What is the Future of MDIs?

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INTRODUCTION

Since their introduction in 1956, the pressurized Metered Dose Inhaler (MDI) has been the most widely used platform used to deliver treatments for asthma and COPD. While the basic subsystems of modern HFA MDIs are the same as their early CFC counterparts, each has been substantially improved. Increased regulatory requirements and the transition to hydrofluoroalkane (HFA) propellants have been primary drivers of this innovation (Figure 1). Valves have been improved to function in HFA propellants, meet more stringent regulatory requirements on dosing uniformity and extractables/leachables. Canister technologies (e.g., novel coatings) have been developed to reduce drug degradation and deposition. The transition to HFA formulations resulted in MDIs with increased lung deposition and technologies to control residual particle size (i.e., the size of the particle remaining after all volatile components evaporate). Transition to HFA propellants led to the development of MDI actuators with improved delivery efficiency. Dose counters have been incorporated for improved patient compliance. Additional improvements are in development. However, it is our opinion that the future of MDIs will be driven more by market factors than by unmet technical requirements. In this paper, we examine factors that will determine the future of MDIs and predict how these factors will shape the next half century of MDI use.

MARKET DYNAMICS INFLUENCING THE FUTURE OF MDIs

The low cost of MDIs (particularly on a cost per dose basis) will be a major factor driving the future of MDIs. Cost pressures in the developed countries and the desire for western style medication in developing countries will secure the future of MDIs. It is estimated that there are 300 million asthma and 230 million COPD sufferers worldwide (1), many in developing countries. MDIs are well suited to meet the needs of the price sensitive and largely generic developing world markets. We believe that many drug developers will choose to utilize MDIs in order to develop products that will be commercially viable in both developed and emerging markets. Additionally, we believe that MDIs will expand into niche markets other than asthma and COPD. MDIs were once a mainstay in the treatment of allergic rhinitis (AR), but were replaced with aqueous pump sprays since the Montreal Protocol did not provide a 'medical use' exception for AR. However, there are several benefits of using MDIs (e.g. removal of preservatives, extension of developed

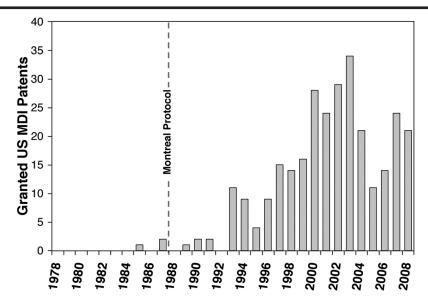


Figure 1. The number of granted US patents with "MDI" in the title, abstract, or claims.

MDI formulations for new indications, preference of some patients) and multiple steroids are currently being developed in HFA MDIs to treat AR. Inhaled systemics (e.g., fast onset for migraine therapy) and localized delivery of proteins and peptides for lung diseases will also provide niche markets for MDIs.

POLITICAL DYNAMICS INFLUENCING THE FUTURE OF MDIs

Political dynamics related to the global warming potential of HFC propellants (such as HFA-134a or HFA-227) could influence the future of MDIs. It should be noted that the environmental impact of HFC propellants is much less established than for CFC propellants. While MDIs constituted a small percentage of the total CFC use, CFCs were the overwhelming source from human activity contributing to stratospheric ozone destruction. There is a much weaker link between HFC propellant use and global warming. HFC propellant is a small contributor of greenhouse gas emissions - approximately 3% of total emissions of CO2 equivalents in 2007 (2). MDIs constitute a very small percentage of HFC use (<2%). Thus, the contribution of HFA MDIs to global warming is negligible. There are wildly varying estimates of future HFA emissions (2), but these estimates are highly speculative. A thorough assessment of the global warming potential of HFA MDIs compared to DPIs should include the full array of processes involved in device manufacturing (e.g., molding of plastic components) - not just the contribution of the HFA propellant. Such an assessment has not yet been done. Despite clear scientific justification for eliminating CFC propellants, CFC MDIs weren't phased out until 21 years after the signing of the Montreal Protocol. We believe that there is a far weaker scientific rationale to eliminate HFA MDIs and that it is highly unlikely that they will be forced off the market any time soon, if ever.

WHAT WILL MDIs OF THE FUTURE LOOK LIKE?

There are a number of technical considerations that will influence the future of MDIs. MDIs will continue to be refined with an emphasis on expanding the range of drugs that can be developed into MDIs and improving dosing consistency. Future MDIs are likely to use fast fill/fast empty (FFFE) valves or other designs to overcome priming effects, optimized elastomers to reduce leachables, and valve and canister coatings to reduce drug deposition for suspension MDIs and drug degradation for solution MDIs. There has been limited market interest in novel actuator technologies since the drug delivery efficiency from current HFA MDIs is usually adequate, but simple cosmetic improvements to actuators are likely as companies seek to gain market differentiation. Higher end actuators such as MAP's Tempo™ inhaler (3) may be utilized for therapies where it is critical to minimize orapharyngeal deposition or where cost is less important. The incorporation of dose counters may be delayed in some developing markets due to cost, but they will eventually be incorporated even in markets where they are not currently required. Spacers will continue to be used by young children and elderly individuals, but we do not expect that the number of adult patients using spacers will significantly increase. Breath-actuated MDI systems have been available since the 1970s, but have not been widely commercialized due to increased cost. However, the prevalence of breath-actuated MDIs may increase as companies seek market differentiation, as managed care providers seek improvements in pharmacoeconomics due to improved patient compliance, and as simpler breath-actuation technologies are developed. Other more significant changes to the MDI (such as unit dose MDIs, adjustable dose MDIs, etc.) are technically feasible and may eventually be commercialized for niche opportunities, but this remains to be seen. Future MDIs are likely to incorporate new formulation technologies that allow for increased respirable doses, improve dosing consistency, and manipulate the size of the delivered aerosol. Numerous technical improvements have been demonstrated but have yet to achieve widespread market acceptance (Table 1). Some of these are certain to reach the market in the future. However, future MDI formulation and hardware innovations will be balanced with the desire to maintain two primary benefits of MDI systems low cost and regulatory familiarity with MDIs. As a result, it is our opinion that future MDIs will not be radically different from existing MDIs.

Table 1.

Technologies expected in future MDIs. Many of these technologies exist, but have not yet achieved widespread use.

Formulation

- Excipients for manipulating particle size (e.g. Modulite®)
- Novel suspension aides
- Engineered particles (e.g. Pulmospheres™)
- Sustained release formulations

Valve

- Fast-fill/fast-empty (e.g. Bespak Easifill and 3M[™] face seal valve)
- · Coatings to reduce deposition
- · Improved elastomers

Canister

- · Coatings to reduce deposition
- Can-in-can or mini-cans for low number of doses

Actuator

- Breath-actuation (e.g. Autohaler ™)
- Airflow manipulation (e.g. Tempo ™)
- Ergonomic/cosmetic improvements

Dose Counters

- Dose-by-dose counters
- · Larger font sizes

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