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Rapid communication

Rethinking the paradigm for the development of inhaled drugs

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ABSTRACT

Nebulized treatment is an important delivery option for the young, elderly, and those with severe chronic respiratory disease, but there is a lack of new nebulized drug products being produced for these patients, leading to the potential for under-treatment. This communication describes a new drug development paradigm as a timely solution to this issue. Often, drug development is initiated with nebulizers in the early stages, to provide cheaper and faster drug development, and then switched to inhaler devices in later clinical trials to address the majority of patients. However, the waste of resource on parallel development of the inhaler can be large due to the high early attrition rate of new drug development. The new paradigm uses the nebulizer to continue drug development through to market, and initiates inhaler development after completion of the riskier early phase studies. New drug safety and efficacy can be assessed faster and more efficiently by using a nebulized formulation rather than developing an inhaler. The results of calculations of expected net present value showed that the new paradigm produced higher expected net present values than the conventional model over a range of economic scenarios. This new paradigm could therefore provide improved returns on investments, as well as more modern drugs in nebulized form for those patients unable to use inhalers.

1. Introduction

Chronic respiratory diseases affect approximately 1 billion people worldwide (World Health Organization, 2007), and rates are expected to rise as a result of the world's aging populations. The control of respiratory disease symptoms is most commonly achieved with the use of inhaled drugs; pressurized metered-dose inhalers (pMDIs) and dry powder inhalers (DPIs) offer convenient rapid delivery of drugs for patients who have adequate coordination and lung function, whereas nebulizers containing drug in aqueous formulation fulfill the delivery requirements of patients unable to use inhalers, such as the young, elderly, and those with more severe disease (Dolovich et al., 2005; Galvin et al., 2010). Most recent drug development programs have focused on inhaler devices; there is currently a lack of new nebulized drug products for patients with the most severe asthma or chronic obstructive pulmonary disease (COPD). This could lead to the situation that some patient groups are under-treated with modern drugs, and with an aging population, the potential impact on the treatment of a significant proportion of patients is of concern. An area of particular concern is the treatment of COPD, which for severe patients is often accomplished using nebulized formulations (Pritchard, 2015). Most nebulized formulations were approved in the last century and have burdensome treatment regimens of many treatments a day (Joint Formulary Committee, 2015), which can affect levels of adherence and could have implications for disease control compared with drugs with more convenient regimens (Bollu et al., 2013). Thus, in COPD, the development of new nebulized treatments suitable for use by the widest range of patients can be considered pressing, although there are signs that some pharma companies are moving to address this (Haumann et al., 2015; Franciosi et al., 2013).

The lack of recent development of new asthma/COPD drugs in the nebulized drug format is surprising, given that it may be difficult to isolate pure drug in the correct physical form for delivery in an inhaler. The potential under-treatment of the young, elderly, and sick may thus be due to a lack of focus on this population sufficiently early in the development cycle. A reappraisal of this has been conducted and presented in this paper to examine the economic and market impact of pursuing an alternative paradigm that raises the priority of patients requiring nebulized treatment.

Abbreviations: DPI, dry powder inhaler; eNPV, expected net present value; LAMA, long-acting muscarinic antagonist; LABA, long-acting β-agonist; NPV, net present value; pMDI, pressurized metered-dose inhaler; COPD, chronic obstructive pulmonary disease.

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2. Issues in development

In embarking on development of an inhaled product, in one development model, nebulizers are used for the early development, (i.e., from Phase 0 to Phase II) because early formulation work to develop a solution or suspension liquid is generally easier, faster, and requires less drug substance compared with inhaler formulations (Pritchard, 2005). This enables the company to get a rapid read-out of the safety and efficacy of the new drug. Furthermore, nebulizers are not as dependent on a patient achieving the correct breathing pattern, compared with inhalers (Cipolla and Gonda, 2011) (pMDIs and DPIs), and modern smart nebulizers provide accurate dosing for ease of bridging to the eventual inhaler device, plus additional data-logging features that may allow interpretation of clinical trial results (Pritchard and Giles, 2014).

With solution formulations, the need to develop particle size reduction processes is avoided, and it is possible to make up the nebulized formulation to be tested extemporaneously at the point of delivery, thereby restricting the validation of shelf life to the bulk formulation only. This can be attractive, because during the early development stages, drug substance is at its rarest and most expensive when batch sizes are not yet at commercial scale. Development of the drug substance typically takes place in discrete campaigns (Steele, 2009); the second campaign can cost in excess of $250 K to produce, which makes the drug as costly as gold dust. It is this material that is used for the pivotal early phase clinical trials. If these trials are to be conducted with an inhaler, then it typically can take 6 full time equivalents and 10-20 kg of drug substance to create inhalable particles of the drug substance, formulate these for the inhaler type chosen, demonstrate pharmaceutical performance of the drug delivered by the device, and establish the shelf life of the product going into the clinical trial (which in itself may necessitate a repeat campaign 2).

Nonetheless, there is a significant downside to waiting for a successful Phase II outcome before embarking on development of the inhaler; the patent clock is running. Typically, it takes 3 years from patent filing to be ready to embark on a Phase I trial (Mestre-Ferrandiz et al., 2012), then a further 7 years to complete the development through to the end of Phase III, and at least a further 10 months for the first review cycle by the regulatory authorities. Thus, half of the patent life expires before the product gets to market. If inhaler development is not started until a successful Phase IIa study, a delay of 2 years is incurred, thereby eroding the patent life by 20%, significantly reducing product profitability. For a drug realizing $1 billion p.a. of global sales, 2 years of lost sales dwarfs the investment in developing an inhaler in parallel to the nebulized product going into Phase I and II trials; therefore major companies will invest at risk in the early development of an inhaler.

Indeed, companies with the resources and expertise available may choose to ignore the option of nebulized therapy and go straight into early clinical studies with pMDI or DPI formulations. However, if the company then overlooks development of a nebulized formulation until the inhaler is launched, it will need to complete further dose ranging and Phase III studies, which could take 5 of the maximum 9 years of patent protection that remain, leaving little market time to recover the investment before the appearance of generic competitors. The company is unlikely to get additional patent cover on the device (general purpose nebulizer) or formulation, unless there are specific formulation issues to be overcome. Hence, this is not an attractive option, and may explain why none of the later generation of long-acting β-agonists (LABAs) or long-acting muscarinic antagonists (LAMAs) have been marketed in nebulized form to date (Pritchard, 2015).

Attrition rates for respiratory compounds are among the highest of all therapeutic areas, with only 3% of molecules that entered Phase II gaining market approval by 2006, and 5% in 2010 (Mestre-Ferrandiz et al., 2012). Looking at breakdown by phase shows that much of this attrition occurs before Phase III, with only 15% of compounds that entered Phase I entering Phase III in between 1994 and 2003. Given the attrition rate for new drugs, is there a way that can mitigate the wasted resource on drug failures expended during the parallel or sole development of an inhaler that can make commercial sense? This communication explores an alternative approach, namely to delay development until the risk in the new molecule has been significantly reduced by successfully completing Phase IIa trials, but crucially, continue the development of a nebulized product through to market, whilst embarking on development of an inhaler in parallel.

3. Assessing financial returns in inhaled product development

To demonstrate the potential financial benefit of taking early phase nebulized formulations all the way to market, calculations of expected net present value (eNPV) were performed. These were based on the likelihood of a respiratory drug passing through successive clinical studies and gaining market approval. The out-of-pocket costs associated with each phase (in 2011 US$) were taken from those estimated by an Office of Health Economics report, but scaled upwards from the average by 40% to reflect the higher overall development costs associated with respiratory projects compared with other therapeutic areas (Mestre-Ferrandiz et al., 2012). The durations spent in each phase were also taken from this report and are summarized in Table 1. Further key assumptions to model sales are listed in Table 2. Of note, it is assumed the company have some focus on the nebulized market, and so begin nebulized development upon successful completion of the Phase III studies with the inhaler, launching some 5 years later. Under the new paradigm, it is assumed the company will not start inhaler development until after a successful Phase IIb dose-ranging study with the nebulizer, some 4 years after commencement of the project.

The scenarios were then modeled under a range of assumptions for rate for discounted cash flow (1–7%). A range of potential sales generated by the inhaler if successfully passing registration ($0.5–5 billion p.a.) were also investigated. For each scenario, the likelihood of incurring the cost of development in each phase was adjusted by the probability of the drug successfully reaching that phase, and then discounted by the appropriate discount rate. In the

Table 1
Summary of assumptions for development, with data from Mestre-Ferrandiz et al. (2012), and Hay et al. (2014).

Phase	Probability of passing phase	For every 100 compounds:		Duration (months)	Cost (2011 US$)
		Pass	Fail		
Pre-clinical		100			
Phase I	0.52	52	48	18	22 M
Phase II	0.28	15	37	30	76 M
Phase III	0.63	9	5	36	181 M
Registration	0.88	8	1	12	41 M