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Mexichem Fluor
Zephex® Brochure

Mexichem FLUOR

pure quality

We are the world leader in medical propellants and have many years experience of operating to the highest current Good Manufacturing Practice (cGMP) standards. Our extensive understanding of the needs, standards and regulatory requirements of the pharmaceutical sector coupled with our expertise in fluorine innovation makes us unique in our industry.

Hector Valle
CEO
Mexichem Fluor

The world's largest supplier of HFA medical propellants

Production of pharmaceutical grade HFA 134a began at the Mexichem Fluor facility in the UK in 1995 - the only dedicated plant of its kind in the world. More recently Mexichem Fluor has added the complementary propellant HFA 227ea to its range of medical products, manufactured by its partner using a dedicated facility in Arkansas, USA*.

ZEPHEX® is the brand for Mexichem Fluor's range of high quality medical propellants. ZEPHEX®134a and ZEPHEX®227ea are manufactured, tested and marketed fully in accordance with the current Good Manufacturing Practice (cGMP) as required by the world's leading regulatory authorities such as the US Food & Drug Administration (FDA) and the UK Medicines and Healthcare Products Regulatory Agency (MHRA). The ZEPHEX® manufacturing facilities were conceived, designed and constructed to the highest cGMP standards and both are scaled to meet global pharmaceutical demand for both pure propellants and blends of these products.

The entire operation from acceptance of feedstock through final product release to customers is managed to the most rigorous Quality Assurance and Quality Control standards in the industry and is backed by the company's world leading gas chromatography analytical methodology.

The Mexichem Fluor range of medical propellants are used in 80% of the worlds CFC replacement asthma inhalers, with the flagship ZEPHEX®134a and ZEPHEX®227ea developed to meet the exacting standards of pharmaceutical companies and regulatory authorities worldwide. The products are manufactured, tested and distributed fully in accordance with current Good Manufacturing Practice (cGMP).

Used in 80% of the world s CFC replacement asthma inhalers, ZEPHEX®134a and ZEPHEX®227ea are high quality medical propellants developed to meet the exacting standards of pharmaceutical companies and regulatory authorities worldwide. The products are manufactured, tested and distributed fully in accordance with current Good Manufacturing Practice (cGMP).

** The product is made to Mexichem Fluor's specifications by its partner under a manufacturing and marketing agreement. Mexichem Fluor performs all final QC.*

Regulatory documentation

The regulatory status of ZEPHEX® propellants has been addressed for the major world markets.

Firstly, both ZEPHEX®134a and ZEPHEX®227ea are produced, analysed and distributed in full accordance with the requirements of current Good Manufacturing Practice (cGMP).

Secondly, Mexichem Fluor can provide, under obligation of confidentiality, the information needed for inclusion in section 3.2.P.4 of the EU CTD for authorisation of medicinal products containing either ZEPHEX®134a or ZEPHEX®227ea.

Thirdly, a Drug Master File for ZEPHEX®134a has been filed with and reviewed by the US FDA. A Drug Master File for ZEPHEX®227ea has been filed with the US FDA.

ZEPHEX®134a and ZEPHEX®227ea are the only medical HFAs where the production and quality control facilities are routinely inspected by a regulatory agency. Even though inspection of Bulk Pharmaceutical Chemical manufacture is not mandatory within the European Union, Mexichem Fluor invites voluntary regular inspection of their manufacturing facilities by the UK Medicines and Healthcare Products Regulatory Agency (MHRA), to ensure that ZEPHEX® propellants remain at the leading edge of cGMP compliance.

Manufacturing

ZEPHEX® propellants are manufactured on state-of-the-art current Good Manufacturing Practice (cGMP) facilities, dedicated to the production of the pharmaceutical grades of these products.

ZEPHEX®134a is produced in the UK on Mexichem Fluor's Medical Products manufacturing complex at Runcorn. Mexichem Fluor's partner using a dedicated facility located in Arkansas, USA, manufactures ZEPHEX® 227ea. Mexichem Fluor retains responsibility for final testing and release of ZEPHEX®227ea even though a partner company manufactures it.

Both facilities were designed and constructed to the highest current Good Manufacturing Practice (cGMP) standards and both are scaled to meet global pharmaceutical demand for these propellants. Both plants have been designed and validated to accept technical grade feedstocks for purification into the pharmaceutical grade. The HFA 134a feedstock is supplied from Mexichem Fluor's major manufacturing plants in the USA and Japan whilst the HFA 227ea feedstock is supplied from its partner's manufacturing plants in the USA.

In addition to the storage capabilities at the manufacturing sites for ZEPHEX®134a and ZEPHEX®227ea, strategic security stocks of both products, where required by customers, can be held in Europe, Asia and the Americas.

Physical properties

Physical property	Units	ZEPHEX®134a	ZEPHEX®227ea
Chemical Name	-	1,1,1,2-Tetrafluoroethane	1,1,1,2,3,3,3-Heptafluoropropane
Chemical Formula	-	CH_2FCF_3	CF_3CHFCF_3
Molecular Weight	-	102.03	170.03
Boiling Point at 1 atm (1.013 bar)	°C °F	-26.07 -14.9	-16.45 2.39
Freezing Point	°C °F	-103.0 153.4	-131.2 -204.16
Critical Temperature	°C °F	101.03 213.9	102.79 217.02
Critical Pressure	bara lb/in^2 abs	40.56 588.3	2987.74 433.22
Critical Volume	m^3/kg ft^3/lb	1.97 x 10^{-3} 0.0316	1.72 x 10^{-3} 0.0276
Liquid Density at 25°C(77°F)	kg/m^3 lb/ft^3	1206.8 75.34	1387 86.59
Saturated vapour density at boiling point	kg/m^3 lb/ft^3	5.26 0.328	35.94 2.244
Liquid Cp at 25°C(77°F)	kJ/kg.K Btu/lb·°F	1.43 0.344	0.8769 0.209
Vapour Cp at 25°C (77°F) and 1 atm (1.013 bar)	kJ/kg.K Btu/lb·°F	0.8512 0.203	
Vapour Pressure at 25°C(77°F)	bara	6.653	4.543
Heat of Vaporization at Boiling Point	kJ/kg.K Btu/lb	216.7 93.2	132.02 56.76
Liquid Thermal Conductivity at 25°C(77°F)	W/m·K Btu/hr·ft°F	0.0824 0.0476	0.054 0.0312
Vapour Thermal Conductivity at 25°C(77°F) and 1 atm (1.013 bar)	W/m·K Btu/hr·ft°F	0.0144 0.00836	0.011 0.0064
Liquid Viscosity at 25°C(77°F)	mPa·a(cP)	0.199	0.240
Vapour Viscosity at 25°C(77°F) and 1 atm(1.013 bar)	mPa·s(cP)	0.013	0.010
Solubility of HFA in Water at 25°C(77°F)	wt%	1.1	
Solubility of Water in HFA at 25°C(77°F)	wt%	0.11	
Flammability Limits in Air at 1 atm (101.3 kPa or 1.012 bar)	vol%	none	none
Autoignition Temperature	°C °F	770 1418	>650 >1100
TSCA Inventory Status	-	Reported/included	
Toxicity AEL (8- and 12-hr TWA)	ppm(v/v)	1000	1000

For further information www.zephex.com

A comprehensive service

Mexichem Fluor provides a comprehensive range of valuable services to medical aerosol customers as an integral part of the ZEPHEX® package:

- A completely independent customer "Acceptance Testing" service, which can independently analyse shipments before they are dispatched to the customer, either as validation of the Mexichem Fluor Certificate of Analysis, or as full acceptance testing.
- Expert storage and transport engineering services, which provide assistance in specification and design of propellant storage facilities especially in the developing world and the tropics.
- Analytical support for the validation and commissioning of storage facilities.
- Expert technical support drawing on a long experience with HFAs.
- Support to establish and implement HFA analytical methods at customer facilities.

Mexichem Fluor aims to satisfy its customer needs at all stages of their product life cycles.

Quality guaranteed

Part of the Mexichem Fluor medical propellant philosophy is to continually reinforce product quality and current Good Manufacturing Practice (cGMP). At every level Mexichem Fluor introduces innovative ideas to ensure quality is guaranteed:

- Dedicated stainless steel containers are used for the supply of ZEPHEX® propellants, to eliminate the problems associated with conventional propellant packages common to the rest of the industry. Within this fleet of stainless steel containers their use is further dedicated to either ZEPHEX®134a or ZEPHEX®227ea.
- Once the sampling has been completed each package is security tagged and the unique tag number is included on the Certificate of Analysis. This ensures that ZEPHEX®134a and ZEPHEX®227ea customers not only know that the product has not been tampered with in transit, but also have auditable proof that the Certificate of Analysis refers to the content of a specific package.
- Each Certificate of Analysis is marked with a hologram. This ensures that ZEPHEX®134a and ZEPHEX®227ea customers know that they are dealing with the original documentation for the container of propellant. The hologram reinforces the original signatures.

Availability worldwide

Mexichem Fluor's medical propellants are available worldwide in dedicated stainless steel, security tagged packaging, either as 10kg, 60kg or 1000kg packages; or for bulk product requirements, ISO tanks with capacity up to 22,000kg.

Quality control

As part of a comprehensive quality control service, 11 different tests are performed to confirm the purity and quality of ZEPHEX®134a and ZEPHEX®227ea. In addition to using state-of-the-art 'Related Impurities Methods' for both products, a wide range of tests are performed, aimed at confirming that Mexichem Fluor's medical propellants meet specification requirements throughout the production process. These tests include determinations specifically to assure the quality of the propellant in the final package, such as non-volatile residue.

To ensure that the analytical techniques used to test Mexichem Fluor's medical propellants give reliable and consistent data, method validation studies have been performed in accordance with technically robust protocols. In addition to these initial studies, the transfer of methods into Quality Control laboratories is also validated. Future developments, and method implementations, would also be the subject of suitable validation programmes.

Not only are ZEPHEX®134a and ZEPHEX®227ea manufactured to the standards required by the pharmaceutical industry, but the test methods which are used are of an equivalent high standard.

Related impurities method

Confirmation of the purity of a product is only as good as the methodologies which are used to assess this most important of attributes. The more searching the method the greater the degree of confidence in the completeness of the result.

Recognising the need for such a method, a major research programme was undertaken within Mexichem Fluor to develop a technique, which resolves from HFA 134a and quantifies all impurities in all currently published specifications for pharmaceutical grade HFA 134a. The sensitivity of this method enables quantification of impurities to levels less than 1ppm w/w.

Building upon the techniques and skills developed during this research programme enabled a similarly powerful method to be developed for the assessment of HFA 227ea.

A choice of propellants

ZEPHEX®134a and ZEPHEX®227ea are low boiling, non-toxic and non-flammable hydrofluoroalkane (HFA) aerosol propellant gases. Both easily comply with the relevant industry toxicological specifications (IPACTI and II). Whilst chemically quite similar, there are sufficient differences to give them physical properties that are complementary. If a formulation chemist has access to both, most MDI formulation challenges should be surmountable by choosing the appropriate HFA or blend thereof.

Generally the chemist should first attempt to achieve a successful formulation using ZEPHEX®134a alone. If this proves not to be possible the chemist should then consider using the higher priced ZEPHEX®227ea either alone or in blend.

The key differing properties of the two propellants are summarised below.

Property	ZEPHEX® 134a	ZEPHEX® 227ea	Comments
Density (kg/m^3 at 25^{o}C)	1206.8	1387	Adjustment of liquid density valuable as a means of stabilising suspensions. Attempt to approach density of suspended solids. Use blending for fine tuning.
Solvency	Polar . Alcohol - like	Less polar. More CFC-like	Description of the relative solvencies of these two HFAs, and how they can be further tuned, is complex. Mexichem Fluor has a detailed predictive understanding of the solvency properties, which it is prepared to share with customers.
Boiling point (^{o}C)	-26.07	-16.45	Atomising power can be tuned by variation of the boiling point.

Mexichem Fluor is always ready to assist in getting an experimental programme underway and where there is a serious interest in ZEPHEX® it will supply an amount of propellant free of charge.