difficult with certain drugs and formulations, reducing the number of therapeutics that can be formulated in this way. PMDIs are also characterized by low lung deposition efficiency and require breath coordination for effective delivery [11, 13].
The Nebulizer: converts a liquid solution or suspension of a drug into fine droplets by air-jet or ultrasonic means that are inhaled by the patient over a couple of minutes. Nebulizer drugs are typically delivered continuously over multiple breaths. Used mostly for elderly, infant, or critically ill patients, nebulization is typically considered to be a less convenient delivery system in terms of portability and delivery time, and is also characterized by low lung deposition efficiency. Nebulizers possess limitations in terms of the formulation of drugs that are degraded by shear and air-water interfaces [12, 13].

Novel drug formulations available
These include mainly the following formulations like liposomes, microspheres and nanoparticles. These formulations increase drug absorption by transporting encapsulated drug across the membrane or retention time and stability of the drug.

1) Liposome
Liposomes are phospholipids vesicles composed by lipid bilayers enclosing one or more aqueous compartment in which drugs and other substances might be included. In recent times, they have been investigated as a vehicle for sustained-release therapy in the treatment of lung disease. Ex: insulin and calcitonin [13, 14, 15].

2) Nanoparticles
Nanoparticles are solid colloidal particles with diameters ranging from 1-1000 nm. They consist of macromolecular materials and which are therapeutically used as adjuvant in vaccines or as drug carriers, in which the active substance is dissolved, entrapped, encapsulated, adsorbed or chemically attached. Nanoparticles penetrate the mucosal membrane by Nanoparticles route and in a limited quantity, since the tight junctions are in the order of 3.9-8.4 Å [13, 16, 17].

3) Microsphere
Microspheres are usually based on muco-adhesive polymers (Chitosan, alginate), which provide various for drug delivery, microspheres may protect the drug from enzymatic metabolism and gives sustain drug release, thereby prolonging its effect [13, 18].

<table>
<thead>
<tr>
<th>Effect</th>
<th>Inhalation</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>First effect after</td>
<td>5 minutes</td>
<td>30-90 minutes</td>
</tr>
<tr>
<td>Maximum effect after</td>
<td>10-30 minutes</td>
<td>2-3 hours</td>
</tr>
<tr>
<td>Total duration of effects</td>
<td>3-4 Hours</td>
<td>4-8 hours</td>
</tr>
</tbody>
</table>

Table 1: Comparison of drug release by inhalation and oral route

Characterization requirement [19, 20]

Table 2: Characterization requirement for pharmaceutical development study

<table>
<thead>
<tr>
<th>Pharmaceutical Development Study</th>
<th>Pressurized Metered Dose Inhalers</th>
<th>Dry Powder Inhalers</th>
<th>Product For Nebulization</th>
<th>Non Pressurized Metered Dose Inhalers</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Physical Characterization:</td>
<td>Yes®</td>
<td>Yes</td>
<td>Yes®</td>
<td>Yes®</td>
</tr>
<tr>
<td>2. Minimum Fill Justification</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>3. Extractables / Leachables</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>4. Delivered Dose Uniformity And Fine Particle Mass Through Container Life:</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>5. Delivered Dose Uniformity And Fine Particle Mass Over Patient Flow Rate Range:</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>6. Fine Particle Mass With Spacer</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7. Single Dose On Particle Mass:</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>8. Particle Size Distribution:</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>9. Actuator And Mouthpiece Deposition:</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>10. Drug Delivery Rate And Total Drug Delivery</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>11. Shaking Requirements</td>
<td>Yes®</td>
<td>No</td>
<td>No</td>
<td>Yes®</td>
</tr>
<tr>
<td>12. Initial And Re-Priming Requirements</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>13. Cleaning Requirements</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>14. Low Temperature Performance</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>15. Performance After Temperature Cycling</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>16. Effect Of Environmental Moisture</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>17. Robustness</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>18. Delivery Device Development</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>19. Preservative Effectiveness/Efficacy</td>
<td>No</td>
<td>No</td>
<td>Yes®</td>
<td>Yes®</td>
</tr>
<tr>
<td>20. Compatibility</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

For suspension
If a preservative is present
1. Physical characterization
Physical characteristics such as solubility, size, shape, density, rigidity, charge, and crystallinity of the drug substance and/or excipients may influence the homogeneity and reproducibility of the finished product. Development studies should include physical characterization of drug substance and excipients, relevant to their effect on the functionality of the product.

2. Minimum Fill Justification
For metered dose inhalers and device-metered dry powder inhalers, a study should be conducted to demonstrate that the individual container minimum fill, as defined by the drug product manufacturing process, is sufficient to provide the labeled number of actuations. The final doses (as defined by the label claim) should meet the drug product specification limits for delivered dose uniformity and fine particle mass.

For pre-metered dry powder inhalers and products for nebulisation, the acceptance criteria for the fill volume and/or weight should be justified in relation to delivered dose uniformity and fine particle mass.

3. Extractables / Leachables
For non-compendia plastic and for rubber container closure components that are in contact with the formulation during storage (e.g., valves), a study should be conducted to determine the extractable profile. Details and justification of the study design (e.g., solvents used, temperature, and storage time) and the results should be provided. It should be determined whether any of the extractable are also leachable present in the formulation at the end of the shelf life of the product or to the point equilibrium is reached, if sooner. The leachable profile should also be determined for compendial plastics and rubber container closure components.

4. Delivered dose uniformity and fine particle mass through container life
A study should be conducted to demonstrate the consistency of the minimum delivered dose (e.g., one or more actuations) and the fine particle mass through the life of the container from the first dose until the last labeled dose. The containers should be used and tested according to the information for the patient with respect to storage orientation and cleaning requirements, as well as minimum dosing interval. It is generally expected that at least ten doses from the combination of the beginning, middle, and end of the container be tested.

5. Delivered dose uniformity and fine particle mass over patient flow rate range
A study should be conducted to demonstrate the consistency of the minimum delivered dose and the fine particle mass over the range of flow rates (through the delivery device) achievable by the intended patient population, at constant volume. The range of flow rates should be justified in relation to clinical studies or published data for the same delivery device. The minimum (e.g., 10th percentile), median, and maximum (e.g., 90th percentile) achievable rate should be investigated.

6. Fine particle mass with spacer/holding chamber use
For inhalation products that may be administered with a spacer or holding chamber, a study should be conducted to determine whether the use of the spacer or holding chamber changes the fine particle mass. If the instructions accompanying the spacer or holding chamber include an in-use cleaning schedule (e.g., weekly cleaning), the fine particle mass should be tested before and after cleaning the spacer or holding chamber according to the instructions provided with the device. The fine particle mass test used for routine testing of the product may be altered to mimic patient performance with the spacer or holding chamber (e.g., a 2 second delay, tidal breathing)

7. Single dose on particle mass
The fine particle mass of one dose should be determined according to the drug product specification fine particle mass method, modified only as necessary to accommodate the reduced sample size. Stage pooling prior to analysis is acceptable. The selection of the pooled stages should be justified. If this study is not feasible due to the sensitivity of the analytical method, data supporting this claim should be provided.

8. Particle Size Distribution
To allow an assessment of the complete profile of the product used in in vivo (pivotal clinical and/or comparative) studies, individual stage particle size distribution data should be provided for the batches used in these studies, as well as data on batches representative of the commercial process. When a range of different strengths is proposed, proportionality in fine particle mass and other size ranges (e.g., mass deposit in the impactor throat) should be considered. For solutions for nebulisation, droplet size distribution may be tested by other methods. (e.g., laser diffraction).

9. Actuator and Mouthpiece deposition
The amount of drug deposited on the actuator or mouthpiece should be determined and, where applicable, demonstrated to be consistent with any correction factor used to support ex-valve (or ex-delivery device) label claims.

10. Shaking requirements
For products requiring shaking before use (according to the instructions for use), a study should be conducted to demonstrate that the shaking instructions provided to the consumer are adequate. The possibility of excessive shaking leading to foaming and inaccurate dosing should be examined by testing the delivered dose uniformity.

11. Initial and Repriming Requirements
The number of priming actuations required until the subsequent doses meet the drug product specification limits for delivered dose uniformity should be determined. Priming instructions should be provided to the health care professional and the consumer. Re-priming instructions, including any necessary instructions with respect to storage orientation, should be provided to the health care professional and the consumer.
12. Cleaning Requirements
Delivered dose uniformity and fine particle mass or droplet size distribution data to support the recommended cleaning instructions provided to the health care professional and the consumer (including method and frequency) should be provided. The study should be conducted under conditions of normal patient usage, in accordance with recommendations for priming, dosing intervals, and typical dosing regimen.

13. Low Temperature performance
A study should be conducted to determine the effect of low temperature storage on the performance of the product. Containers should be stored in various orientations for at least 3 hours at a temperature below freezing (0 °C), and then immediately tested.

14. Temperature cycling performance
A study should be conducted to determine the effect of temperature cycling on the performance of the product. Containers should be stored in various orientations and cycled between recommended storage conditions and a temperature below freezing (0 °C). For suspensions, cycling between the recommended storage conditions and a high temperature (e.g., 40 °C) should be considered, and may be combined with the low temperature cycling study. Storage time should be at least 24 hours under each condition, and containers should be stored under each condition at least five times. The containers should be examined visually for any obvious defects, and tests such as leak rate, weight loss, delivered dose uniformity, fine particle mass, related substances and moisture content should be performed. Any changes from initial results should be assessed for their significance.

15. Effect of environmental moisture
The effect of environmental moisture on product performance should be investigated during development. For pre-metered products using capsules, special attention should be paid to brittleness of the capsules under various humidity conditions.

16. Robustness
The product performance should be investigated under conditions to simulate use by patients. This includes activating the delivery device at the frequency indicated in the instructions for use. Carrying the delivery device between use and simulation of dropping the delivery device, etc., and the robustness of any lockout mechanism should be considered.

17. Compatibility
If the product is to be diluted prior to administration, compatibility should be demonstrated with all diluents over the range of dilution proposed in the labelling. These studies should preferably be conducted on aged samples, and should cover the duration of storage of the diluted product indicated in the labelling. Where the labelling specifies co-administration with other drugs, compatibility should be demonstrated with respect to the principal drug as well as the co-administered drug. Parameters such as precipitation, pH, droplet size distribution, output rate and total drug output should be tested, and differences from the original product should be assessed for their significance.

Quality control test (evaluation TEST): [21][22]
1. Containers
Containers are examined for defects in the lining. Q.C aspects include a degree of conductivity of electric current as a measure of exposed metals, glass containers examined for flaws.

2. Flame Extension Test
This test indicates the effect of an aerosol formulation on the extension of an open flame. The product is sprayed for 4 Sec. into flame. Depending on the nature of the formulation, the flame is extended, and exact length was measured with a ruler.

3. Flash Point
It can be determined by using standard Tag Open Cap apparatus.

Procedure: Aerosol product is chilled to temperature of - 25 0 F and transferred to the test apparatus. Temperature of test liquid increased slowly, and the temperature at which the vapors ignite is taken a flash point. Calculated for flammable component, which in the case of topical hydrocarbons.

4. Measurement Of Vapor Pressure
Measurement of vapor pressure determined by pressure gauge. Variation in pressure indicates the presence of air in the headspace.

5. Measurement Of Density
It can be determined by Hydrometer or a Pycnometer.

Procedure: A pressure tube is fitted with metal fingers and hoke valve, which allow for the introduction of liquids under pressure. The hydrometer is placed into the glass pressure tube. Sufficient sample is introduced through the valve to cause the hydrometer to rise half way up the length of the tube. The density can be read directly.

6. Moisture Content
To determine the moisture Karl Fischer widely used. Gas chromatography has also been used.

7. Identification of propellants
For this mainly Gas Chromatography and Infrared spectrophotometer have been used.

8. Spray Pattern
Spray pattern. Spray the product on the coated (dye +talc) Paper. Depending upon the nature of aerosol water /oil soluble dye is used.

9. Dosage With Metered Valves
Several points must be considered: 1) reproducibility of dosage each time the valve is depressed and2) amount of medication actually received by the patient.

Procedure: Dosage with Metered valves Weigh accurately the filled container. Dispense no. Of doses. Reweigh the container & calculate the weight difference. Weight diff/ No. of times dose dispensed gives Avg. dose. We should note the time of the each dose dispensed also. The dose is measured in grams/Sec.
10. Net content
Net content the difference in the weight of the full container and tarred container gives the content in the container.
Net wt = gross weight - Tare wt.

11. Foam Stability
Foam stability it can be determined by visual examination.
Time for given mass to penetrate the foam Time for given rod that is inserted in the foam to fall. Use of rational viscometers.

12. Partial Size Determination
Particle size determination it is done by cascade impactor & light scatter decay methods.

13. Leakage Test
Leakage test Aerosol containers are completely immersed in hot water bath until the temperature reaches 54.4ºc and is tested for leakage. Is done by measuring the crimp’s dimension & comparing. Final testing of valve closure is done by passing filled containers through a water bath.

14. Biological Testing
A) Therapeutic activity
For inhalation aerosols: It depends on the particle size.
For topical aerosols: It is applied to test areas & adsorption of therapeutic ingredient is determined.

B) Toxicity
For inhalation aerosols: Exposing test animals to vapor sprayed from an aerosol container.
For topical aerosols: Irritation & chilling effects are determined.

Marketed Formulation: [23, 24, 25]
1. Asthelin CFC free inhaler (Salbutamol pressurized inhalation BP) – CIPLA
2. Ventolin Euphaler (salbutamol) –GLAXO WELLCOME
3. Xopenex HFA (levalbuterol tartrate inhalation aerosol) – SEPRACOR INC.
4. Ipravent inhaler (ipratropium pressurized inhalation BP) – CIPLA
5. Qvar (beclomethasone dipropionate HFA)-IVAX
6. Symbicort (budesonide+formoterol) -ASTRAZENECACorporation
7. RELVARTM ELLIPTA® (Europe/Japan) (Asthma / COPD) - GlaxoSmithKline® (SKYPEPHARMA)
8. ANOROTM ELLIPTA® (COPD) - GlaxoSmithKline**(SKYPEPHARMA)
9. BREOTM ELLIPTA® (COPD) - GlaxoSmithKline**(SKYPEPHARMA)
10. Flutiform® (fluticasone propionate + formoterol fumarate dihydrate) – *(SKYPEPHARMA)
11. Zyflo CR® (Zileuton) –cornerstone therapeutics Inc *(SKYPEPHARMA)
12. Foradil ® aerosizer (formoterol fumarate inhalation powder) –MERCK & CO INC.
13. Advair diskus (fluticasone propriate) – GLAXOSMITHKLINE
14. Aridol –(mannitol) – PHARMAXIS INC
15. Burton-asthma inhaler (Salbutamol)

Applications[13]
- Applications of drug delivery in Asthma and COPD.
Today’s inhaled drug delivery market is conquered by the three main classes of drug such as bronchodilators, corticosteroids, and anti cholinergic. All these three classes of drugs are given by pulmonary route only. Levosalbutamol inhalers are present in the market to treat asthma. Titropium inhalers are present in market to treat COPD [26].

- Applications of drug delivery in diabetes.
The first attempts at intrapulmonary delivery were made in the 1920s. Several companies are working on insulin inhalers than any other insulin delivery option [27].

- Applications of drug delivery in Angina pectoris.
An aerosol form has been tested in Europe and has been found comparable to sublingual nitroglycerine. In particular, its efficacy has been found better than nitroglycerine tablets in patients with dry mouth. Isosorbide aerosol has also been reported of use in hypertensive emergency [28].

- Applications in drug delivery In Pulmonary arterial hypertension.
In 2004, the FDA approved Ventavis (iloprost), an inhaled treatment for pulmonary arterial hypertension, made by CoTherix (South San Francisco, CA, U. S. A.). In pulmonary arterial hypertension, severe restriction of blood vessels results in early death. Iloprost naturally dilates blood vessels [29].

- Application of drug delivery in cancer chemotherapy.
Aerosol delivery of the anticancer agent’s difluoro methylornithine and 5-fluorouracil reduced lung tumours in mice 50 % and 60 %, respectively. Interleukin-2 stimulates immune function in cancer patients, but injections cause fever, malaise, and local swelling [30].

- Applications in drug delivery for bone disorder.
A pulmonary formulation inhaled through the mouth that delivers calcitonin or PTH into the deep lung should improve the bioavailability and efficacy of the drugs [30].

- Inhaled drug delivery for tuberculosis therapy.
Supplementing conventional therapy with inhaled anti-TB therapy may allow therapeutic concentrations of drug to penetrate effectively into lung lesions and treat the resident mycobacteria [31].

- Application of drug delivery of opioids as pain therapeutics.
The pulmonary route has excellent potential for treating noninvasively severe pain in the postoperative setting and in malignant disease. So by giving pain killer via pulmonary route we can give parental efficacy with oral convenience to patients. So the pulmonary drug delivery is unproblematic to control pain [32].

- Gene therapy via pulmonary route.
There are many problems to be overcome before clinical
Applications are practical. Some of these are safety, successful transfer of sufficient genetic material to appropriate tissue, adequate gene expression, maintenance of expression over time, and efficacy of expression.[13]

Conclusion
Pulmonary drug delivery is a vital research area, which impacts the treatment of illnesses including asthma, chronic obstructive pulmonary disease and various other diseases. There have been a number of significant achievements in technologies to express and deliver drugs by pulmonary route. However the issues for drug companies and patients concerning pulmonary delivery revolve around economic evaluations, approvals, administration and managed health care. Because the drug administration through pulmonary route is a complicated and complex process, which comprising not only on aspects from technology but also from physiology, clinical application or patient use. As these issues are resolved, pulmonary delivery will be probably regarded as one of the most important drug delivery alternative.

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34. Skyepharma - Approved inhalation products - flutiform, Partners: Mundipharma, Kyorin