



# Zephex<sup>®</sup> 152a

## Overview

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# 1. Introduction

HFA-152a (1,1-difluoroethane) has been subject to an extensive research and development program, as a low-carbon pressurised metered-dose inhaler (pMDI) propellant alternative to (1,1,1,2-tetrafluoroethane) HFA-134a and (1,1,1,2,3,3,3-heptafluoropropane) HFA-227ea.

To date, HFA-152a has been shown to have an attractive combination of environmental and formulation performance properties.<sup>1</sup>

For several years there has been increasing environmental, regulatory and stakeholder pressure to reduce the carbon footprint associated with the use of pressurised metered-dose inhalers (pMDIs). Many organisations, for example the UK National Health Service, have introduced carbon footprint reduction targets.<sup>2</sup> Despite its clinical importance, the pMDI has been a very visible focal point for environmental action. Currently pMDIs account for a major part of the carbon footprint of many pharmaceutical companies, who have their own shareholder commitments to reduce corporate carbon footprint levels.

To address these concerns and to help meet their own environmental sustainability targets, Koura is developing and introducing a low carbon pMDI propellant product with our branded Zephex® 152a. This complex programme of work is made up of a series of different activities. This includes, but is not limited to:

- Determining clinical safety in use (inhalation safety).
- Formulation performance in pMDI devices.
- Propellant supply for formulation development and associated registrations.
- Manufacture and purification to produce Zephex® 152a, at commercial quantities, to meet the expected demand and cGMP standards.

## 2. Environmental Benefit

It is estimated that more than 800 million pMDIs are manufactured annually worldwide using up to 11,500 tons of propellant.<sup>3</sup> The adoption of the Montreal Protocol in 1989 initiated the development of the predominant HFA propellants currently used in pMDIs today.

HFA-134a and HFA-227ea replaced the ozone-depleting chlorofluorocarbons CFC-12 and CFC-11. Although these focused on reducing the impact on atmospheric ozone depletion, the introduction of the HFA propellants also resulted in almost an order-of-magnitude reduction in the Global Warming Potential (GWP) associated with pMDI usage.<sup>4</sup>

Having essentially completed the transition from ozone-depleting CFCs and HCFCs across a spectrum of applications, including pMDIs, there is now growing concern regarding the GWP of many hydrofluorocarbons, including HFA-134a and HFA-227ea.

HFA-152a has a significantly lower environmental GWP than HFA-134a or HFA-227ea.

HFA-134a has a GWP (100-year timescale relative to CO<sub>2</sub>) of 1,300 and HFA-227ea has a GWP of 3,350, whereas HFA-152a has a GWP of 138.<sup>5</sup>

This has led to the introduction of regulations in many parts of the world that places controls on the usage of these substances, including the F-Gas (517/2014) regulation<sup>6</sup> in Europe and the American Innovation and Manufacturing act<sup>7</sup> (AIM) in the US.

Both regulations aim to phase down the use of HFAs, often in specific commercial applications or uses, especially where an alternative lower GWP HFA can be utilized acceptably.

Both sets of these regulations are underpinned by the Kigali amendment<sup>8</sup> to the Montreal Protocol which sets minimum phase down levels for specific global regions.

In April of 2022 a proposal for the regulation of the European council to repeal regulation 517/2014 was published.<sup>9</sup> A few 'options' are proposed and to be debated. For the pMDI manufacturing sector, this would potentially put to an end the exemption, which has been in place since the publication of the 2014 regulation.

It is expected that these regulatory steps will adversely impact the manufacturing supply chain for these medical-grade propellants. This in turn will likely lead to substantially reduced availability and increased costs going forward. Accordingly, industry has been looking for potential alternatives to these HFAs in both industrial and medical application sectors.

A peer-reviewed Life Cycle Analysis has shown that pMDIs formulated with HFA-152a have a carbon footprint that is equivalent to other propellant-free technologies such as Dry Powder Inhalers (DPIs) and Soft Mist Inhalers (SMIs).<sup>11,12</sup>

Accordingly, once approved for pMDI use, Koura's Zephex<sup>®</sup> 152a has the potential to take environmental factors out of consideration when selecting the most appropriate inhalation treatment platform for patients. This allows the prescriber to base their choice on the key factors of clinical efficacy, cost and patient-preference.

### 3. Inhalation Safety Studies

Zephex<sup>®</sup> 152a is manufactured to cGMP for use in research activities by both Koura and Koura's customers.

Whilst environmental sustainability is clearly an attractive goal for any commercial product, a new pMDI propellant must not come at the cost of any significant compromise to patient inhalation safety.

Since its initiation in 2015, Zephex<sup>®</sup> 152a has been the subject of an extensive suite of inhalation safety testing that is nearing completion. Although the program is still in progress, results to date on both acute and sub-chronic safety tests have been very encouraging, with Zephex<sup>®</sup> 152a having a similar profile to that of Zephex<sup>®</sup> 134a.

The Zephex<sup>®</sup> 152a propellant inhalation safety programme is expected to be completed in 2023.

### 4. Regulatory Landscape

There are still several familiar regulatory hurdles to overcome before a new product can be placed on the market.

Throughout the inhalation safety programme, Koura have been in continuous dialog with global regulatory bodies. On completion and review of the safety programme, the Zephex<sup>®</sup> 152a toxicology DMF will be available for reference by pharmaceutical companies for their formulated product submissions in a manner analogous to that of the current pMDI propellants: HFA-134a and HFA-227ea. In addition, a separate Zephex<sup>®</sup> 152a manufacturing and quality DMF will also become available.

The viability of Zephex<sup>®</sup> 152a as a commercial pMDI propellant has been endorsed by Chiesi who recently announced their intention to launch Zephex<sup>®</sup> 152a pMDI products by 2025.<sup>13</sup> Although the development and regulatory stage will go on for some years beyond the 2023 propellant timescale, this represents the start of a transition from many of the existing HFA-227ea and HFA-134a based products.

Registration of new formulations based on Zephex<sup>®</sup> 152a may also provide an opportunity for device manufacturers to introduce updated product or device innovations. These are the innovations that may otherwise struggle to overcome the inertial and cost hurdles, associated with product development.

## 5. Technical Performance

Transition from the historic CFC propellants to the current HFA propellants presented several technical challenges with respect to differences in formulation behaviour and materials compatibility. Table 1 displays a series of properties, comparing current medical inhalation propellants with HFA-152a.

Property	134a	227ea	152a
BP (°C)	-26.2	-17.1	-24.7
Vap. Press (barg, 25°C)	5.65	2.89	4.95
Liq. Density (g/cc, 25°C)	1.22	1.41	0.90
Liq. Viscosity (cP)	0.21	0.26	0.16
Flammability in Air (% Vol, 1 atm)	NA	NA	LFL: 3.7%
Vapour Dipole Moment (Debye)	2.06	1.46	2.26
Solubility of Water in HFA (25°C, % w/w)	0.11	0.06	0.22
GWP (100-year time horizon)	1340	3300	134

**Table 1**

From its use in the refrigeration and insulation foam applications, there is a basic understanding of the behaviours of HFA-152a in contact with elastomers and polymers. As a hydrofluorocarbon, the fluid would be expected to behave more like HFA-134a than like CFC-12, this is broadly what has been observed.

From some recent work by Koura, HFA-152a appears to have good compatibility with existing valve materials and designs. Additionally, Aptar Pharma, a world renowned pMDI part maker, have recently concluded similar results.<sup>14</sup>

There may be scope for further performance optimisation, for example plume behaviours, as formulations based on HFA -152a are developed and refined. 3M, now Kindeva, utilised a theoretical model to show that predicted spray force of current propellants versus HFA-152a is similar.<sup>15</sup> This is clearly a welcome development given the complexity, costs and time associated with the design and manufacture of a new pMDI valve.

## 6. Zephex<sup>®</sup> 152a Availability and Commercial production

Zephex<sup>®</sup> 152a is available in both R&D and commercial quantities. Koura announced the opening of a Zephex<sup>®</sup> 152a GMP manufacturing plant in April 2022 <sup>16</sup> The plant can produce several hundred tonnes of Zephex<sup>®</sup> 152a and commenced commercial production in quarter 4, 2022. The DMF for Zephex<sup>®</sup> 152a will shortly be finalised to meet customer commercialisation requirements.

Availability of representative Zephex<sup>®</sup> 152a at this scale will help facilitate the development of formulations and devices, regulatory studies and early-years commercialisation of products based on Zephex<sup>®</sup> 152a.

## 7. HFA-152a Safety Overview

Unlike HFA-134a and HFA-227ea, HFA-152a is flammable.<sup>17</sup> Traditionally, lack of flammability was a prerequisite for a pMDI propellant. Despite its flammability, Koura are confident that the propellant can be handled safely at all scales.

There are two major scenarios to consider when considering the flammability of pMDI propellants:

- End-user safety
- pMDI manufacturing safety.

## 8. End-user Safety of pMDIs Containing Zephex<sup>®</sup> 152a

HFA-134a is itself non-flammable. However, many of the pMDI formulations on the market containing significant levels of ethanol are flammable and have been used for many years without significant patient safety impact. This is not surprising. Unlike the continuous flow valves used in many consumer aerosol products, the metered emissions from a pMDI are small and result in a very small spatial volume where a potentially flammable composition might exist.

Early quantitative risk assessment (QRA) studies<sup>18</sup> confirm that the flammability associated with HFA-152a is unlikely to have any significant impact on patient safety. For reference, even though HFA-152a may be classified as 'flammable' the relatively low risk in aerosol products is recognised under the US Consumer Products Safety Commission<sup>19</sup> where HFA-152a aerosols are classed as non-flammable in the absence of other flammable cosolvents such as ethanol.

## 9. Manufacturing of pMDIs Containing Zephex<sup>®</sup> 152a

For pMDI manufacturing facilities, Zephex<sup>®</sup> 152a flammability is likely to require a degree of reconfiguration of many existing pMDI manufacturing and filling facilities to ensure safe manufacture. Measures required to mitigate the flammability hazard are well understood from the industrial and consumer aerosol sectors but need to be translated into a cGMP-manufacturing environment.

Such aerosol manufacturing capabilities already exist, albeit for topical pharmaceutical products. Koura has investigated options for both facility reconfiguration and for design of new facilities, that will ensure safe operation with Zephex<sup>®</sup> 152a.

A 2-stage filling approach, where the need for a large mixing vessel is eliminated, provides the pMDI manufacturer with a reduced risk approach. This *may* then allow a degree of retrofitting of the current facility, significantly reducing overall costs. Koura, are currently working with a number of clients, supported by third parties, in supporting this approach.

An alternative pMDI API dosing technique based on Dry Powder technology, could eliminate the need of a mixing vessel at both development and manufacturing scales and pave the way for a reconfiguration of the current pMDI supply chain to suit low GWP propellants. Koura have investigated the applicability of this technology to dispensing APIs into MDI cans at bench and pilot scale and evaluated the impact on formulation stability with promising results.

Please contact us to discuss further.

## 10. Summary

Koura and our parent company Orbia, have a strong environmental and sustainability focus. As part of this drive, we are fully committed to see our low GWP propellant offering, Zephex® 152a succeed in the global pharmaceutical pMDI market.

Our development medical inhalation propellant has considerably lower GWP than today's offerings. Alongside this, we believe our clients will discover exciting formulation properties and benefits with Zephex® 152a.

Koura will offer a full package of support within the technical, engineering and regulatory sectors. We are confident that this will aid our customers through both their research & development projects, through to their commercialisation undertaking.

Contact us at [zephxsales@kouraglobal.com](mailto:zephxsales@kouraglobal.com) for further information.



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