DEVELOPMENT OF DRUG DEVICE COMBINATION PRODUCTS
I. INHALED THERAPEUTIC PRODUCTS IN THE US MARKET
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INTRODUCTION

The benefits of inhaled therapy for the treatment of lung and systemic diseases have been recognized for many years. In comparison with oral or parenteral formulations, therapeutic doses of drug can be delivered locally into the airways to cause local effects within the lung or systemic effects throughout the body. In many cases, systemic effects can are minimized along with rapid onset and duration of action. Today, inhaled drugs such as bronchodilators and corticosteroids are gold standards for the treatment of diseases such as Asthma and Chronic Obstructive Pulmonary Disease (COPD). Systemic therapy of Cystic Fibrosis, Diabetes, Pulmonary Arterial Hypertension (PAH), Influenza and Schizophrenia are now available via aerosol delivery. Several new frontiers for treatment of diseases such as Idiopathic Pulmonary Fibrosis, Diabetes, Ventilator Associated Pneumonia, Migraine and Multi Drug-Resistant Tuberculosis are currently under research.

Inhaled therapy is delivered to the patients using devices to generate the aerosol of appropriate particle size. Several devices called Nebulizers deliver medication as a solution or suspension. Such devices are sold separately from the drug. The medication sold in the form of a nebule or respule. From a regulatory perspective the drug is approved separately from the nebulizer and the physician has the option of choosing the nebulizer of their choice to prescribe to the patient. There are several types of inhalation therapeutic devices that deliver medication as a Drug/Device Combination Product. These include the Pressurized Metered Dose Inhalers (pMDI's), Dry Powder Inhalers (DPI's) and Solution/Suspension delivering devices that are integrated with the drug. Table 1 lists some characteristics of an Ideal Inhaler.

Table 1: Ideal Characteristics of Inhalers[1]

Dose reliability and reproducibility
High lung-deposition efficiency
Mass Median Aerodynamic Diameter <5 microns
Simple to use and handle
Short treatment time
Portable
Multiple-dose capability
Durable
Cost-effective
Minimal/No drug released to ambient-air
No bacterial contamination through the use life of product
Patient and Health care professional friendly

In the United States, inhaled therapeutics are classified as Combination Products from a regulatory perspective. Combination products are generally complex in nature. This review details the different inhaled products that are currently in the market as well as outlines the different considerations in the development of these combination products.

PRODUCT TYPES

Pressurized Metered Dose Inhalers:

A metered-dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs, in the form of a short burst of aerosolized medicine. Pressurized MDI products contain therapeutically active ingredients dissolved or suspended in a propellant, a mixture of propellants, or a mixture of solvents, propellants, and/or other excipients in compact pressurized aerosol dispensers[2]. The formulation of a pMDI usually contains the drug dissolved or suspended in a solvent and a propellant. The device component of a pMDI consists of a canister, a metering valve and the actuator. A dose counter may or may not be built into the actuator or may be placed separately on the device. One device (Aerospan™

HFA, Meda Pharmaceuticals) incorporates a small chamber in the actuator. A pMDI product may discharge up to several hundred metered doses of one or more drug substances. Depending on the product, each actuation may contain from a few micrograms (mcg) up to milligrams (mg) of the active ingredients delivered in a volume typically between 25 and 100 microliters[2].

Pressurized MDI's have been the dominant means of delivery of drug to the lungs for the last 30 years, and world-wide[2], they still constitute a majority of the global market. Table 2 shows the advantages and disadvantages of pMDI's. In terms of effectiveness and usability pMDI's exhibit several disadvantages over other similar aerosol products. The most prescribed pMDIs are inefficient and are not user friendly. Results for MDIs showed that between 8–16% of the metered dose was deposited in the lungs[3]. Pressurized MDIs require good co-ordination between dose activation and inhalation in order to ensure correct inhalation and deposition of the drug. Poor coordination is frequent and associated with poor disease control[4]. Pressurized MDI's also require an optimal inspiratory flow, a full inspiration from functional residual capacity and breath hold of at least 6 seconds[5]. Therefore, correct use of these inhalers requires intensive training by the physician and regular technique re-testing may also be necessary[6]. Some suspension-based p-MDI's require shaking before use in order to thoroughly mix drug and propellant. Patients often forget this which may make drug delivery unreliable. It is reported that many as 90% of patients cannot use their MDI correctly[7]. Common mistakes include failure to continuously inhale slowly after activation of the inhaler, failure to exhale fully before the inhalation[7,8], activation the inhaler before inhalation or at the end of inhalation and concluding inhaler activation while holding breath[8,9]. Deposition rates with MDIs depend on inhalation technique[10]. MDIs can be used with a valved-holding chamber device to improve drug deposition in the lungs, but this device is very bulky. However, use of an MDI without a valved-holding chamber device results in high deposition of the therapeutic agent in the mouth and pharynx[11]. It is worth noting that there are significant differences in dose output from different combinations of MDIs and spacers[12].Finally, while most new pMDI's include a dose counter, several older formulations still do not have a dose counter making it difficult for the patient to determine when their canister is empty.

Table 2: Advantages and Disadvantages of pMDIs[13]

Advantages	Disadvantages
• Compact, Portable, Robust, Convenient, Unobtrusive, Multidose • Shorter treatment times compared to traditional Nebulizers • Good Delivered Dose Content Uniformity • Aerosol is independent of patient's inhalation • Inexpensive to manufacture in bulk • Pressurized contents prevent ingress of microbes	• Many patients cannot use correctly and may receive low and/or variable lung dose • Not Breath Actuated • Lung deposition could be lower compared to DPI's • Difficult to deliver larger doses • Need Priming and in some cases shaking prior to actuation • Many pMDI's do not have a dose counter • Several pMDI's have to be used with valved-holding chambers to remove larger particles

Table 3 shows the pMDI products currently available in the US market. With the removal of the older generation chlorofluorocarbon (CFC) based products over the past decade; the use of pMDI's has reduced in the United States. Dry Powder Inhalers and other newer dosage forms have emerged as the dosage forms of choice for development by the pharmaceutical companies.

Table 3: Pressurized Metered Dose Inhalers (pMDI's) in the United States Marketplace

Product Name	Disease State	Drug	Device	Manufacturer	Dose [mcg/puff]	Number of Actuations	Inactive Ingredients
Advair® HFA	Asthma	Fluticasone Propionate and Salmeterol Xinafoate	Aerosol Canister with or without Dose Counter	GlaxoSmithKline	45/21, 115/21, 230/21	120	HFA 134a Only
Aerospan® HFA	Asthma	Flunisolide		Meda	80	60,120	Ethanol + HFA 134a
Alvesco®	Asthma	Ciclesonide		Sunovion Pharmaceuticals	80, 160	60	Ethanol + HFA 134a
Asmanex® HFA	Asthma	Mometasone furoate		Merck	110, 220	120	HFA-227, Ethanol and Oleic acid
Atrovent® HFA	Asthma	Ipratropium Bromide		Boehringer Ingelheim	17	200	Sterile Water + Dehydrated Alcohol + Anhydrous Citric Acid + HFA 134a
Bevespi® Aerosphere	COPD	Glycopyrrolate and Fomoterol Fumarate		Pearl Therapeutics	9/4.8	120	HFA134a, porous particles (comprised fo DSPC and calcium choride)
Dulera®	Asthma	Mometasone furoate and fomoterol fumarate		Merck	5/100, 5/200	60 and 120	HFA-227, Anhydrous Alcohol, Oleic Acid
Flovent® HFA	Asthma	Fluticasone Propionate		GlaxoSmithKline	44, 100, 220	120	HFA 134a Only
ProAir® HFA	Asthma	Albuterol Sulfate		Teva	108	200	Ethanol (11.5% w/w) + HFA 134a
Proventil® HFA	Asthma	Albuterol Sulfate		Merck	108	200	Ethanol (15% w/w) + Oleic Acid (About 0.1% w/w) + HFA 134a
Qvar® 40, Qvar® 80	Asthma	Beclomethasone Dipropionate		Teva	40, 80	100	Ethanol + HFA 134a
Symbicort®	Asthma	Budesonide and Formoterol Fumarate		AstraZeneca	80/4.5, 160/4.5	60	PEG 1000 + PVP K25 + HFA 227ea
Ventolin® HFA	Asthma	Albuterol Sulfate		GlaxoSmithKline	108	200	HFA 134a Only
Xopenex HFA®	Asthma	Levalbuterol Tartrate		Sunovion Pharmaceuticals	45	200	Ethanol + Oleic Acid + HFA 134a

Dry Powder Inhalers:
A Dry Powder Inhaler (DPI) is a device that delivers medication to the lungs in the form of a dry powder. Most DPI formulations consist of micronized drug blended with larger carrier particles, which enhance flow, reduce aggregation, and aid in dispersion. A combination of intrinsic physicochemical properties, particle size, shape, surface area, and morphology affects the forces of interaction and aerodynamic properties, which in turn determine fluidization, dispersion, delivery to the lungs, and deposition in the peripheral airways. When a DPI is actuated, the formulation is fluidized and enters the patient's airways. Under the influence of inspiratory airflow, the drug particles separate from the carrier particles and are carried deep into the lungs, while the larger carrier particles impact on the oropharyngeal surfaces and are cleared. If the cohesive forces acting on the powder are too strong, the shear of the airflow may not be sufficient to separate the drug from the carrier particles, which results in low deposition efficiency. . The critical factors driving the therapeutic effectiveness of a respiratory drug through a Dry Powder Inhaler (DPI) is the generation of an inhalation flow rate sufficient to trigger the dose and disaggregate the drug, thus producing a particulate of optimal size able to reach the therapeutic target within the lung.

Dry Powder Inhalers can be easy to use and portable. Such an inhaler can be manufactured easily and can be relatively low in terms of cost. DPIs, as a class of delivery device, have numerous advantages over pMDIs. They are breath activated, precluding the need for the patient to co-ordinate actuation with inhalation. This assists the effective drug delivery to the lungs. As a general rule, DPI's offer a higher lung deposition than pMDI's. Additionally, patients often express a preference for DPIs. For example, in elderly patients breath-activated inhalers are used correctly and are preferred by patients over pMDIs[14]. DPIs do have some limitations of design, cost effectiveness and user-friendliness. Table 4 shows the advantages and disadvantages of DPIs and Table 6 shows the DPI products currently available in the US market.

Table 4: Advantages and Disadvantages of DPIs[13]

Advantages	Disadvantages
• Quick and convenient to use • Usually compact and portable • Little or no patient coordination of breathing required • No propellants needed • Could deliver relatively higher doses than pMDI's • Formulations can be relatively stable in a "dry" form	• Aerosol formation and deposition may depend on inspiratory effort • Unit dose DPS's could be perceived as inconvenient • Powders may be moisture sensitive providing inconsistent therapy • There are many different types of DPI's. If patients are taking different types, there could be confusion in instructions • Development and manufacture is usually more complex and expensive

There are several DPIs currently on the market or being developed by the pharmaceutical industry. These devices are divided into single-unit dose devices, multi-dose reservoir device and multi-unit dose devices. Table 5 shows the different technologies of DPI's. The Neohaler®, Aerolizer® and Podhaler™ are examples of single-unit dose devices. Doses are individually loaded into gelatin capsules or blisters, each of which is loaded into the inhaler immediately before use. With multi-dose reservoir devices the drug is metered from a reservoir of freely flowing powder. Examples of these devices are Flexhaler®, Pressair®, RespiClick® and Twisthaler®. The Ellipta®, Diskhaler® and Diskus® are examples of multi-unit dose devices. They contain a series of capsules or blisters within the devices. As one dose is delivered, the next dose is ready for delivery.

Single-Unit Dose Devices require that a new capsule be inserted into device prior to inhalation. This makes this device cumbersome to use, makes dose-counting difficult and can give rise to higher dose variability. Further, higher temperatures can soften capsules making their perforation difficult. Finally, a high inspiratory flow must be achieved to generate a fine particle fraction[15].

Multi-Dose Devices offer good deposition with sufficient inspiratory flow. Such devices are prone to being affected by higher humidity conditions[16]. These devices also Turbuhalers also require a relatively high inspiratory flow of 60 l/min for optimal drug delivery. This may not be achievable, especially in younger children, elderly patients and other patients with a low peak inspiratory flow rate. The particle size inhaled is very much dependent on the patients' inspiratory flow rate[17]. Finally, these devices require dose priming which may result in patient confusion.

Multi-Unit Dose Devices offer some advantages over the Single-unit and Multi-dose devices. However, in some cases the metered dose is not completely emptied as the patient is not able to inspire fully. The mouthpiece is also not user friendly, and it is costly to produce because of the level of complexity. Finally, these devices also require a high inspiratory flow in order to achieve proper dosing which may not be feasible for certain populations of patients or certain disease states.

Table 5: Dry Powder Inhaler Technologies

DPI Technology	Drug (Product)	Company	How it works
Single-Unit Dose			
Neohaler®	Indacaterol (Arcapta™) Glycopyrrolate (Seebri™) Glycopyrrolate /Indacaterol (Utibron®)	Novartis	Plastic device to inhale medication that uses a capsule. A capsule is placed in the device. When the buttons are pressed, the capsule is pierced and medication can be inhaled. These devices are breath activated.
Aerolizer®	Fomoterol (Foradil®)	Merck	
Handihaler®	Tiotropium (Spiriva®)	Boehringer Ingelheim	
Podhaler™	Tobramycin (Tobi®)	Novartis	
Cartridge Device	Insulin (Afrezza®)	Mannkind	Plastic device to inhale medication that uses a cartridge. The cartridges are color coded by dose. The cartridge is inserted into the device, a mouthpiece cover is removed and medication can be inhaled. The device is breath actuated.
Staccato Device	Loxapine (Adasuve®)	Alexza	This device generates aerosol by evaporation and condensation. The device contains a thin film which is heated. The drug evaporates and condenses as an aerosol. The device is breath actuated
Multi-dose Reservoir			
Flexhaler®	Budesonide (Pulmicort)	Astra Zeneca	Plastic device that contains several doses of medication. Each dose is "loaded" by turning the bottom grip on one side and then back. The device is breath actuated.
Pressair™	Aclidinium (Tudorza™)	Astra Zeneca	Plastic device that contains several doses of medication. Each dose is "loaded" by pressing the button. The device is breath actuated.
RespiClick®	Albuterol (ProAir®)	Teva	Plastic device that contains several doses of medication. Each dose is "loaded" by opening the cap. The device is breath actuated.
Twisthaler®	Mometasone (Asmanex®)	Merck	Plastic device that contains several doses of medication. Each dose is "loaded" by lifting the cap. The device is breath actuated.
Multi-Unit dose			
Accuhaler	Salmeterol (Serevent)	GlaxoSmith-Kline	Plastic device with multiple blisters. Each blister is loaded to expose the medication prior to inhalation. These devices are breath actuated.
Diskus®	Fluticasone/ Salmaterol (Advair®) Fluticasone (Flovent®)		
Diskhaler®	Zanamivir (Relenza®)		
Ellipta®	Fluticasone/Umeclidium/Vilanterol (Trelegy) Umeclidium/ Vilanterol (Anoro®) Fluticasone (Arnuity™) Fluticasone/ Vilanterol (Breo®) Umecldinium (Incruse®)		

Table 6: Dry Powder Inhalers (DPI's) in the United States Market

Product Name	Disease State	Drug	Device	Manufacturer	Dose per puff	Number of Doses	Inactive Ingredients
Adasuve®	Schizophrenia	Loxapine	Single-Unit Dose – Thin Film	Alexza	10 mg base	5 units per carton	None
Advair® Diskus®	Asthma	Fluticasone Propionate and Salmeterol Xinafoate	Multi- Dose - Blister	GlaxoSmithKline	100/50, 250/50, 500/50 mcg	60	Lactose (contains milk proteins)
Afrezza®	Diabetes	Recombinant Human Insulin	Single-Unit Dose - Cartridge	Mannkind	4,8,12 units	60,90, 120 cartridges	Fumaryl Diketopiperazine, Polysorbate 80
Anoro® Ellipta®	COPD	Umeclidinium bromide and Vilanterol trifenatate	Multi-Unit Dose - Blister	GlaxoSmithKline	62.5/25 mcg	30	Lactose Monohydrate (contains milk protein), Magnesium Stearate
Arcapta™ Neohaler®	COPD	Indacaterol Maleate	Single-Unit Dose - Capsule	Novartis	75 mcg base	30 Capsules	Lactose Monohydrate (contains trace levels of milk protein)
Arnuity™ Ellipta®	Asthma	Fluticasone Furoate	Multi-Unit Dose - Blister	GlaxoSmithKline	100, 200 mcg	30	Lactose Monohydrate (contains milk protein)
Asmanex® Twisthaler®	Asthma	Mometasone Furoate	Multi-Dose Reservoir - Powder Dose Dispenser	Merck	110, 220 mcg	30	Lactose (contains milk proteins)
					220 mcg	60, 120	
Breo® Ellipta®	Asthma/COPD	Fluticasone Furoate and Vilanterol Trifenatate	Multi-Unit Dose - Blister	GlaxoSmithKline	100/25, 200/25 mcg	30	Lactose Monohydrate (contains milk protein), Magnesium Stearate
Flovent® Diskus®	Asthma	Fluticasone Propionate	Multi-Unit Dose - Blister	GlaxoSmithKline	50, 100, 250 mcg	60	Lactose (contains milk proteins)
Foradil® Aerolizer®	Asthma	Formoterol Fumarate	Single Unit Dose - Capsule	Merck	12 mcg	60 capsules	Lactose (contains milk proteins)
Incruse® Ellipta®	COPD	Umeclidinium bromide	Multi-Unit Dose - Blister	GlaxoSmithKline	62.5 mcg	30	Lactose Monohydrate (contains milk protein), Magnesium Stearate
Proair® RespiClick®	Asthma	Albuterol Sulfate	Multi-Dose Reservoir - Powder Dose Dispenser	Teva	90 mcg	200	Lactose (may contain milk proteins)
Pulmicort Flexhaler®	Asthma	Budesonide	Multi-Dose Reservoir - Powder Dose Dispenser	AstraZeneca	90, 180 mcg	60, 120	Lactose (contains milk proteins)
Relenza® Diskhaler®	Influenza	Zanamivir	Multi-Unit Dose - Blister	GlaxoSmithKline	5 mg/dose	20	Lactose (contains milk proteins)
Seebri™ Neohaler®	COPD	Glycopyrrolate	Single-Unit Dose - Capsule	Novartis	15.6 mcg	60 Capsules	Lactose Monohydrate (contains milk protein), Magnesium Stearate

Product Name	Disease State	Drug	Device	Manufacturer	Dose per puff	Number of Doses	Inactive Ingredients
Serevent Accuhaler	Asthma	Salmeterol Xinafoate	Multi-Unit Dose - Blister	GlaxoSmithKline	50 mcg	60	Lactose (contains milk proteins)
Spiriva® Handihaler®	Asthma	Tiotropium Bromide	Single-Unit Dose - Capsule	Boehringer Ingelheim Pharmaceuticals	18 mcg	30	Lactose (contains milk proteins)
Trelegy Ellipta®	COPD	Fluticasone Furoate, Umeclidinium and Vilanterol Trifenatate	Multi-Unit Dose - Blister	GlaxoSmithKline	Strip 1:100 mcg Fluticasone Furoate; Strip 2: 62.5 mcg Umeclidinium /25 mcg Vilanterol Trifenatate	30 blisters	Strip 1: Fluticasone furoate- Lactose monohydrate (12.3 mg) Strip 2: Umeclidinium bromide/vilanterol trifenatate - magnesium stearate (75 mcg), and lactose monohydrate (12.3 mg)
Tobi® Podhaler™	Cystic Fibrosis	Tobramycin	Single-Unit Dose - Capsule	Novartis	28 mg	56 capsules	1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), Calcium Chloride, and Sulfuric Acid (for pH adjustment)
Tudorza™ Pressair™	COPD	Aclidinium Bromide	Multi-Dose Reservoir - Powder Dose Dispenser	Astra Zeneca	400 mcg	30 and 60	Lactose Monohydrate
Utibron® Neohaler®	COPD	Glycopyrrolate and Indacaterol maleate	Single-Unit Dose - Capsule	Novartis	15.6/27.5 mcg	60 Capsules	Lactose Monohydrate (contains milk protein), Magnesium Stearate

Solution/Suspension Combination Products:

Soft-Mist Inhalers

Soft-Mist Inhalers (SMIs) use liquid formulations similar to those in nebulizers, but are generally multi-dose devices that have the potential to compete with pMDIs and DPIs. SMI's contains sufficient doses of a formulation for one-month's dosing, stored in a fluid reservoir[18]. Currently there is one device in the market called the Respimat. The Respimat Soft Mist Inhaler is powered by the energy of a compressed spring inside the inhaler; no propellants are required. Individual doses are delivered via a nozzle system as a slow-moving aerosol cloud (hence the term ''soft mist''). The velocity of the spray from and SMI is similar to a pMDI[19], however, scintigraphy studies have shown that lung deposition can be significantly higher than that of a pMDI[20]. SMIs are a ''press and breathe'' device, and the correct inhalation technique closely resembles that used with a pMDI. While coordination between firing and inhaling is required, the low spray velocity and long duration of the aerosol cloud (typically 1–1.5 s) enables patients to coordinate firing and inhaling more easily than with a pMDI[21]. Table 7 shows the advantages and disadvantages of SMIs.

Table 7: Advantages and Disadvantages of SMIs[22]

Advantages	Disadvantages
• Compact and Portable • Multi-dose Device • Convenient • Do not contain propellants • Lower particle sizes • Lower spray velocity compared to pMDIs • Relatively higher lung deposition • Easier to use than pMDIs. • Valved-holding chamber not required	• Not breath-actuated • Complicated method for preparation of first dose • Additional actuation required if device is not used for a long period of time • Require preservatives like benzalkonium chloride. Long term effects of inhaled preservatives are not known

Nebulizers combined with Drugs

Other than the traditional delivery systems discussed above, there are some drugs that are approved with specific nebulizers. One such product, Ventavis®, is approved for the delivery of inhaled iloprost using the i-neb™ Adaptive Aerosol Delivery (AAD®) System. The device is a vibrating mesh device and is breath actuated. Software in the i-neb AAD System analyzes the patient's breathing pattern and pulses aerosol only during inspiration, thereby avoiding aerosol waste during expiration. The device can also log information. Studies have shown a significantly high lung deposition with this device. Table 8 shows the advantages and disadvantages of the i-neb system.

Table 8: Advantages and Disadvantages of i-Neb[23]

Advantages	Disadvantages
• Slow and deep breathing possible for optimal lung deposition • Breath actuation prevents drug exposure to caregivers • Allows patient feedback thru visual and tactile signals • Patient compliance thru logging system • Small amount of drug wastage due to low residual volumes	• Bulky system • Not easy to use • Vibrating-mesh devices tend to clog • Cannot be used for children < 2 years of age or with mechanically ventilated patients • Several drugs cannot be mixed together

Table 9 shows the Solution/Suspension Combination Products that are available in the US market.

Table 9: Solution/Suspension Combination Products in the United States Marketplace

Product Name	Disease State	Drug	Device	Manufacturer	Dose per puff	Number of Doses	Inactive Ingredients
Soft Mist Inhalers							
Combivent® Respimat®	COPD	Albuterol Sulfate and Ipratropium Bromide	Respimat with cartridge	Boehringer Ingelheim	120/20 mcg	120 actuations	Water, Benzalkonium Chloride, Disodium Edetate, Hydrochloric Acid
Spiriva® Respimat®	Asthma, COPD	Tiotropium Bromide	Respimat with cartridge	Boehringer Ingelheim	12.5 and 25 mcg	60 actuations	Water, Benzalkonium Chloride, Disodium Edetate, Hydrochloric Acid
Striverdi® Respimat®	COPD	Olodaterol hydrochloride	Respimat with cartridge	Boehringer Ingelheim	2.5 mcg base	60 actuations	Water, Benzalkonium Chloride, Disodium Edetate, Anhydrous Citric Acid
Stiolto® Respimat®	COPD	Olodaterol hydrochloride and Tiotropium Bromide	Respimat with cartridge	Boehringer Ingelheim	2.5 mcg base/2.5 mcg base	60 actuations	Water, Benzalkonium Chloride, Disodium Edetate, Hydrochloric Acid
Nebulizers combined with Drugs							
Cayston®	Cystic Fibrosis	Aztreonam	Altera Nebulizer	Gilead Sciences, Inc.	75 mg/Vial	84	Lyophilized product with Lysine. Sodium Chloride (diluent)
Nebupent®	Pneumocystis jiroveci pneumonia (PJP)	Pentamidine Isethionate	Respigard II Nebulizer	Fresenius Kabi	300 mg/vial	1	Lyophilized product to be diluted with 6 mL of Sterile Water for injection
Tyvaso®	Pulmonary Arterial Hypertension (PAH)	Treprostinil	Customized Nebulizer	GlaxoSmithkline	0.6 mg/mL; 2.9 mL ampoule	28 ampules	Sodium Chloride, Sodium Citrate, Sodium Hydroxide, Hydrochloric Acid, and Water for injection.
Ventavis®	Pulmonary Arterial Hypertension (PAH)	Iloprost	i-neb AAD System	Actelion	10/20 mcg/mL; 1 mL ampule	30 ampules	Tromethamine, Ethanol, Sodium Chloride, Hydrochloric Acid for pH adjustment, and Water for Injection

Nebulized Products:

Nebulizers convert a liquid into a aerosol for medical purposes. These products are still widely in use for inhaled therapeutics in medical practice in hospitals as well as for individual use. Nebulizers work on several different principles. Those driven by compressed air are termed “jet” nebulizers while those powered by a vibrating piezoelectric crystal are termed “ultrasonic” nebulizers. Jet nebulizers can be constant output, breath enhanced or breath actuated. In a constant output nebulizer, the aerosol is delivered at a constant rate through a venturi effect. In a breath-enhanced nebulizer, the air is added during inhalation that enhances the aerosol output during inhalation. Breath actuated nebulizers operate only during inhalation providing less wastage of medication during exhalation. Ultrasonic nebulizers employ a piezoelectric crystal that vibrates. The droplets are then forced through a mesh creating the aerosol. Table 10 shows the advantages and disadvantages of nebulizers:

Table 10: Advantages and Disadvantages of Nebulized Products

Advantages	Disadvantages
• Jet Nebulizers are usually cheaper alternatives to traditional pMDIs and Dry Powder Inhalers • No propellants needed • Nebulizers and the drugs are sold separately allowing the physicians/patients to mix and match different nebulizers with different drugs • Can be used with solution and suspension formulations • Relatively larger volumes can be nebulized allowing for larger doses to be nebulized. • The devices are generally approved as a 510(k) while the drugs are approved separately using an NDA/ANDA route. • Several generic alternatives are available since formulations and approvals may be less complicated.	• Jet nebulizers are generally bulky and require an external power source making them non-portable • Treatment times are generally significantly longer than pMDIs or Dry Powder Inhalers • Vibrating-mesh devices tend to clog • Vibrating-mesh devices generally provide larger particle sizes • Jet Nebulizers tend to have a significantly higher residual volume left in the nebulizer of wasted drug • Continuous Jet nebulization can be inhaled by caregivers

Table 11 shows the Nebulization Drugs that are available in the US market. These drugs are not associated with any one specific device and as such are not considered “Drug-Device Combination Products”.

SUMMARY

Inhalation is an effective route of drug administration for treating diseases. This route ensures that drugs are delivered directly to their site of action where they exert the required local effect. Inhaled Therapeutics are currently being used for the treatment of many respiratory diseases and are now successfully being used for other non-respiratory diseases. This paper reviews the varied products that are in the market today. Future papers will review the requirements required to develop Drug-Device combination products.

Table 11: Nebulization Drugs in the US Marketplace

Drug	Product Name	Manufacturer	Strength	Concentration [mg/mL]	No. of mL per Vial	Reference Listed Drug (RLD)	Inactive Ingredients
Acetylcysteine	Acetylcysteine	Luitpold Pharmaceuticals Inc	10%	100	30 mL	Yes	Edetate disodium, hihydrate, Sodium Hydroxide and Hydrochloric Acid
	Acetylcysteine	Hospira Inc, Alvogen Inc, Roxane Laboratories, Inc				No	
	Acetylcysteine	Luitpold Pharmaceuticals Inc	20%	200		Yes	Edetate disodium, hihydrate, Sodium Hydroxide and Hydrochloric Acid
	Acetylcysteine	Hospira Inc, Alvogen Inc, Roxane Laboratories, Inc				No	
Albuterol Sulfate	AccuNeb®	Dey Pharma (Mylan)	EQ 0.021% Base	0.63	3	Yes	Sodium Chloride and Sulfuric acid
	Albuterol Sulfate	Nephron Pharmaceuticals Corporation, Watson Laboratories, Inc				No	
	AccuNeb®	Dey Pharma (Mylan)	EQ 0.042% Base	1.25	3	Yes	Sodium Chloride and Sulfuric acid
	Albuterol Sulfate	Nephron Pharmaceuticals Corporation, Watson Laboratories, Inc				No	
	Albuterol Sulfate	Nephron Corp	EQ 0.083% Base	2.5	3	Yes	Sodium Chloride and Sulfuric Acid
	Albuterol Sulfate	The Ritedose Corp				No	
Arformoterol Tartrate	Brovana®	Sunovion Pharmaceuticals	EQ 0.015MG Base/2ML	15	2	Yes	Isotonic Saline Solution, pH-adjusted to 5.0 with Citric Acid and Sodium Citrate
Budesonide	Pulmicort	AstraZeneca Pharmaceuticals LP	0.25MG/2ML	0.25	2	Yes	Disodium Edetate, Sodium Chloride, Sodium Citrate, Citric Acid, Polysorbate 80 and Water for Injection
	Budesonide	Sandoz Inc, Impax Laboratories, Inc, Apotex Ijc, Teva Pharmaceuticals				No	
	Pulmicort	AstraZeneca Pharmaceuticals LP	0.5MG/2ML	0.5	2	Yes	Disodium Edetate, Sodium Chloride, Sodium Citrate, Citric Acid, Polysorbate 80 and Water for Injection
	Budesonide	Sandoz Inc, Impax Laboratories Inc, Apotex Inc, Teva Pharmaceuticals				No	
	Pulmicort	AstraZeneca Pharmaceuticals LP	1MG/2ML	1	2	Yes	Disodium Edetate, Sodium Chloride, Sodium Citrate, Citric

Drug	Product Name	Manufacturer	Strength	Concentration [mg/mL]	No. of mL per Vial	Reference Listed Drug (RLD)	Inactive Ingredients
	Budesonide	Teva Pharmaceuticals, Sandoz Inc				No	Acid, Polysorbate 80 and Water for Injection
Cromolyn Sodium	Cromolyn Sodium	Teva Pharmaceuticals USA	10MG/ML	10	1	Yes	Purified Water
	Cromolyn Sodium	Mylan Speciality LP, Wockhardt				No	
Formoterol	Perforomist®	Dey Pharma (Mylan)	0.02MG/2ML	20	2	Yes	Sterile aqueous solution with NaCl, pH-adjusted to 5.0 with Citric Acid and Sodium Citrate
Ipratropium Bromide and Albuterol Sulfate	Ipratropium Bromide and Albuterol Sulfate	Nephrom Pharmaceuticals Corporation, Teva Pharmaceuticals, Watson Pharmaceuticals, Cipla Ltd, The Ritedose Corp	EQ 0.083% Base; 0.017%	(0.5/2.5)	3	No	Isotonic Saline Solution and Hydrochloric Acid
Ipratropium Bromide	Ipratropium Bromide	The Ritedose Corp	0.02%	(0.5/2.5)	2.5	Yes	Sodium Chloride and Hydrochloric Acid
	Ipratropium Bromide	Nephron Corp, Bausch and Lomb Pharmaceuticals Inc, Watson Laboratories Inc, Landela Pharmaceutical, Aurobindo Pharma Ltd.				No	
Levalbuterol	Xopenex® Inhalation Solution	Oak Pharmaceuticals Inc Subsidiary of Akron Inc	EQ 0.0103% Base	0.31	3	Yes	Sodium Chloride and Hydrochloric Acid
	Levalbuterol Hydrochloride	The Ritedose Corp, Teva Pharmaceuticals, Cipla Ltd, Myan Speciality, Impax Laboratories				No	
	Xopenex® Inhalation Solution	Oak Pharmaceuticals Inc Subsidiary of Akron Inc	EQ 0.021% Base	0.63	3	Yes	Sodium Chloride and Hydrochloric Acid
	Levalbuterol Hydrochloride	The Ritedose Corp, Teva Pharmaceuticals, Cipla Ltd, Myan Speciality, Impax Laboratories				No	
	Xopenex® Inhalation Solution	Oak Pharmaceuticals Inc Subsidiary of Akron Inc	EQ 0.042% Base	1.25	3	Yes	Sodium Chloride and Hydrochloric Acid

Drug	Product Name	Manufacturer	Strength	Concentration [mg/mL]	No. of mL per Vial	Reference Listed Drug (RLD)	Inactive Ingredients
	Levalbuterol Hydrochloride	The Ritedose Corp, Teva Pharmaceuticals, Cipla Ltd, Myan Speciality, Impax Laboratories				No	
	Xopenex® Inhalation Solution	Oak Pharmaceuticals Inc Subsidiary of Akron Inc	EQ 0.25% Base	1.25/0.5	0.5	Yes	Sodium Chloride and Hydrochloric Acid
	Levalbuterol Hydrochloride	Teva Pharmaceuticals, Mylan Speciality				No	
Pentetate Zinc (or calcium) Trisodium	Pentetate Zinc (or calcium) Trisodium	Hameln Pharma Plus Gmbh	EQ 1GM Base/ML(EQ 200 MG Base/ML	200	5	Yes	n/a
Ribavirin	Virazole	Valeant Pharmaceuticals international			Lyophilized product to be diluted with sterile water for injection or sterile water for inhalaiton	Yes	
	Ribavirin	Navinta LLC	6GM/Vial	6GM/Vial		No	n/a
Tobramycin	Tobi®	Novartis	300MG/5ML	300	5	Yes	Sodium chloride, WFI, Sulfuric Acid and NaOH
	Tobramycin	Teva Pharmaceuticals USA, Akron Inc, Amneal Pharmaceuticals, Katibis Pak				No	
Tobramycin	Bethkis® (to be used with Pari LC Plus nebulizer)	Chiesi USA Inc	300MG/4ML	300	4	Yes	Sodium Chloride, sulfuric acid, sodium hydroxide

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