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What is the future of HFA pMDIs? A patent-based perspective

A significant number of patent expiries may create opportunities for pMDI innovation

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Introduction

Over the last 20 years, inhalation drug delivery has been adjusting to the phase out of chlorofluorocarbon (CFC) propellants. Following the signature of the Montreal Protocol[1] on September 16, 1987, there has been a rush to re-formulate pressure metered dose inhalers (pMDIs) using alternative propellant systems. This has led to the advent of dry powder inhalers (DPIs), and to a prolific HFA (hydrofluoroalkane) pMDI patent field, resulting in a crowded patent landscape. The complexity of this landscape has led to myth and confusion with respect to the risks and opportunities in formulating HFA pMDIs. This review aims to improve understanding of the intellectual property (IP) landscape. Understanding the past could help industry participants plan the future of pMDI inhalation delivery.

Method of analysis

This analysis of the HFA pMDI patent landscape is based on an extensive search of patent databases using Cambridge IP's IP Landscape methodology. A mixture of commercial and publicly available database services were used, which provided coverage of most key countries (for both patent applications and grants). These included the US Patent and Trademark Office, the Japanese Patent Office, the European Patent Office and key European national patent authorities and most large countries covered by the INPADOC (International Patent Documentation Center) patent database. The time span ranged from 1968 to the present. Due to delays in patent application publications, it is possible that data for 2010 and part of 2009 will be under-represented in this dataset. A patent dataset of 843 HFA-related patents focused on or related to pMDI applications was used as the primary dataset.

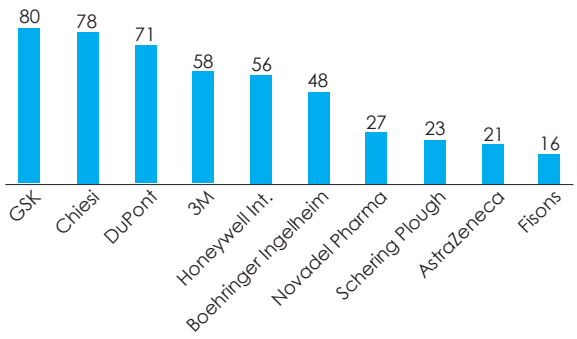
The patent disclosures collected in this work mentioned a number of propellants in addition to HFAs, CO_2, NO_2 and other inorganic propellants. Overlaps between various HFA mixtures, as well as dual uses were evidenced. Out of the 658 patents and applications that mention the use of HFAs, 242 patents cover propellant mixtures; 191 patents mention HFA 227; 241 patents mention HFA 134a; while 262 patents do not specify which HFA is used. Furthermore, 154 patents cover other types of HFAs (e.g. octafluorobutane). The 29 inorganic propellant references include 14 mentioning CO_2, 4 mentioning NO_2, and 17 mentioning other molecules (such as He or N_2). Further, 282 patents and applications mention the use of additives for inhalation, which were split into three categories: use of ethanol (50 patents), surfactants or polymers (99 patents) and other additives (186 patents). These other additives include salts, taste-masking agents, alcohols other than ethanol, lysine and antioxidants.

The top ten HFA propellant assignees are summarized in Figure 1. "Propellant patents" mean all patents including those mentioning DPI, nasal, nebuliser, DME, CFC and others, while, "pMDI specific patents" focus on the strict definition of HFA pMDI patents. GSK holds the highest number of HFA propellant-focused patents and applications. It is one of the largest portfolios of pMDI-focused propellant patents, confirming industry perceptions of its leadership sta-

tus in the field of HFA pMDI formulation. Chiesi, in second place, demonstrates its dedication to HFA pMDI development and its ethanol-based platform Modulite. Many of Chiesi patents are co-owned with UK-based Vectura, highlighting the established and well known collaboration between the two companies. Dupont, in third position, reflects its activity in propellant manufacturing overall. AstraZeneca, in fourth position, is the only assignee in which all of the HFA patents are dedicated to pMDIs.

Figure 1

Top ten patent assignees in HFA pMDI space



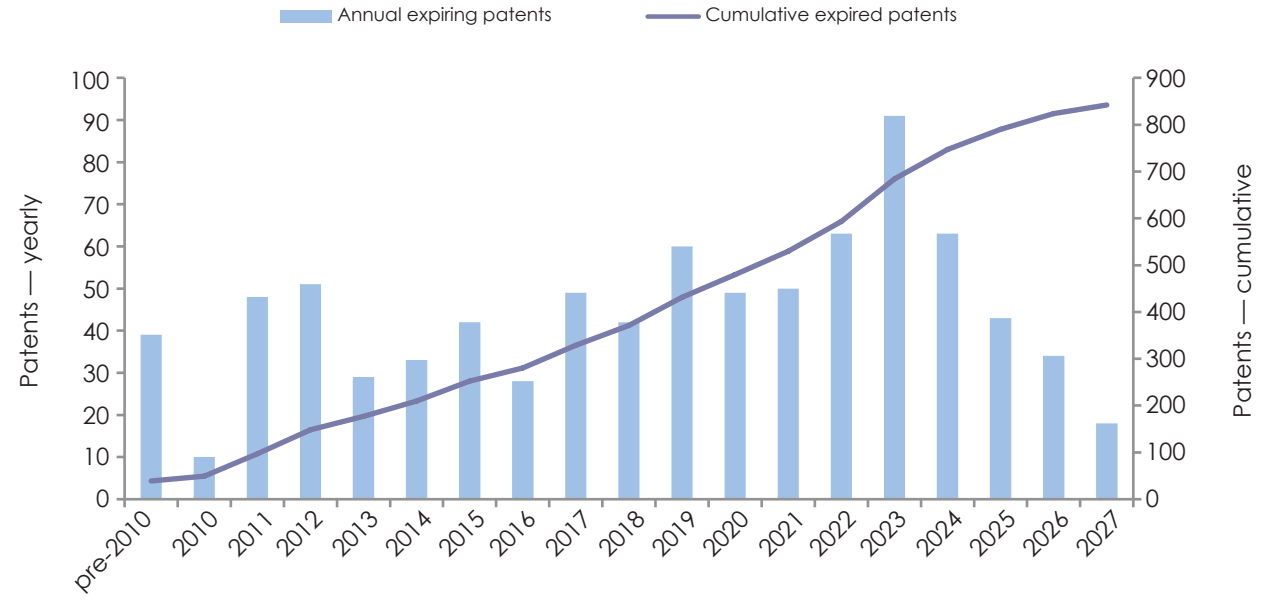
Patent expiries over the next five to ten years

Given the large number of pMDI patents filed since 1987, over the next five to ten years, a drastic reduction in the number of patents in force can be expected. However, complex patenting strategies around products can, in some cases, extend the *de facto* protection of a specific technology, even if the original patents have expired. In the initial years of 1989 and 1990, HFA 134a propellants were more readily available, and initial uses and product trials led to a higher use of HFA 134a. Since then, the field has seen rapid growth in the patents associated with fluorocarbon-related patents. By 2008, a total of 658 patents used some type of fluorocarbon molecules in the inhalation space overall (and of those, at least 432 were explicitly HFA 227 or HFA 134 related). Since 2004, the number of publications in the pMDI research space has been in decline, demonstrating a rather mature formulation field and a shift of interest to DPIs and other forms of inhalers. Correspondingly, the number of patents due to expire is now increasing.

The statistical analysis of HFA propellant patents shows that a substantial change in the patent landscape is to be expected in the field over the next few years. At the aggregate level, the industry will see a decrease in valid patents over the next ten years. While currently only about five percent of the patents in this technology space have expired, in the next five years, this will increase to 17 percent, while in the next ten years, approximately 36 percent of the patents will expire. Figure 2 gives an indication of expected expiry times of HFA patents. Expiration is defined as 20 years after first application. Expiration will differ by jurisdiction and the history of the patent or patent family. Further analysis is required to define with precision the expiry of a patent or patent family, whether due to the end of its legal life, non-payment of fees or other events.

Figure 2

Distribution of patents by expiration year for HFA 227 and HFA 134 propellants



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Forthcoming expiries mean new opportunities

The "opening up" of the HFA pMDI patent landscape may create significant opportunities for innovation in the formulation community, where the risk of patent infringement may have been an inhibiting factor to innovation thus far. It will be of considerable interest to observe whether such opportunities are seized by the generics industry, emerging markets players or incumbents. Even for established industry players, such developments can bring benefits: there may be opportunities for greater innova-

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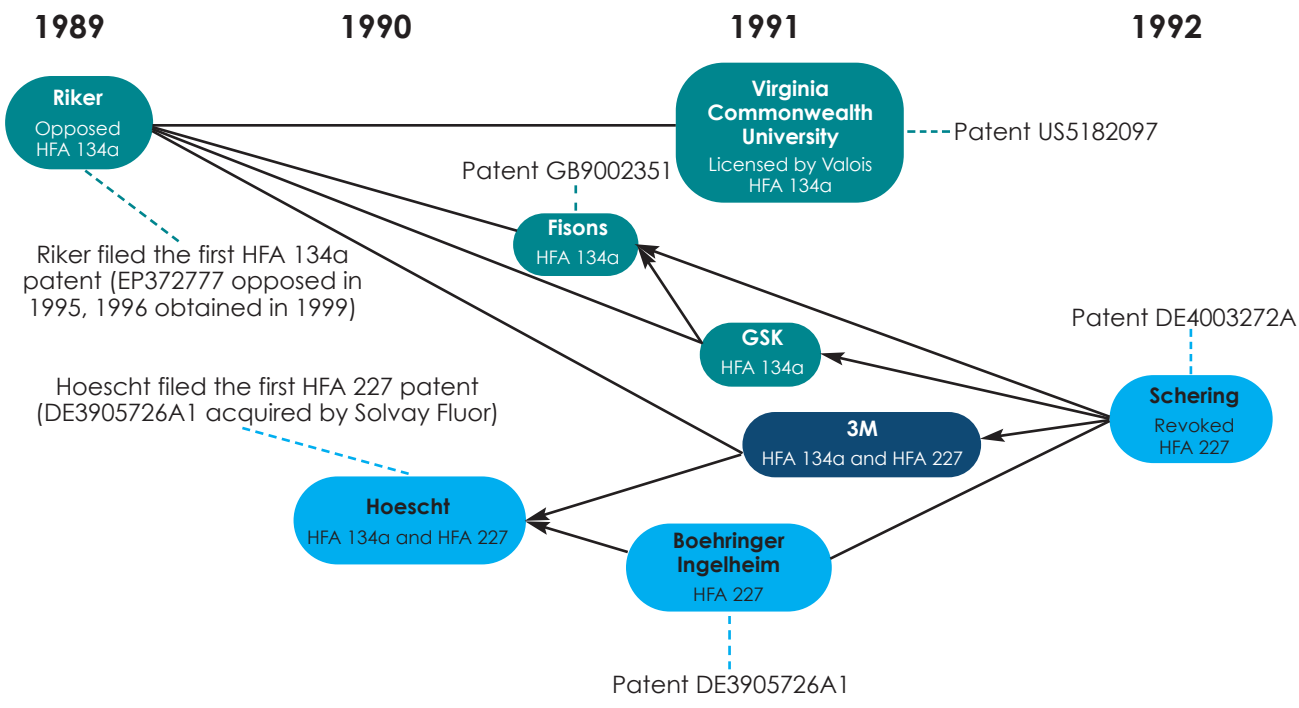
Patents of fluorocarbon propellants: Who was first?

The earliest patent application mentioning fluorocarbons as suitable propellants for pMDIs was published in 1987.[2] The earliest patent specifically mentioning HFA use, with a direct example using HFA 134a, was filed on December 6, 1988[3] by Ryker Laboratories. This invention was subsequently submitted for a European patent application on November 27, 1989.[4] It describes a self-propelling aerosol formulation which may be free from CFCs, comprises a medicament, 1,1,1,2-tetrafluoroethane, a surface active agent and at least one compound having a higher polarity than 1,1,1,2-tetrafluoroethane. Oppositions to this patent were identified in 1995, 1996 and finally obtained in 1999 by Norton Healthcare Ltd, Schering Corporation, Boehringer Ingelheim GMBH, Smithkline Beecham Plc and Fisons Plc, amongst others. The second-oldest patent family finds it origins in a filing in 1991[5] by Fisons Plc describing the use of HFA 134a.

Patenting of the use of HFA 227 can be traced to two patent applications. The oldest application was filed by Hoechst[6] on December 6, 1990 (now owned by Solvay Fluor). It describes the use of HFA 227 and mixtures for inhalation delivery. A second important application was filed by Boehringer Ingelheim on February 3, 1990.[7] It describes a novel, advantageous vehicle gas mixture containing two or more components, at least one of which is a partly fluorinated lower alkane, that may be used in medical preparations.[8] These patent applications constitute traceable prior art for the use of HFA in pMDI formulations but have now been superseded by further applications and grants by patent family members. While Hoescht's patent is the original HFA 227 related patent, the Boehringer Ingelheim patent family has had the biggest impact in the industrial field, as measured by backwards citations. As this analysis shows, the question of 'who was first' is fairly complex.

Figure 3

Schematic of the history of landmark HFA patents



tion and a larger variety of pMDI products, as well as increased variety of sources of HFAs. In combination with increasing purchasing power in key developing economies, the total monetizeable market for pMDIs and HFA formulations may well compensate reduced profitability on previously protected product lines.

The patent filing timelines highlighted in this review and the overall activity in the field illustrate that while tremendous creative activity has surrounded the field of HFA pMDI formulation in the past two decades, pMDI propellant research may have gone through a peak. It is possible that patenting of HFA pMDI formulations has seen its "gold rush" and rewards are now being harvested by those who had the foresight to invest in this field. The decline of inventiveness in the field is felt in the number of recent pMDI patent filings, but also in the market share of pMDIs versus dry powder inhalers and in the number of DPI products being launched. This is particularly marked in the EU and increasingly so in the US.

Based on these statistics, it can be suggested that a number of the patent applications filed over the last 20 years section will lead to a number of patent expiries over the next few years. This has one major consequence. HFA formulation routes, hitherto not available generally, will become accessible to many more players, and in particular to the generics industry. However, expiry timelines need to be reviewed on a base by case basis. The case of the Boehringer Ingelheim patent DE3905726a1 mentioned in Figure 3 is a good example. It was first filed in 1992, but only granted after a number of modifications and withdrawals in 2007, thus bestowing a much longer exclusivity to the invention than could be predicted from theoretical expiry timelines.

From a commercial point of view, the future for HFA pMDI products is uncertain. The intellectual property landscape is only one factor. Other elements, such as market needs, new therapies, the role of Brazil, Russia, India and China (the BRIC countries) and further environmental regulations will dictate the future of HFA pMDI formulations as much as the IP landscape.

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Greater detail on the patent and statistics provided in this review can be found at www.Boliven.com/landscapes/PMDIs.

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