Inhaled drug product development: A unique form of product life cycle management

Pursuing inhaled therapies offers opportunities for changing route of administration, expanding indications, adopting fixed-dose combinations and developing different formulation/device combinations

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Introduction

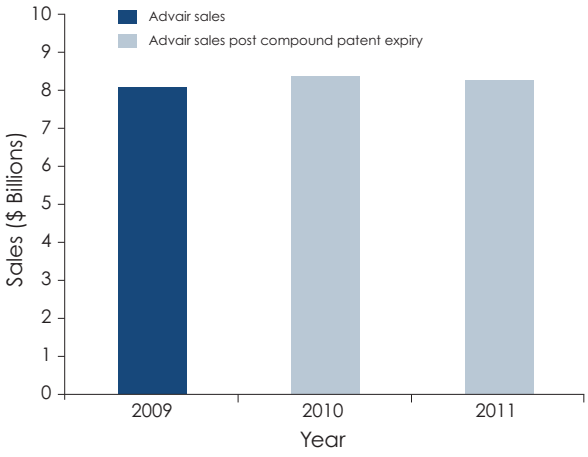
Pulmonary drug delivery offers unique opportunities for extending certain therapeutic categories of drug in what might be perceived as a unique form of product life cycle management (PLM).The lung has special anatomical and physiological features that are unique for local and systemic drug delivery and is the site of functional deficiencies associated with serious diseases such as asthma and chronic obstructive pulmonary disease (COPD). Since the first inhaled corticosteroid (ICS), beclomethasone dipropionate, was introduced in 1972, a significant number of locally- and systemically-acting drug molecules have been reformulated into inhaled drug products resulting in increased efficacy and minimized side effects.[1]

Classical PLM involves modest formulation changes to accommodate the original indication (e.g., controlled release oral dosage forms to follow immediate release drug products) or extension to new indications. It should be evident that pulmonary delivery is unique in that the scope of work required for formulation and delivery for this very specialized application requires a level of commitment similar to that of a new product.

However, the clinical benefits and strong resistance of inhaled products to brand erosion makes pulmonary administration very attractive for PLM. Advair (GlaxoSmithKline), the current market leader in the anti-asthmatic drug market is, from a post hoc perspective, an example of successful PLM. Unlike traditional dosage forms, Advair continues to record stable sales, approximately $8 billion, even after the patent on the compound expired in 2010 (Figure 1).[2] This is mainly attributed to the complexity in developing inhaled drug products which require proper design of a device-formulation interface to achieve bioequivalence.[3,4]

Figure 1

Advair sales prior to and following compound patent expiry. Data were collected from GSK annual reports, 2009-2011.



The following summary of approaches to pulmonary drug delivery as a PLM strategy, while not comprehensive, gives an overview from the perspective of changing route of administration, expanding indications, adopting fixed-dose combinations and developing different formulation/device combinations.

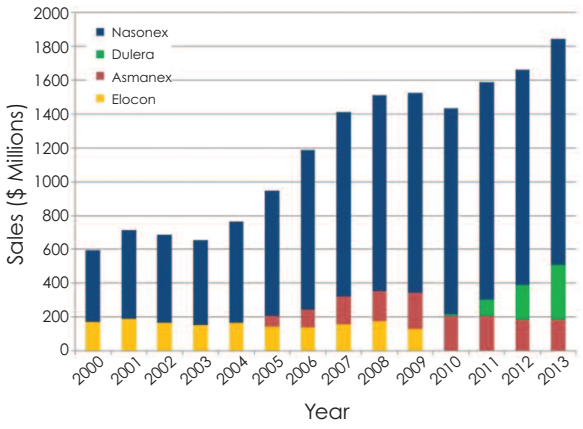
Expanding indications

Expanding clinical indications is one of the most successful PLM development strategies, as it enables pharmaceutical companies to enter new markets. Nasonex (Merck & Co.), a nasal spray for seasonal allergic rhinitis, provides an example. From its origins as a topical ointment, mometasone furoate was reformulated as a nasal spray, becoming the first approved nasal corticosteroid. As shown in

Figure 2, total revenue was significantly increased by the addition of Nasonex to the mometasone furoate product family.

Figure 2

Product value extension through delivery modalities, additional indications and fixed-dose combinations: Mometasone furoate data were obtained from Merck's annual reports. Elocon sales were not reported after 2009.



In addition, mometasone furoate was approved as a dry powder inhaler (DPI) and a metered dose inhaler (MDI) for asthma therapy. These are marketed under the brand names Asmanex (Merck & Co.) and Dulera (Merck & Co.) and introduced in 2005 and 2010, respectively. Dulera is a fixed-dose combination that contains a long-acting bronchodilator and inhaled corticosteroid, while Asmanex is a mono therapy containing mometasone furoate. Sales of Asmanex remained stable after the Dulera launch. Timing is a crucial factor in the successful launch of a next-generation product. Ideally, transition from an initial product to a new product should be smooth, so as not to compete for resources and market attention.

Changing route of administration

Delivery of a molecule through a new route of drug administration offers a number of benefits. From a clinical perspective, it could offer improved safety and efficacy and therefore improve patient compliance. Pulmonary drug delivery has been widely accepted as an alternative route of drug administration. In particular, inhaled therapy is known to be the most effective method to treat airway diseases such as asthma, COPD and cystic fibrosis (CF). In addition, applications for inhaled drug delivery are not limited only to locally-acting drugs, but can be used for systemically-acting molecules such as insulin for diabetes and dihydroergotamine for migraine. Consequently, there has been considerable effort to deliver drug molecules to and through the lungs to improve patient compliance as well as therapeutic efficacy.

Inhaled corticosteroids pioneered PLM as a new route of drug administration. Traditionally, corticosteroids were orally administered for patients with severe or chronic asthma, yet they demonstrated poor asthma control and severe side effects.[5] The concept of delivering topically-acting steroids, namely budesonide and beclomethasone dipropionate, directly to the lung revolutionized asthma therapy and contributed to dramatic reduction of asthma morbidity and mortality.[1,5]

Treatment of cystic fibrosis is another area that has greatly benefited from local drug delivery to the lung. Among the most common genetic disorders in the United States, CF causes viscous secretions due to abnormal transport of chloride and sodium across the epithelium. In its 2014 global report, GBI Research indicated the value of the cystic fibrosis market is expected to increase from $1.2 billion in 2012 to almost $4.5 billion in 2019, across the leading eight developed nations. This equates to a compound annual growth rate of 30.4%.[6]

Currently, there are two leading products, Pulmozyme (Genentech) and TOBI (Novartis Pharmaceuticals), which are both inhaled, and which recorded $600 and $317 million worldwide sales, respectively, in 2012. Pulmozyme is an enzyme that was originally developed to hydrolyze the DNA in sputum of CF patients and reduce the sputum viscoelasticity. TOBI is an antibiotic (tobramycin) that was reformulated from an injectable formulation to treat bacterial infections in the lung, particularly *Pseudomonas aeruginosa*.[7] As there is no cure for CF, the goals of treatment are to ease severity of symptoms and slow advancement of the disease. Antibiotics are the most important aspect of treatment since large numbers of CF patients suffer from respiratory infections. The traditional approach to aminoglycoside dosing with tobramycin involves administering a 1 to 3 mg/kg intravenous injection every eight hours in adults since aminoglycosides are not absorbed through the gastrointestinal tract due to their polar nature.[8] TOBI is the first inhaled antibiotic product that has significantly improved patient compliance by delivering a high dose medication non-invasively using a nebulizer.[7,9] Wertz et al. also reported that total CF treatment cost decreased by 17% after starting inhaled tobramycin therapy.[9]

Given the successful launch of TOBI, treatment of respiratory diseases through the inhaled route is getting attention in the international pharmaceutical market and several additional inhaled antibiotics under development, such as amikacin and ciprofloxacin, both from Bayer/Novartis.[10] There has also been increased interest in novel therapeutic approaches aimed at the CF genetic defect, rather than bacterial infections,[11] which is expected to increase growth of the CF market.

Exubera (Pfizer) inhaled dry powder insulin, was the first marketed inhaled biomolecule. Until Exubera was approved, there were many uncertainties about switching the delivery route of biomolecules from injection to inhalation. However, approval of Exubera by both US and European authorities increased confidence in the respiratory drug development community. The approval showed that inhalation for systemic application could be successful for PLM and further opened the inhalation route to regulators, prescribers and patients.

Afrezza, an inhaled dry powder insulin product from MannKind, has recently been approved by the US Food and Drug Administration (FDA) and a licensing agreement with Sanofi has been announced. This product utilizes a more compact device than Exubera and is expected to help increase patient compliance. There is now much anticipation regarding Afrezza and its potential to impact diabetes treatment.

Diversifying formulations and delivery devices

Reformulation of existing drug products, which accounts for more than 60% of newly-approved drugs,[12] can be one of the most important forms of PLM. As existing drugs are already considered safe, their regulatory pathways may be more straightforward. A variety of new inhaled formulations and device designs have reached the market and have had significant commercial impact.

In inhaled drug delivery, drug delivery efficiency is predominantly governed by the performance of aerosol generating devices.[13] Unlike other dosage forms, inhaled products require proper hand-breath coordination to actuate devices, therefore the products prescribed can vary with patients' abilities and conditions. For instance, devices that do not require significant coordination and high inspiratory flow rate to generate aerosols, such as metered dose inhalers and nebulizers, can be preferred for pediatric and elderly patients.[14-16] It can be common to reformulate existing drug products into various types of inhalers to expand a product's spectrum. As shown in Table 1, a majority of inhaled products are offered in both DPI and MDI forms.

The TOBI Podhaler (dry powder tobramycin) is an inhaler reformulated from the TOBI nebulization solution. Reformulation reduced the dose by approximately one third of the original formulation and improved portability by eliminating the nebulizer and compressor. In addition, the DPI was designed to have low device resistance so CF patients with limited inspiratory flow rates are better able to achieve desired drug delivery efficiency. TOBI solution was launched in 1997 and the Podhaler was launched in 2012. However, sales of tobramycin solution may not drop drastically since the original nebulizer is the preferred route of administration in the pediatric population.[14-16]

Fixed-dose combinations

Fixed-dose combination (FDC) inhaled products have recently become popular in the management of asthma and COPD. In chronic inflammatory diseases characterized by recurrent attacks of breathlessness and wheezing, both bronchodilators and anti-inflammatory drugs are used to manage acute symptoms and chronic inflammation.[17] Currently, delivery of a long-acting beta-agonist (LABA) and an ICS via combined inhaled drug delivery systems has gained widespread acceptance for the management of both asthma and COPD.[18] Many studies have demonstrated the clinical benefit of adding a LABA to ICS for patients with mild, moderate and severe persistent asthma. As shown in Table 1, the sales of fixed-dose combination inhaled products reached about $13 billion in 2012, which is approximately 50% of the total asthma/COPD market. The main drivers behind these FDC products are convenience and the resulting benefits of patient compliance.[19] Synergistic effects of co-administered active pharmaceutical ingredients (APIs) are also a contributing factor that makes fixed-dose combination products more favorable to physicians and patients alike.

The development of inhaled fixed-dose combination products is notoriously challenging when com-

Table 1

Examples of fixed-dose combination inhaled products on the market

Product	Dosage	Company	APIs	Worldwide Sales ($ Billions)*
Advair	DPI, MDI	GSK	Salmeterol xinafoate (LABA) Fluticasone propionate (ICS)	8.2
Symbicort	DPI, MDI	AstraZeneca	Formoterol fumarate dihydrate (LABA) Budesonide (ICS)	3.2
Combivent Respimat	Spray mist	Boehringer Ingelheim	Ipratropium bromide (Anticholinergic) Albuterol sulfate (SABA)	1.2
Dulera	MDI	Merck	Formoterol fumarate dihydrate (LABA) Mometasone furoate (ICS)	0.4

* LABA: long-acting beta-agonist, SABA: short-acting beta-agonist, ICS: inhaled corticosteroids. Data were collected from the 2012 annual reports of each company.

pared to traditional pharmaceutical dosage forms since this type of dosage form requires tailored particle engineering processes along with proper device-formulation optimization. Advair is certainly the best PLM outcome through a fixed-dose combination approach. The primary contributing factors of Advair's success are the improved therapeutic effect in addition to an increase in patient adherence.[19] Several studies have shown that the two APIs in Advair, fluticasone propionate and salmeterol xinafoate, have a higher chance of co-deposition on the same target cell compared to concurrent delivery of the same APIs through separate inhalers. As synergistic effects can only be achieved when the two APIs reach the same target cell at the same time, the co-association of the two APIs is one of the most important factors to consider at the development stage.[20, 21]

Other challenges for fixed-dose combination products include strict regulatory requirements and decreased brand erosion following patent expiry. However, recently there has been increased interest in triple therapy involving anticholinergics, LABAs and ICS, which are expected to be the next generation of asthma and COPD medications.

Conclusion

Developing inhaled therapies can be considered a unique form of product life cycle management. Despite its formidable challenges, there are a variety of opportunities to pursue, including changing route of administration, expanding indications, adopting fixed-dose combinations and developing different formulation/device combinations. As evidenced with examples in the preceding sections, inhaled products offer significant options for patient care and management of local airway diseases. Several exciting opportunities in fixed-dose combinations for local and systemic drug delivery exist and are expected to be an area for further innovation and intellectual property generation.

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