CURRENT MARKET

• Inhalation global market total value = $39 billion (USD)
  • DPI’s = 60% (Projected CAGR 16.9% ANNUALLY THROUGH 2024)
  • pMDI’s = 40%

• 940 million devices sold annually

• 50% of current global market ($32 billion USD) for Asthma and COPD medications to lose patent protection by 2016
## SALES IN 2017

<table>
<thead>
<tr>
<th>Product name</th>
<th>Company</th>
<th>US sales, USD million</th>
<th>European sales, EUR million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advair Discus / Seretide</td>
<td>GSK</td>
<td>4,755</td>
<td>905.8</td>
</tr>
<tr>
<td>Spiriva Handihaler</td>
<td>BoehringerIngelheim</td>
<td>3,055</td>
<td>817.5</td>
</tr>
<tr>
<td>Symbicort</td>
<td>AstraZeneca</td>
<td>2,995</td>
<td>917.1</td>
</tr>
<tr>
<td>Breo Elipta</td>
<td>GSK</td>
<td>1,613</td>
<td>203.3</td>
</tr>
<tr>
<td>Proair HFA / Salamol, Sulbutamol</td>
<td>TEVA</td>
<td>1,453</td>
<td>50.6</td>
</tr>
<tr>
<td>Ventolin</td>
<td>GSK</td>
<td>1,393</td>
<td>129.2</td>
</tr>
<tr>
<td>Flovent HFA / Flixtotide</td>
<td>GSK</td>
<td>1,235</td>
<td>94.1</td>
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<tr>
<td>Beclazone / Beclometasone (generics)</td>
<td>TEVA</td>
<td>845.2</td>
<td>227.8</td>
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<tr>
<td>Combivent Respimat</td>
<td>BoehringerIngelheim</td>
<td>795.4</td>
<td>11.5</td>
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<tr>
<td>Dulera</td>
<td>Merck</td>
<td>718.9</td>
<td>-</td>
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<tr>
<td>Pulmozyme</td>
<td>Roche</td>
<td>675.5</td>
<td>104.1</td>
</tr>
<tr>
<td>Budesonide (generic)</td>
<td>TEVA</td>
<td>615.6</td>
<td>163.9</td>
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<tr>
<td>Anoro Ellipta</td>
<td>GSK</td>
<td>563.6</td>
<td>69.9</td>
</tr>
<tr>
<td>Product name</td>
<td>Company</td>
<td>US sales, USD million</td>
<td>European sales , EUR million</td>
</tr>
<tr>
<td>---------------------------</td>
<td>---------------</td>
<td>-----------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Foster</td>
<td>Chiesi</td>
<td>-</td>
<td>612.6</td>
</tr>
<tr>
<td>Brovana</td>
<td>Sumitomo Dainippo Pharma</td>
<td>481.0</td>
<td>-</td>
</tr>
<tr>
<td>Incruse Ellipta</td>
<td>GSK</td>
<td>470.2</td>
<td>54.9</td>
</tr>
<tr>
<td>Pulmicort (Budesonide)</td>
<td>AstraZeneca</td>
<td>287.6</td>
<td>81.9</td>
</tr>
<tr>
<td>Ultibro Breezhaler</td>
<td>Novartis</td>
<td>-</td>
<td>262.2</td>
</tr>
<tr>
<td>Atrovent</td>
<td>Boehringer Ingelheim</td>
<td>256.3</td>
<td>46.4</td>
</tr>
<tr>
<td>Asmanex</td>
<td>Merck</td>
<td>240.7</td>
<td>5.2</td>
</tr>
<tr>
<td>Formoterol (generics)</td>
<td>Mylan</td>
<td>209.3</td>
<td>162.5</td>
</tr>
<tr>
<td>Stiolto Respimat</td>
<td>Boehringer Ingelheim</td>
<td>183.2</td>
<td>131.9</td>
</tr>
<tr>
<td>Tobi</td>
<td>Novartis</td>
<td>110.1</td>
<td>45.9</td>
</tr>
<tr>
<td>Eklira Genuair</td>
<td>AstraZeneca</td>
<td>107.3</td>
<td>44.7</td>
</tr>
<tr>
<td>Serevent</td>
<td>GSK</td>
<td>105.1</td>
<td>41.5</td>
</tr>
<tr>
<td>Flutiform</td>
<td>Mundipharma</td>
<td>-</td>
<td>113.4</td>
</tr>
</tbody>
</table>
CURRENT MARKET TRENDS

• Effective drug delivery-critical opportunity area
  • Focus on DPI’s, novel inhalation technologies, and improved MDI’s

• Generic market restructuring
  • Focus on higher margins and innovative products
VARIOUS RESPIRATORY DISEASES

- Multiple sclerosis
- Lung cancer
- Cystic fibrosis
- Asthma
- Idiopathic pulmonary fibrosis
- Non-cystic fibrosis bronchiectasis
- Respiratory syncytial virus
- Influenza
- Bronchitis
- Tuberculosis
- Acute respiratory distress syndrome (ARDS)
- COPD
PRODUCTS FOR RESPIRATORY DISEASES OTHER THAN ASTHMA AND COPD

2006
GSK Zanamivir® (Relenza®) – a flu vaccine approved in 2006

2013
Novartis Tobi PodHaler® approved March 2013 for the treatment of pseudomonas aeruginosa infection in CF Patients

2014
FDA orphan drug approval for idiopathic pulmonary fibrosis in Oct 2014 for nintedanib and pirfenidone

2015
Rapamycin — also known as sirolimus — was approved by the Food and Drug Administration in May 2015 to treat lymphangioleiomyomatosis (LAM), a potentially fatal disease characterized by abnormal proliferation of smooth muscle cells in the lungs
COMPARISON OF ROUTES

Parenteral
- IV
- IM, SC

Passive
- Transdermal
- Skin, Muscle, Mucosa

Iontophoresis

Oral
- Dosage Form
- Gut Lumen
- Gut Wall
- Liver

Degradation or metabolism; poor solubility

Inhalation
- Lungs/alveoli

Systemic Circulation

Effect Site

Elimination

Response
ADVANTAGES OF INHALATION

Systemic Rx
• avoids injections and p.o. absorption (proteins and peptides, hydrophobic small molecules)

Pulmonary Disease Rx
• allergy/inflammation, anaphylaxis (most lung diseases arise from inhaled agents), parenchymal disease (silicosis, asbestosis)

Vaccination
• mucosal and systemic (inhaled>>s.c.)

Safety
• wide therapeutic window, 10-20% of systemic dose for equivalent therapy of lung disease

Low cost
• Rx of asthma and COPD
SOME THERAPEUTIC AREAS EVALUATED FOR TREATMENT BY THE PULMONARY ROUTE

- Human growth hormone
- Diabetes
- Agitation
- Migraine
- Analgesia
- Parkinson's
- Anxiety
- Smoking Cessation
- Insomnia
- Seizures
- Antibiotics
- Measles
- Post-menopausal osteoporosis
- Pituitary dwarfism
APPROVALS FOR SYSTEMIC THERAPEUTICS ADMINISTERED
BY THE PULMONARY ROUTE

2006
Exubera (dry powder inhaled insulin) approved by FDA and EMA in January 2006

2011
Adasuve (staccato loxapine) approved by FDA in December 2012

2014
Afrezza (dry powder inhaled insulin) approved by FDA in June 2014
URT – GATEKEEPER OF THE LRT

Aerodynamic filtration
~ 30 L/min

Upper Respiratory Tract (URT)

Lower Respiratory Tract (LRT)

>10µm

5-10µm

0.5-3µm
DEEP LUNG AEROSOL DELIVERY – KEY ASPECTS

Formulation
The key to aerosol delivery
• MMAD (GSD)*
• Low adhesive forces

Device
Low dispersive energy, if drug well formulated

Physiological factors
• Vi (Inhaled Volume), Vt (Tidal Volume), RV (Residual Volume)+, f/breath-hold

Disease states
• Obstructive / non-obstructive

* MMAD = Mass Median Aerodynamic Diameter
* GSD = Geometric Standard Deviation
AIRWAY PENETRANCE AND PARTICLE SIZE

Deposition (%)

Particle size (µm)

< 10µm
< 6µm
< 3µm
~ 1µm

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ENGINEERED RESPIRABLE PARTICLES

Micronized dry powder

Engineered dry powder

Porous particles

Pulmosol©

Pulmosphere©

Acknowledgements: John Patton, Ph.D.-Founder & Former CSO at Inhale Therapeutics Systems; Michael Newhouse, M.D.-Former Director, Medical Affairs at Inhale Therapeutics Systems; Micael Eldon, Ph.D.-Former Director & Research Fellow at Inhale Therapeutics Systems
ENGINEERED RESPIRABLE PARTICLES

Acknowledgements: John Patton, Ph.D.-Founder & Former CSO at Inhale Therapeutics Systems; Michael Newhouse, M.D.-Former Director, Medical Affairs at Inhale Therapeutics Systems; Micael Eldon, Ph.D.-Former Director & Research Fellow at Inhale Therapeutics Systems
LUNG DEPOSITION FOR ENGINEERED DRY POWDER AND NEBULIZED TOBRAMYCIN

Lung deposition for TIP and TIS in healthy volunteers as determined by Gamma Scintigraphy

<table>
<thead>
<tr>
<th></th>
<th>TIP (T-326 Inhaler)(^{(20)})</th>
<th>TIS (PARI-LC(^{®}) Plus)(^{(32)})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nominal dose of tobramycin</td>
<td>80 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>Deposition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>34.2% (27 mg)</td>
<td>9.2% (27 mg)</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>43.6% (35 mg)</td>
<td>16.0% (48 mg)</td>
</tr>
<tr>
<td>Device</td>
<td>21.7% (17 mg)</td>
<td>43.5% (131 mg)</td>
</tr>
<tr>
<td>Exhaled</td>
<td>0.2% (0 mg)</td>
<td>28.3% (85 mg)</td>
</tr>
<tr>
<td>Total lung deposition</td>
<td>27.4 mg</td>
<td>27.3 mg</td>
</tr>
<tr>
<td>Intersubject variability</td>
<td>17%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Reference: Journal of Aerosol Medicine and Pulmonary Drug Delivery 24 (4) 2011 (pp 175-182)
DEPOSITION AS A FUNCTION OF AEROSOL CHARACTERISTICS

Acknowledgements: John Patton, Ph.D.-Founder & Former CSO at Inhale Therapeutics Systems; Michael Newhouse, M.D.-Former Director, Medical Affairs at Inhale Therapeutics Systems; Micael Eldon, Ph.D.-Former Director & Research Fellow at Inhale Therapeutics Systems
AIRWAY EPITHELIUM

Human bronchi
3-5mm diameter

Human terminal bronchioles
0.5-1mm diameter

Human alveoli
250µm diameter

Ciliated cell

Goblet cell

Basal cell

Basement membrane

Brush cell

Type I cell

2µm aerosol particle

0.07µm fluid

0.1-0.2µm

8µm

58µm

Air-blood Interface

SEM courtesy Dr. E. Weibel

Nature Reviews | Drug Discovery

Acknowledgements: John Patton, Ph.D.-Founder & Former CSO at Inhale Therapeutics Systems; Michael Newhouse, M.D.-Former Director, Medical Affairs at Inhale Therapeutics Systems; Micael Eldon, Ph.D.-Former Director & Research Fellow at Inhale Therapeutics Systems
Schematic of the PulmoSphere™ manufacturing process. An emulsion-based feedstock is prepared by high-pressure homogenization. The emulsion consists of oil droplets (Perflubron) dispersed in a continuous water phase. The oil droplets are stabilized by a monolayer of a phospholipid (distearoylphosphatidylcholine). The tobramycin drug substance and calcium chloride excipient are dissolved in the continuous phase of the emulsion. The feedstock is atomized with a twin fluid nozzle into a spray dryer. As the atomized droplets containing dispersed emulsion droplets are dried, the slow diffusing emulsion droplets are concentrated at the droplet interface. As the drying continues, a shell is formed at the surface of the atomized droplet. Eventually, the Perflubron evaporates leaving behind pores in the particle shell. The resulting dry powder comprising porous particles is collected from the airstream with a cyclone separator.

Reference: Journal of Aerosol Medicine and Pulmonary Drug Delivery 24 (4) 2011 (pp 175-182)
EVOLUTION OF DRY POWDER INHALATION

Exubera®
- Mouthpiece
- Clear chamber
- Insulin release unit
- Base
- Insulin blister
- Air pump

Afrezza®
- Removable purple mouthpiece cover
- White mouthpiece
- Cartridge
- Top of inhaler
- White cartridge cup
- Bottom of inhaler
- Purple base
PORTABLE BREATH-ACTUATED T-326 INHALER

The portable breath-actuated T-326 Inhaler.
A hypromellose capsule is loaded into the device by first removing the mouthpiece and inserting the capsule into the chamber. The mouthpiece is screwed back onto the body. The button is depressed to pierce the capsule, and the patient then inhales through the mouthpiece. The capsule rotates rapidly in the chamber causing powder to be emptied from the capsule.

Reference: Journal of Aerosol Medicine and Pulmonary Drug Delivery 24 (4) 2011 (pp 175-182)
HYDROPHOBIC SMALL MOLECULES DELIVERED DIRECTLY TO CNS STACCATO LOXAPINE (ADASUVE)

- Alexza's Technology Foundation
- The heart of the hand-held Staccato® system is a heat package with a stainless steel substrate, onto which a thin film of unformulated drug is coated. When the patient draws a normal breath through the Staccato system, the substrate surface instantaneously heats to create a condensation aerosol.
505(b)(2) APPLICATIONS

Dosage Form (Route of Administration)
• Change of dosage form (e.g. solid oral to inhaled)

Strength
• Change to a higher or lower strength (frequency of administration)

Substitution or Modification of Active Ingredient
• Change in the active ingredient of a previously approved combination product, or change in the salt form, ester, chelate, complex, racemate or enantiomer of an active ingredient in a listed drug containing the same active moiety
# 505(b)(2) APPLICATIONS

## Definition of a 505(b)(2) application

A 505(b)(2) application is one described under section 505(b)(2) of the act as an application for which one or more of the investigations relied upon by the applicant for approval "were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted" (21 U.S.C. 355(b)(2)). This provision expressly permits FDA to rely for approval of an NDA, on data not developed by the applicant such as published literature or the agency’s finding of safety and effectiveness of a previously approved drug.

## What type of patent and/or exclusivity protection is a 505(b)(2) application eligible for?

- A 505(b)(2) application may itself be granted 3 years of Hatch-Waxman exclusivity if one or more of the clinical investigations, other than BA/BE studies, was essential to approval of the application and was conducted or sponsored by the applicant (21 CFR 314.50(j); 314.108(b)(4) and (5)).

- A 505(b)(2) application may also be granted 5 years of exclusivity if it is for a new chemical entity (e.g. a pro-drug or a modified active substance previously approved) (21 CFR 314.50(j); 314.108(b)(2)).

- A 505(b)(2) application may also be eligible for orphan drug exclusivity (21 CFR 314.20-316.36) or pediatric exclusivity (section 505A of the Act).
IMPORTANT STEPS IN PLANNING

Pre-IND meeting request and briefing package to Regulatory Agency (Preparation Time for Type B Pre-IND Meeting = 6 Months)

• Outline of existing information (combination of literature references and previously approved NDA filings)

• Nonclinical and clinical bridging studies to define Phase III clinical dosing (Focus on safety)

• API is safe for delivery to the lungs (Separate Phase I or combined with Phase III Protocol)

• Clinical Efficacy end point is achievable (Phase III)

• Determination of clinical endpoints for the label claim (Patient recruitment including exclusion criteria)

• Definition of inhaled dose and delivery device for Phase III
INHALATION AND NASAL

Development services for all inhaled dosage forms
- Metered dose inhalers (MDIs)
- Dry powder inhalers (DPIs)
- Solutions and suspensions for nebulization
- Nasal sprays (liquid and powder)

Support for New Chemical Entity (NCE), 505(b)(2) and generic pathways (ANDA)
INHALATION AND NASAL DELIVERY SYSTEMS

**Meter dose inhalers (MDIs)**
- Propellant driven delivery of drug to lungs
- Made up of can, valve, propellant, drug(s), and actuator
- Capable of delivering µg to 5mg of drug per actuation
- Contains up to 200 actuations

**Dry powder inhalers (DPIs)**
- Breath driven delivery of drugs to lungs
- Made up of drug with or without carrier, mouthpiece, and with capsule or reservoir based system
- 10-50mg payload of Inhaled Dry Powder

**Nebulizers**
- Mist generated from a drug in liquid that is inhaled to the lungs
- Made up of nebul solution, medicine cup, mouthpiece, mask, and compressor

**Nasal sprays**
- Spray delivered via pump action to the nasal cavity
- Made up of bottle, aqueous formulation, pump, and dip tube
## INHALATION AND NASAL TESTING

<table>
<thead>
<tr>
<th>Test</th>
<th>MDI</th>
<th>DPI</th>
<th>Nebulizer</th>
<th>Nasal</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPLC Assay, ID, impurities &amp; degradation products</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Aerodynamic particle size (Next Generation, Fast Screening, and Andersen Cascade Impactor)</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
</tr>
<tr>
<td>Emitted dose at constant flow</td>
<td>●</td>
<td>●</td>
<td></td>
<td>●</td>
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<tr>
<td>Emitted dose with breath simulation</td>
<td>●</td>
<td>●</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dose content uniformity through life, if multi-dose</td>
<td>●</td>
<td>●</td>
<td></td>
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<tr>
<td>Water Content by Karl-Fischer (coulometric and volumetric)</td>
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<td>●</td>
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<tr>
<td>Foreign particulate matter / microscopic evaluation</td>
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<td></td>
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<tr>
<td>Excipient assays (ethanol content)</td>
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<tr>
<td>Weight loss or leakage rate</td>
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<td></td>
<td></td>
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<td>Spray pattern / plume geometry (outsourced)</td>
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<td>pH, osmolality, viscosity</td>
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<td></td>
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<td>●</td>
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<tr>
<td>Microbial limits (outsourced)</td>
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<td>●</td>
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</tbody>
</table>
INHALATION AND NASAL SPECIALIZED EQUIPMENT

- Cascade impactors for aerodynamic particle size
- Laser diffraction instrument for volumetric particle size distribution
- Breathing simulator (artificial lung)
- Jet mill, spray dryer, and high speed homogenizers
- Blenders
- Temperature / humidity control chambers
THANK YOU