DAIKIN | Positively Innovative

SOLKANE™ 227 pharma and 134a pharma

PROPELLANTS

Daikin Industries, Ltd.

has acquired Solvay S.A.'s German-based pharma propellants and refrigerant business effective May 5th, 2015. Daikin will continue the production of HFA propellants 227 pharma and 134a pharma at the Frankfurt works under the Solkane™ trademark, to the same standards as before. Solkane™ is a trademark of the Solvay Group.

SOLKANE™ 227 pharma / SOLKANE™ 134a pharma

SOLKANE™ pharma – Special Pharmaceutical Grade

- Highest purity guaranteed by manufacture in dedicated facilities according to cGMP
- High-level quality control
- Specifically developed sophisticated analytical methods
- Worldwide Regulatory Affairs support in accordance with drug active substances

HFA Propellants for Use in Medical Sprays

SOLKANE™ 227 pharma and SOLKANE™ 134a pharma, also known as:

- HFA 227, HFC 227 or 1,1,1,2,3,3,3-heptafluoropropane and
- HFA 134a, HFC 134a or 1,1,1,2,-tetrafluoroethane

respectively, are used in medical sprays such as:

- MDIs (Metered Dose Inhalers, also called asthma sprays or pharmaceutical aerosols inhaled by the patient),
- nasal sprays
- foam sprays and
- other oral/topical sprays

to propel the active ingredient which is dispersed or solubilised in the **h**ydro**f**luoro**a**lkane (hereinafter referred to as HFA propellant).

Neither HFA 227 nor HFA 134a contain chlorine and they are thus non-ozone depleting. Furthermore, they are non-flammable and chemically inert. This makes them (from a safety and toxicological point of view) ideal candidates for use in medical products. Moreover, because HFA 227 and HFA 134a have thermodynamic and physical properties closely resembling the **c**hloro**f**luoro**c**arbons CFC 11, CFC 12 and CFC 114 traditionally used in medical sprays, they were proposed to replace these ozone-depleting CFCs currently being phased out under the terms of the Montreal Protocol.

Accordingly, HFA 227 and HFA 134a were developed in a special pharmaceutical grade as SOLKANE™ 227 pharma and SOLKANE™ 134a pharma specifically for use in medical products. They are of the highest quality as required for sensitive routes of administration – in the case of MDIs, via inhalation to the lung.

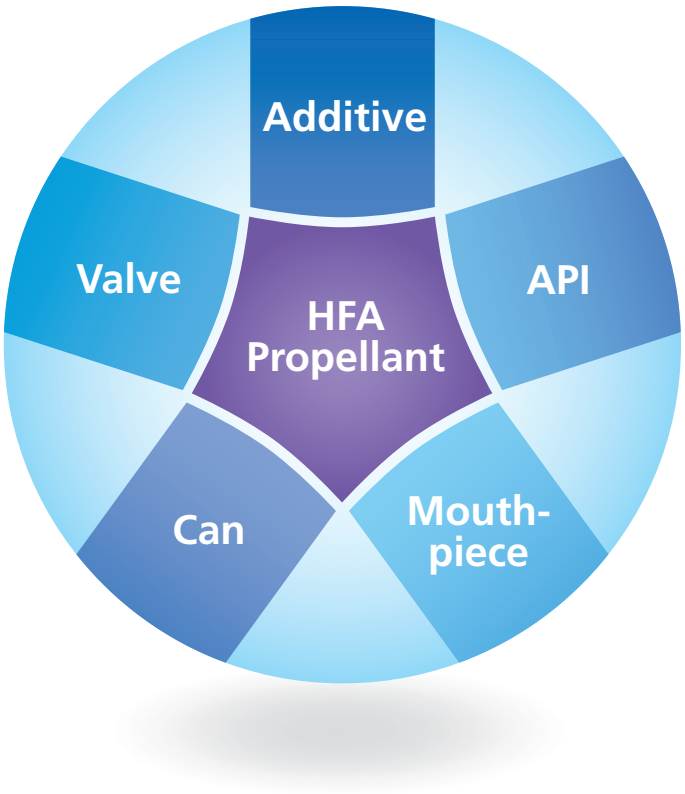


Fig. 1: The world of pressurized Metered Dose Inhalers

The main differences to ordinary "technical grade" SOLKANE™ 227 and SOLKANE™ 134a – predominantly used as refrigerants and fire extinguishing agents – are:

(i) the higher purity obtained by additional manufacturing processes specifically developed and applied to meet the stringent specifications set out for pharmaceutical grade products,

(ii) manufacturing in dedicated facilities according to the current good manufacturing practice guidelines,

(iii) high-level quality control using analytical methods specifically developed to screen more than 60 impurities in the propellants at levels below one part per million,

(iv) registration of the manufacturing processes and quality control systems according to the standards for drug active substances, although both HFA 227 and HFA 134a are classed as exipients.

SOLKANE™ pharma – HFA Propellants for Medical Sprays

Including
- MDIs (Metered Dose Inhalers) also known as pharmaceutical aerosols or asthma sprays for the treatment of asthma, COPD (Chronic Obstructive Pulmonary Disease) and respiratory infections
- nasal sprays for the treatment of allergic rhinitis
- foam sprays
- oral and topical sprays (e.g. nerve sensitisation, tooth vitality, pain relaxation)

to replace the fully halogenated ozone depleting chlorofluorocarbons

- CFC 11, CFC 12 and CFC 114

traditionally used in medical sprays, which are being phased out under the terms of the Montreal Protocol, by the non-ozone depleting hydrofluoroalkanes

- HFA 227, or blends thereof
- and HFA 134a.

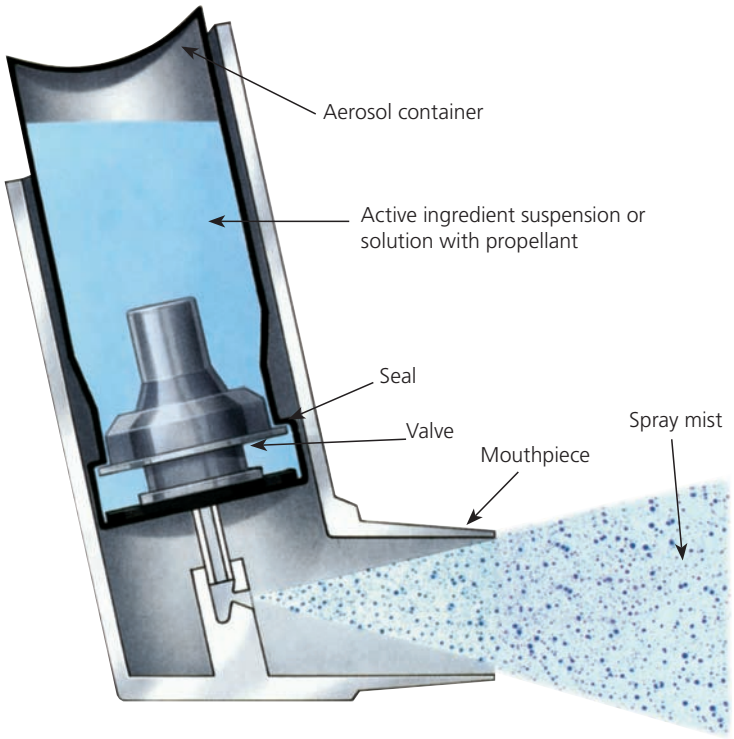


Fig. 2: Metered Dose Inhaler (MDI)

History of the Pharmaceutical Propellants HFA 227 and HFA 134a – IPACT I, IPACT II

When it was confirmed in the 1980s that fully halogenated CFCs harm the ozone layer in the upper stratosphere, extensive investigations were carried out to identify suitable CFC replacement components for various applications including MDIs.

In 1989, a consortium by the name of IPACT I (International Pharmaceutical Aerosol Consortium for Toxicity Testing) formed to investigate HFA 134a as a potential CFC replacement candidate for use in medical sprays. This was followed by IPACT II for HFA 227 in 1990. Both IPACT I and IPACT II comprise major pharmaceutical aerosol manufacturers sponsoring the extensive toxicological tests for HFA 227 and HFA 134a to confirm their use for medical products including MDIs.

The main studies – carried out from 1990 to 1993/4 and laid down in IPACT I/II dossiers submitted to all major countries for support of medical product applications containing HFA 227 and HFA 134a – were reviewed by the European Health Authorities (CPMP – Committee for Proprietary Medicinal Products) and received positive opinions as cited:

SOLKANE™ pharma – History of the Pharmaceutical Propellants HFA 227 and HFA 134a – IPACT I, IPACT II

1989/1990	Formation of two consortia: IPACT I for the toxicological testing of HFA 134a IPACT II for the toxicological testing of HFA 227
1990 – 1993/4	Main toxicological studies carried out with former Hoechst AG, later Solvay, now Daikin, as sole supplier of the pharmaceutical grade HFA 227
July 1994	CPMP positive opinion for HFA 134a with published specifications
September 1995	CPMP positive opinion for HFA 227 "at the specification applied for" for Hoechst, now Daikin-quality; specifications not disclosed
July 1998/April 2001	CPMP reviews of the SOLKANE™ 227 pharma DMFs/Amendments
Dec. 1998/June 2001	Final assessments and CPMP "approval" of all changes received with the final conclusion: **"HFA 227 produced at Frankfurt manufacturing site, SOLKANE™ 227 pharma, is a suitable alternative to CFCs currently used in the formulation of medicinal products, including metered dose inhalers for the treatment of asthma."** [6]

IPACT I International Pharmaceutical Aerosol Consortium for Toxicity Testing of HFA 134a
IPACT II International Pharmaceutical Aerosol Consortium for Toxicity Testing of HFA 227
CPMP Committee for Proprietary Medicinal Products

"The Committee considers that HFA 134a of the specified quality (in annex) could be a suitable alternative to the CFCs currently used in the formulation of medicinal products, incl. metered dose inhalers for the treatment of asthma." [1]. In this report, the specifications for HFA 134a were disclosed in the annex.

The positive opinion for HFA 227 was similar, but did not publish the specifications. Instead, it referred to "the specification as applied for" as follows: "The Committee considers that HFA 227 at the specification applied for is a suitable alternative to the CFCs currently used in the formulation of medicinal products, incl. metered dose inhalers for the treatment of asthma." [6].

Thus, both HFA 277 and HFA 134a can be used in medical products when they comply with the quality assessed by Health Authorities. In the case of HFA 227 it must comply with Daikin's quality standards because all the IPACT II toxicological studies were carried out with Daikin's (formerly Hoechst AG, Solvay) support as the sole supplier of HFA 227. Solvay (formerly Hoechst AG, now Daikin) submitted its Drug Master File (DMF) for the manufacture and quality control of HFA 227 as part of the IPACT II dossier.

In the case of HFA 134a, the quality must comply with the quality standards as disclosed in Europe by the CPMP as referred to above, or for the U.S. market as proposed by the U.S. Food and Drug Administration's Center for Drug Evaluation and Research (FDA CDER) October 1998 Draft Guidance for Industry on MDIs and DPIs (Dry Powder Inhaler)[3].

Since then, Solvay (now Daikin) has optimised its manufacturing processes and quality with many DMF updates, and finally initiated an independently coordinated CPMP review of all amendments. These were finally "approved" in December 1998 and June 2001 with the following conclusion:

Conclusion

The toxicological properties of HFA 227 were previously assessed to an adequate extent (CPMP/391/97).

Comparing the purity of SOLKANE™ 227 pharma with that of the Hoechst test batches used to perform the toxicity tests reported by IPACT II, it can be concluded that SOLKANE™ 227 pharma complies with the pharmaceutical grade specifications for this compound and that it contains less concentrations of the comparable impurities than the Hoechst tox test batches. [...]

Overall Conclusion

HFA 227 produced at Frankfurt manufacturing site, SOLKANE™ 227 pharma, is a suitable alternative to the CFCs currently used in the formulation of medicinal products, including metered dose inhalers for the treatment of asthma." [6]

The approved DMFs were subsequently submitted to all countries for customer support.

As such a review is unique in the case of HFA 227, Daikin is setting the standard for HFA 227 in the medical world.

In the case of SOLKANE™ 134a pharma, Solvay (now Daikin) submitted its Drug Master Files in Canada in 2001, in the USA in 2002, and to the rest of the world, including all European countries in 2003. Hereby Daikin fully complies with all specifications published by the CPMP [1, 4, 5] as mentioned above and the FDA [3].

Quality Control and Specifications

In the case of HFA 134a, two quality standards have already been published: one by the CPMP as mentioned before[1], and one proposed by the FDA in a draft guideline[3]; accordingly, the quality shall comply with these standards.

In Europe a Norflurane Monograph No. 2257 is available containing Daikins GC-MS (gas chromatography - mass spectrometry) and Non-Volatile Matter Methods. The quality of Daikins Solkane 134a pharma is equal to or even higher than proposed in the published monograph and fully complies with the published CPMP and FDA specifications for use in inhalation products. The latter specifications were developed on the results of the toxicity testing studies by IPACT I, mandatory for safety of the patients inhaling MDI propellant formulations. As a result, HFA 134a pharma specifications in the USA and Europe are still supplier related.

As seen from the table which lists all impurities mentioned in these standards, sophisticated analytical methods are required to identify and detect all impurities without interference from the others. Solvay (now Daikin) has developed a GC-MS method especially for this purpose which allows the control of each of the listed impurities at limits of detection (LODs) below 1 ppm (v/v).

Fig. 3: Cleaning cylinders prior to use for SOLKANE™ 134a pharma according to Standard Operating Procedures (SOPs) in the area designated for SOLKANE™ pharma products only

SOLKANE™ pharma – Impurities of HFA 134a Proposed by CPMP/FDA in Comparison to Daikin Quality

Volatile Related Substance	Limit (ppm)		Norflurane Production Batches
	FDA (October 98 draft guidance)	CPMP (July 94 press release)	typical values (ppm (m/m))
CFC 114a	≤ 25	≤ 1000(1)	n.d.
HCC 40	≤ 5	≤ 50	n.d.
HCFC 1122	≤ 5	–	< 0.4
HCFC 124	≤ 100	≤ 1000(1)	n.d.
HCFC 133a	≤ 5	≤ 5	n.d.
HCFC 22	≤ 50	≤ 1000(1)	n.d.
HCFC 31	≤ 5	≤ 5	n.d.
HFC 125	≤ 5	≤ 1000(1)	n.d.
HFC 134	≤ 1000	≤ 1000(1)	15
HFC 143a	≤ 10	≤ 1000(1)	n.d.
HFC 152a	≤ 300	≤ 1000(1)	n.d.
CFC 114	≤ 5	≤ 1000(1)	n.d.
HFC 1234yf	≤ 5	–	n.d.
HFC 1225ye	≤ 5	–	n.d.
HFC 1243zf	≤ 5	–	1
CFC 217ba	≤ 5	–	1
HFC 134a (assay)	≥ 99.9	≥ 99.8	> 99.99
CFC 115	≤ 5	≤ 1000(1)	n.d.
CFC 12	≤ 100	≤ 1000(1)	n.d.
HCFC 1122a	≤ 5	–	n.d.
HFC 245cb	≤ 5	≤ 1000(1)	n.d.
HFC 23	≤ 5	–	n.d.
HFC 32	≤ 5	–	n.d.
HFC 152	≤ 5	≤ 5	n.d.
HFC 1123	≤ 5	–	n.d.
FC 1318my-cis	≤ 5	–	n.d.
FC 1318my-trans	≤ 5	–	n.d.
HFC 1132	≤ 5	–	n.d.
HFC 1336mzz	≤ 5	–	n.d.
HCFC 123	≤ 5	≤ 1000(1)	n.d.
HCFC 123a	≤ 5	≤ 1000(1)	n.d.
HCFC 124a	≤ 5	≤ 1000(1)	n.d.
HCFC 132b	≤ 5	≤ 5	n.d.
HCFC 161	≤ 30	–	n.d.
HCFC 1121	≤ 5	–	n.d.
CFC 11	≤ 5	≤ 1000(1)	n.d.
CFC 12B1	≤ 5	–	n.d.
CFC 13	≤ 5	–	n.d.
CFC 113	≤ 5	–	n.d.
CFC 1112a	≤ 5	–	n.d.
Total unsaturates	≤ 5	≤ 5	1
Sum of others	≤ 50	≤ 50	n.d.
Individual unidentified impurities	≤ 5	–	n.d.
Total unidentified impurities	≤ 10	–	n.d.
Any other identified saturated impurity	≤ 5	–	n.d.
Total impurities	≤ 1000	–	17

(1) Not more than 1000 ppm alone or in combination; n.d.: not detected

Fig. 4: Comparison of the FDA draft proposal for impurity limits in pharmaceutical HFA 134a and CPMP specifications with the SOLKANE™ 134a pharma quality from six production batches

The Daikin specifications for SOLKANE™ 227 pharma and SOLKANE™ 134a pharma are listed as follows:

Daikin Specifications	SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
Contents	≥ 99.99 % vol.	≥ 99.9 % vol.
Identification	Complies with MS library	Complies with MS library
Water	≤ 10 µg/g	≤ 10 µg/g
Non-volatile Matter	≤ 20 ppm (m/m)	≤ 50 ppm (m/m)
Volatile Related Substances (Impurity Profile)	Described in the Daikin DMF for apaflurane (HFA 227)	Described in the Daikin DMF for norflurane (HFA 134a)
Acidity	≤ 0.1 µg/g (as HF)	≤ 0.1 µg/g (as HCl)

Fig. 5: Electronic bar code scanning of SOLKANE™ 134a pharma cylinders for identification and traceability

Fig. 6: Analytical laboratory of the Daikin Refrigerants Europe GmbH Frankfurt works for the routine quality control of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma

Manufacture of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma by Daikin

The production of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma adhere to the stringent good manufacturing practice guidelines and continuously updated quality standards. For example, the small steel cylinders are thoroughly inspected and flushed according to SOPs prior to filling, and an electronic bar code system is used which allows every consignment to be traced throughout the world.

Daikin's analytical laboratories are state-of-the-art and new analytical methods have been developed and validated for both SOLKANE™ 227 pharma and SOLKANE™ 134a pharma to meet the latest standards. Routine quality controls are carried out at levels of less than 1 ppm for more than 60 impurities in line with CPMP/FDA Guidelines.

Daikin has filed Drug Master Files for both products in all countries for cross-reference to support drug applications containing SOLKANE™ 227 pharma or SOLKANE™ 134a pharma.

The Frankfurt manufacturing site owned by Daikin can look back on more than 25 years of experience in the manufacture and supply of the propellants HFA 227 and HFA 134a for pharmaceutical aerosols and is considered as a center of competence in this field – providing support for its customers in all technical, analytical and regulatory areas.

Fig. 7: Visual inspection of dedicated SOLKANE™ 134a pharma cylinders as part of Daikin's quality control

Fig. 8: Well-trained Daikin personnel at the production site in Frankfurt: Daikin's key to success

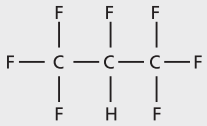
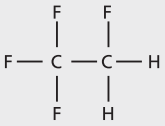
SOLKANE™ pharma – Daikin's Center of Competence

- Extensive experience in pharmaceutical propellants, supplying the pharmaceutical industry with HFAs since 1989
- New validated production facilities established in 1996/2001 in Frankfurt (Germany) meeting the highest quality standards according to cGMP (Current Good Manufacturing Practice)
- Highly qualified staff – continuous personnel training
- Traceability of each consignment via computer-controlled filling operations
- Manufacture of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma in highest purity using patented processes
- Product handling according to SOPs in SOLKANE™ pharma-designated areas only
- All equipment dedicated to SOLKANE™ pharma
- Availability of analytical GC-MS methods to screen more than 60 impurities at LODs < 1 ppm (in-house development)
- Active customer support for technical, analytical, and regulatory issues
- Maintenance of DMFs worldwide with active submission of variation procedures with CPMP/FDA for the establishment of specifications/analytical methods
- Active support of the EDQM/USP (European Directorate for the Quality of Medicines and Healthcare / US Pharmacopeial Convention) working groups and the HFA 227/134a consortia for the establishment of harmonized test methods and specifications

Fig. 9: Electronic bar code scanning of SOLKANE™ 227 pharma one tonne cylinders for identification and traceability

Physical Properties

Nomenclature

	SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
Structural Formula		
Molecular Formula	C_3HF_7	$C_2H_2F_4$
Chemical Name	1,1,1,2,3,3,3-Heptafluoropropane	1,1,1,2-Tetrafluoroethane
Chemical Family	Fluorinated Hydrocarbon	Fluorinated Hydrocarbon
ASHRAE* Nomenclature/ Laboratory Codes *American Society of Heating, Refrigerating and Air Conditioning Engineers	HFA 227, HFA 227ea HFC 227, HFC 227ea R 227, R 227ea	HFA 134a (**H**ydro**F**luoro**A**lkane) HFC 134a (**H**ydro**F**luoro**C**arbon) R 134a
International Nonproprietary Name (INN)	Apaflurane	Norflurane
Brand Name:	SOLKANE™ 227 pharma HFA 227 pharma	SOLKANE™ 134a pharma HFA 134a pharma

Description

	SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
Physical Form at 25 °C	Gaseous	Gaseous
Colour	Colourless	Colourless
Odor	Faint ethereal odor	Faint ethereal odor
Flammability	Non-flammable	Non-flammable
Toxicity	No appreciable toxic effect	No appreciable toxic effect
Ozone Depletion Potential (ODP)	Zero	Zero
Global Warming Potential (GWP)[9] related to CO_2 = 1.0 (100 years ITH*) *ITH = integrated time horizon	3,220	1,430
Atmospheric Lifetime[9]	34.2 years	14 years
Storage	Liquefied gas under pressure in steel cylinder	Liquefied gas under pressure in steel cylinder

Physical Data [SI Units]

		SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
Chemical Name		1,1,1,2,3,3,3-Heptafluoropropane	1,1,1,2-Tetrafluoroethane
Chemical Formula		$CF_3–CFH–CF_3$	$CF_3–CH_2F$
Molar Mass	g/mol	170.03	102.03
Boiling Point at 1.1013 bar[10]	°C	–16.5	–26.3
Freezing Point[10]	°C	–131	–101
Critical Data: HFA 227[12]; HFA 134a[11]			
Critical Temperature	°C	101.90	101.15
Critical Pressure	bar	29.52	40.64
Critical Density	kg/l	0.592	0.507
Critical Volume	l/kg	1.69	1.97

Temperature		0 °C	20 °C	40 °C	0 °C	20 °C	40 °C
Pressure of the Vapour	bar	1.96	3.90	7.03	2.93	5.72	10.16
Density of the Liquid	kg/dm³	1.482	1.408	1.322	1.296	1.226	1.148
Density of the Saturated Vapour	kg/dm³	0.0159	0.0310	0.0564	0.0145	0.0280	0.0504
Specific Heat Capacity of the Liquid	kJ/(kg·K)	1.096	1.148	1.222	1.337	1.402	1.505
Thermal Conductivity of the Liquid	mW/(m·K)	65.05	59.45	53.85	94.2	85.7	77.1
Dynamic Viscosity of the Liquid	mPa·s	0.346	0.267	0.210	0.273	0.211	0.162
Surface Tension of the Liquid	mN/m	9.31	6.96	4.80	11.49	8.69	6.06
Dielectric Constant Liquid Phase HFA 227[14]; HFA 134a[13]		4.6	4.1	3.6	11.3	9.8	8.3

Thermal Stability

	SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
Temperature Below Which no Evident Degradation Occurs	475 °C[15]	368 °C[16]

Refractive Index

		SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
$n_{20°C}$[17]	calculated value	1.2207	1.1746
$n_{20°C}$[18]	measured value	1.2207	n.d.

Physical Data [US/UK Units]

		SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
Chemical Name		1,1,1,2,3,3,3-Heptafluoropropane	1,1,1,2-Tetrafluoroethane
Chemical Formula		$CF_3–CFH–CF_3$	$CF_3–CH_2F$
Molar Mass	g/mol	170.03	102.03
Boiling Point at 1 atm[10]	°F	3.9	–15.3
Freezing Point[10]	°F	–203.8	–149.8
Critical Data: HFA 227[12]; HFA 134a[11]			
Critical Temperature	°F	215.4	214.1
Critical Pressure	psia	424.7	589.4
Critical Density	lb/ft³	38.77	31.65
Critical Volume	ft³/lb	0.026	0.032

Temperature		32 °F	68 °F	104 °F	32 °F	68 °F	104 °F
Pressure of the Vapour	psia	28.43	56.56	101.96	42.50	82.96	147.36
Density of the Liquid	lb/ft³	92.518	87.898	82.530	80.907	76.537	71.667
Density of the Saturated Vapour	lb/ft³	0.993	1.935	3.521	0.905	1.748	3.146
Specific Heat Capacity of the Liquid	Btu/lb °F	0.262	0.274	0.292	0.319	0.335	0.359
Thermal Conductivity of the Liquid	Btu/hr·ft °F	0.0346	0.0316	0.0287	0.0532	0.0482	0.0432
Dynamic Viscosity of the Liquid	lbf/ft²	$2.3E^{-04}$	$1.8E^{-04}$	$1.3E^{-04}$	$1.8E^{-04}$	$1.4E^{-04}$	$1.1E^{-04}$
Surface Tension of the Liquid	lbf/ft	$6.4E^{-04}$	$4.8E^{-04}$	$3.3E^{-04}$	$7.9E^{-04}$	$5.9E^{-04}$	$4.2E^{-04}$
Dielectric Constant Liquid Phase HFA 227[14]; HFA 134a[13]		4.6	4.1	3.6	11.3	9.8	8.3

Thermal Stability

	SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
Temperature Below Which no Evident Degradation Occurs	887 °F[15]	694 °F[16]

Refractive Index

		SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
$n_{20°C}$[17]	calculated value	1.2207	1.1746
$n_{20°C}$[18]	measured value	1.2207	n.d.

Vapour Table Wet Vapour Range SOLKANE™ 227 pharma [19] [SI Units]

t [°C]	p [bar]	rho´ [kg/dm³]	rho´´ [kg/m³]	v´ [dm³/kg]	v´´ [dm³/kg]	h´ [kJ/kg]	h´´ [kJ/kg]	r [kJ/kg]	s´ [kJ/(kg·K)]	s´´ [kJ/(kg·K)]
–60	0.10	1.652	0.94	0.605	1068.06	137.91	285.75	147.84	0.7447	1.4383
–55	0.13	1.641	1.27	0.610	786.40	142.68	288.86	146.18	0.7669	1.4370
–50	0.18	1.628	1.70	0.614	588.58	147.53	292.01	144.49	0.7888	1.4363
–45	0.25	1.616	2.24	0.619	447.16	152.45	295.18	142.74	0.8106	1.4362
–40	0.32	1.603	2.90	0.624	344.47	157.44	298.38	140.93	0.8322	1.4367
–35	0.42	1.589	3.72	0.629	268.78	162.52	301.59	139.07	0.8537	1.4377
–30	0.54	1.575	4.71	0.635	212.21	167.66	304.81	137.15	0.8751	1.4391
–25	0.69	1.561	5.90	0.641	169.39	172.87	308.05	135.17	0.8963	1.4410
–20	0.87	1.546	7.32	0.647	136.57	178.16	311.29	133.13	0.9173	1.4432
–15	1.08	1.531	9.00	0.653	111.14	183.52	314.54	131.02	0.9382	1.4458
–10	1.33	1.515	10.96	0.660	91.22	188.95	317.79	128.84	0.9590	1.4486
–5	1.62	1.499	13.25	0.667	75.46	194.44	321.03	126.59	0.9796	1.4517
0	1.96	1.482	15.90	0.675	62.88	200.00	324.27	124.27	1.0000	1.4550
5	2.35	1.465	18.96	0.683	52.74	205.64	327.50	121.86	1.0204	1.4585
10	2.80	1.446	22.47	0.691	44.51	211.33	330.71	119.38	1.0406	1.4622
15	3.32	1.428	26.48	0.700	37.77	217.10	333.91	116.81	1.0606	1.4660
20	3.90	1.408	31.05	0.710	32.21	222.93	337.08	114.14	1.0806	1.4700
25	4.56	1.388	36.24	0.720	27.59	228.84	340.22	111.38	1.1004	1.4740
30	5.29	1.367	42.15	0.732	23.73	234.82	343.32	108.50	1.1201	1.4780
35	6.11	1.345	48.84	0.744	20.48	240.87	346.37	105.50	1.1397	1.4821
40	7.03	1.322	56.43	0.756	17.72	247.01	349.37	102.36	1.1593	1.4861
45	8.04	1.298	65.05	0.771	15.37	253.24	352.30	99.06	1.1788	1.4901
50	9.16	1.272	74.85	0.786	13.36	259.58	355.15	95.57	1.1982	1.4940
55	10.40	1.246	86.03	0.803	11.62	266.02	357.90	91.87	1.2177	1.4977
60	11.75	1.217	98.85	0.822	10.12	272.60	360.52	87.92	1.2373	1.5012
65	13.24	1.187	113.64	0.843	8.80	279.34	362.99	83.65	1.2570	1.5044
70	14.87	1.154	130.87	0.867	7.64	286.26	365.25	78.99	1.2769	1.5071

Density in g/l

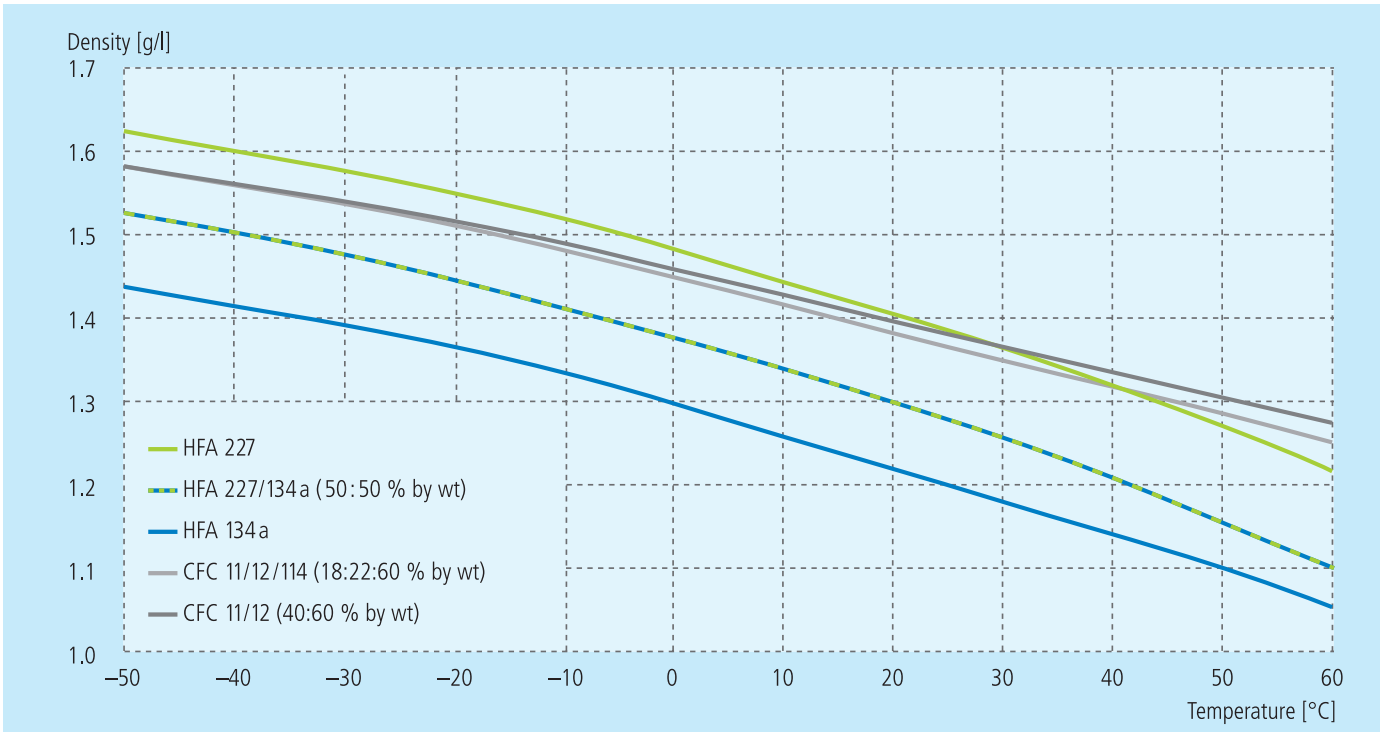


Fig. 10: Density of liquid of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma [19] including a 50:50 blend depending on temperature in comparison to CFC blends (CFC 11/12 as 40:60 and CFC 11/12/114 as 18:22:60) [20]

Vapour Table Wet Vapour Range SOLKANE™ 134a pharma [19] [SI Units]

t [°C]	p [bar]	rho´ [kg/dm³]	rho´´ [kg/m³]	v´ [dm³/kg]	v´´ [dm³/kg]	h´ [kJ/kg]	h´´ [kJ/kg]	r [kJ/kg]	s´ [kJ/(kg·K)]	s´´ [kJ/(kg·K)]
–60	0.16	1.475	0.93	0.678	1078.97	123.16	361.37	238.21	0.6859	1.8012
–55	0.22	1.461	1.25	0.684	802.33	129.49	364.53	235.04	0.7135	1.7904
–50	0.29	1.447	1.65	0.691	606.16	135.75	367.70	231.95	0.7409	1.7808
–45	0.39	1.433	2.15	0.698	464.67	141.98	370.86	228.89	0.7681	1.7722
–40	0.51	1.418	2.77	0.705	361.01	148.21	374.02	225.81	0.7950	1.7645
–35	0.66	1.404	3.52	0.712	283.94	154.47	377.17	222.70	0.8217	1.7576
–30	0.84	1.389	4.43	0.720	225.87	160.77	380.31	219.54	0.8480	1.7515
–25	1.06	1.374	5.51	0.728	181.55	167.13	383.42	216.29	0.8741	1.7460
–20	1.33	1.359	6.79	0.736	147.33	173.56	386.51	212.95	0.8999	1.7412
–15	1.64	1.343	8.29	0.744	120.61	180.06	389.56	209.51	0.9254	1.7369
–10	2.01	1.327	10.05	0.753	99.54	186.63	392.58	205.95	0.9505	1.7331
–5	2.43	1.311	12.08	0.763	82.76	193.27	395.56	202.29	0.9754	1.7297
0	2.93	1.295	14.43	0.772	69.28	200.00	398.49	198.49	1.0000	1.7267
5	3.50	1.278	17.14	0.782	58.35	206.79	401.37	194.58	1.0243	1.7241
10	4.15	1.261	20.23	0.793	49.43	213.65	404.19	190.54	1.0484	1.7217
15	4.88	1.243	23.76	0.804	42.08	220.58	406.94	186.35	1.0723	1.7196
20	5.72	1.225	27.78	0.816	35.99	227.59	409.61	182.02	1.0960	1.7176
25	6.65	1.206	32.35	0.829	30.91	234.67	412.20	177.53	1.1195	1.7158
30	7.70	1.187	37.53	0.842	26.65	241.83	414.69	172.86	1.1429	1.7141
35	8.87	1.167	43.40	0.857	23.04	249.08	417.07	168.00	1.1663	1.7124
40	10.17	1.146	50.06	0.872	19.98	256.43	419.33	162.90	1.1897	1.7107
45	11.60	1.125	57.62	0.889	17.36	263.90	421.44	157.54	1.2132	1.7090
50	13.18	1.102	66.21	0.908	15.10	271.52	423.38	151.86	1.2367	1.7071
55	14.92	1.078	76.03	0.928	13.15	279.32	425.12	145.80	1.2605	1.7049
60	16.82	1.053	87.28	0.950	11.46	287.33	426.63	139.30	1.2845	1.7024
65	18.90	1.026	100.27	0.975	9.97	295.60	427.84	132.24	1.3089	1.6994
70	21.17	0.996	115.42	1.004	8.66	304.18	428.70	124.52	1.3337	1.6957

Vapour Pressure in bar

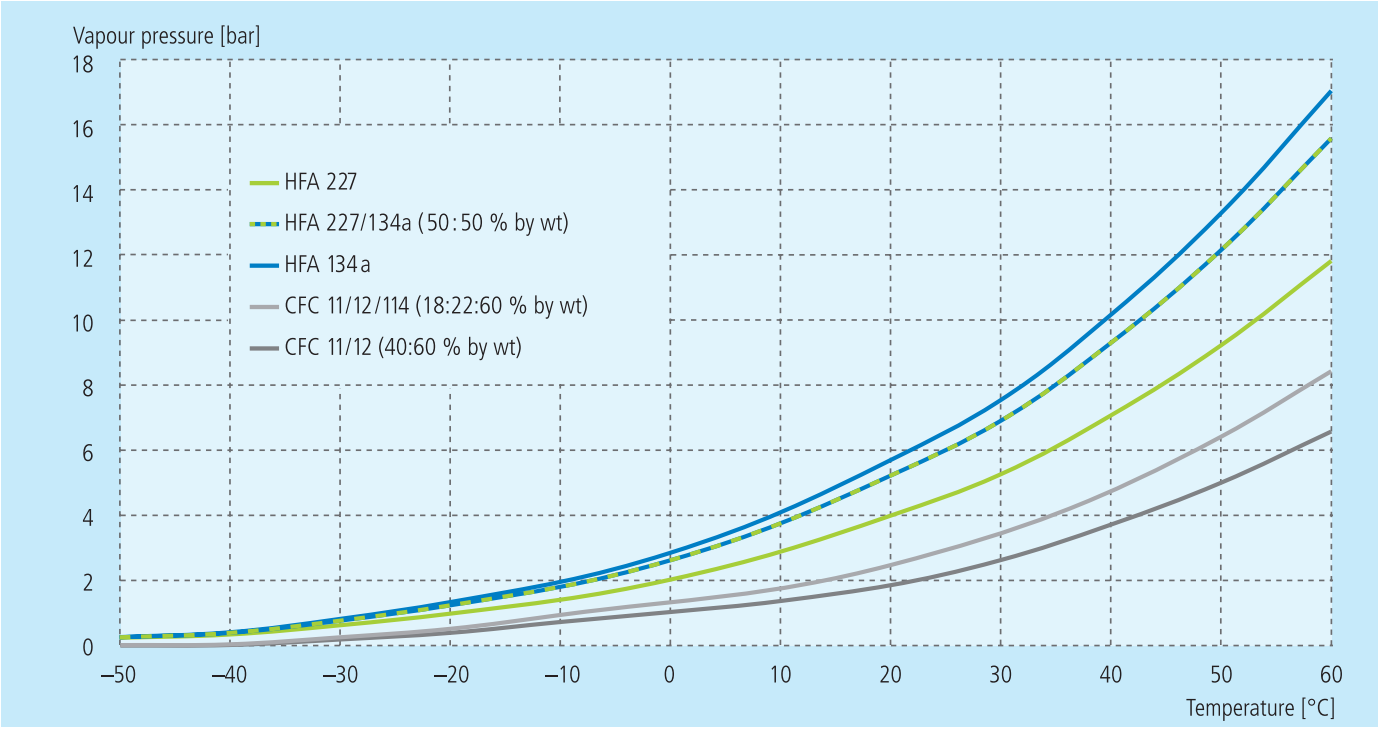


Fig. 11: Vapour pressure of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma [19] including a 50:50 blend depending on temperature in comparison to CFC blends (CFC 11/12 as 40:60 and CFC 11/12/114 as 18:22:60) [20]

Vapour Table Wet Vapour Range SOLKANE™ 227 pharma [19] [US/UK Units]

t [°F]	P [psia]	rho´ [lb/ft³]	rho´´ [lb/ft³]	v´ [ft³/lb]	v´´ [ft³/lb]	h´ [Btu/lb]	h´´ [Btu/lb]	r [Btu/lb]	s´ [Btu/R·lb]	s´´ [Btu/R·lb]
–76	1.45	103.13	0.06	0.0097	17.041	59.28	122.85	63.57	0.1778	0.3435
–67	1.89	102.44	0.08	0.0098	12.613	61.34	124.19	62.85	0.1831	0.3432
–58	2.61	101.63	0.11	0.0098	9.423	63.42	125.54	62.12	0.1884	0.3431
–49	3.63	100.88	0.14	0.0099	7.151	65.54	126.90	61.36	0.1936	0.3430
–40	4.64	100.07	0.18	0.0100	5.524	67.69	128.28	60.59	0.1988	0.3431
–31	6.09	99.20	0.23	0.0101	4.306	69.87	129.66	59.79	0.2039	0.3434
–22	7.83	98.32	0.29	0.0102	3.401	72.08	131.04	58.96	0.2090	0.3437
–13	10.01	97.45	0.37	0.0103	2.715	74.32	132.44	58.11	0.2141	0.3442
–4	12.62	96.51	0.46	0.0104	2.188	76.59	133.83	57.24	0.2191	0.3447
5	15.66	95.58	0.56	0.0105	1.780	78.90	135.23	56.33	0.2241	0.3453
14	19.29	94.58	0.68	0.0106	1.462	81.23	136.62	55.39	0.2291	0.3460
23	23.50	93.58	0.83	0.0107	1.209	83.59	138.02	54.42	0.2340	0.3467
32	28.43	92.52	0.99	0.0108	1.007	85.98	139.41	53.43	0.2388	0.3475
41	34.08	91.46	1.18	0.0109	0.845	88.41	140.80	52.39	0.2437	0.3484
50	40.61	90.27	1.40	0.0111	0.713	90.86	142.18	51.32	0.2485	0.3492
59	48.15	89.15	1.65	0.0112	0.605	93.34	143.55	50.22	0.2533	0.3501
68	56.56	87.90	1.94	0.0114	0.516	95.84	144.92	49.07	0.2581	0.3511
77	66.14	86.65	2.26	0.0115	0.442	98.38	146.27	47.88	0.2628	0.3521
86	76.73	85.34	2.63	0.0117	0.380	100.95	147.60	46.65	0.2675	0.3530
95	88.62	83.97	3.05	0.0119	0.328	103.55	148.91	45.36	0.2722	0.3540
104	101.96	82.53	3.52	0.0121	0.284	106.19	150.20	44.01	0.2769	0.3549
113	116.61	81.03	4.06	0.0123	0.246	108.87	151.46	42.59	0.2816	0.3559
122	132.85	79.41	4.67	0.0126	0.214	111.60	152.69	41.09	0.2862	0.3568
131	150.84	77.79	5.37	0.0129	0.186	114.37	153.87	39.50	0.2908	0.3577
140	170.42	75.97	6.17	0.0132	0.162	117.20	154.99	37.80	0.2955	0.3586
149	192.03	74.10	7.09	0.0135	0.141	120.09	156.06	35.96	0.3002	0.3593
158	215.67	72.04	8.17	0.0139	0.122	123.07	157.03	33.96	0.3050	0.3600

Density in lb/ft³

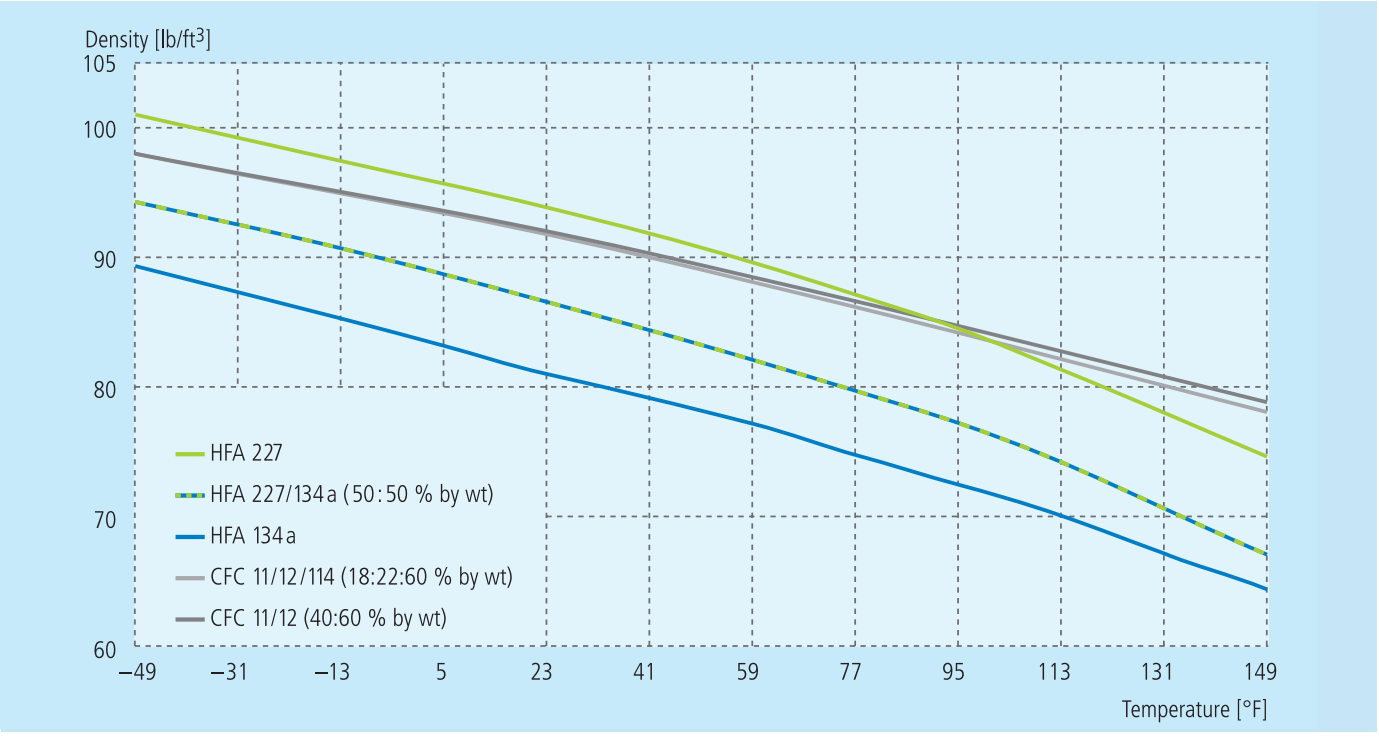


Fig. 12: Density of liquid SOLKANE™ 227 pharma and SOLKANE™ 134a pharma[19] including a 50:50 blend depending on temperature in comparison to CFC blends (CFC 11/12 as 40:60 and CFC 11/12/114 as 18:22:60)[20]

Vapour Table Wet Vapour Range SOLKANE™ 134a pharma [19] [US/UK Units]

t [°F]	p [psia]	rho´ [lb/ft³]	rho´´ [lb/ft³]	v´ [ft³/lb]	v´´ [ft³/lb]	h´ [Btu/lb]	h´´ [Btu/lb]	r [Btu/lb]	s´ [Btu/R·lb]	s´´ [Btu/R·lb]
–76	2.32	92.08	0.06	0.0109	17.224	52.96	155.39	102.43	0.1639	0.4305
–67	3.19	91.21	0.08	0.0110	12.814	55.68	156.75	101.07	0.1705	0.4279
–58	4.21	90.34	0.10	0.0111	9.708	58.37	158.11	99.74	0.1771	0.4256
–49	5.66	89.46	0.13	0.0112	7.450	61.05	159.47	98.42	0.1836	0.4236
–40	7.40	88.53	0.17	0.0113	5.783	63.73	160.83	97.10	0.1900	0.4217
–31	9.57	87.65	0.22	0.0114	4.551	66.42	162.18	95.76	0.1964	0.4201
–22	12.18	86.72	0.28	0.0115	3.616	69.13	163.53	94.40	0.2027	0.4186
–13	15.37	85.78	0.34	0.0117	2.907	71.87	164.87	93.00	0.2089	0.4173
–4	19.29	84.84	0.42	0.0118	2.359	74.63	166.20	91.57	0.2151	0.4161
5	23.79	83.84	0.52	0.0119	1.932	77.43	167.51	90.09	0.2212	0.4151
14	29.15	82.84	0.63	0.0121	1.594	80.25	168.81	88.56	0.2272	0.4142
23	35.24	81.85	0.75	0.0122	1.326	83.11	170.09	86.98	0.2331	0.4134
32	42.50	80.85	0.90	0.0124	1.110	86.00	171.35	85.35	0.2390	0.4127
41	50.76	79.79	1.07	0.0125	0.935	88.92	172.59	83.67	0.2448	0.4121
50	60.19	78.72	1.26	0.0127	0.792	91.87	173.80	81.93	0.2506	0.4115
59	70.78	77.60	1.48	0.0129	0.674	94.85	174.98	80.13	0.2563	0.4110
68	82.96	76.48	1.73	0.0131	0.577	97.86	176.13	78.27	0.2619	0.4105
77	96.45	75.29	2.02	0.0133	0.495	100.91	177.25	76.34	0.2676	0.4101
86	111.68	74.10	2.34	0.0135	0.427	103.99	178.32	74.33	0.2732	0.4097
95	128.65	72.86	2.71	0.0137	0.369	107.10	179.34	72.24	0.2787	0.4093
104	147.51	71.54	3.13	0.0140	0.320	110.26	180.31	70.05	0.2843	0.4089
113	168.25	70.23	3.60	0.0142	0.278	113.48	181.22	67.74	0.2900	0.4085
122	191.16	68.80	4.13	0.0145	0.242	116.75	182.05	65.30	0.2956	0.4080
131	216.40	67.30	4.75	0.0149	0.211	120.11	182.80	62.69	0.3013	0.4075
140	243.96	65.74	5.45	0.0152	0.184	123.55	183.45	59.90	0.3070	0.4069
149	274.13	64.05	6.26	0.0156	0.160	127.11	183.97	56.86	0.3128	0.4062
158	307.05	62.18	7.21	0.0161	0.139	130.80	184.34	53.54	0.3188	0.4053

Vapour Pressure in psia

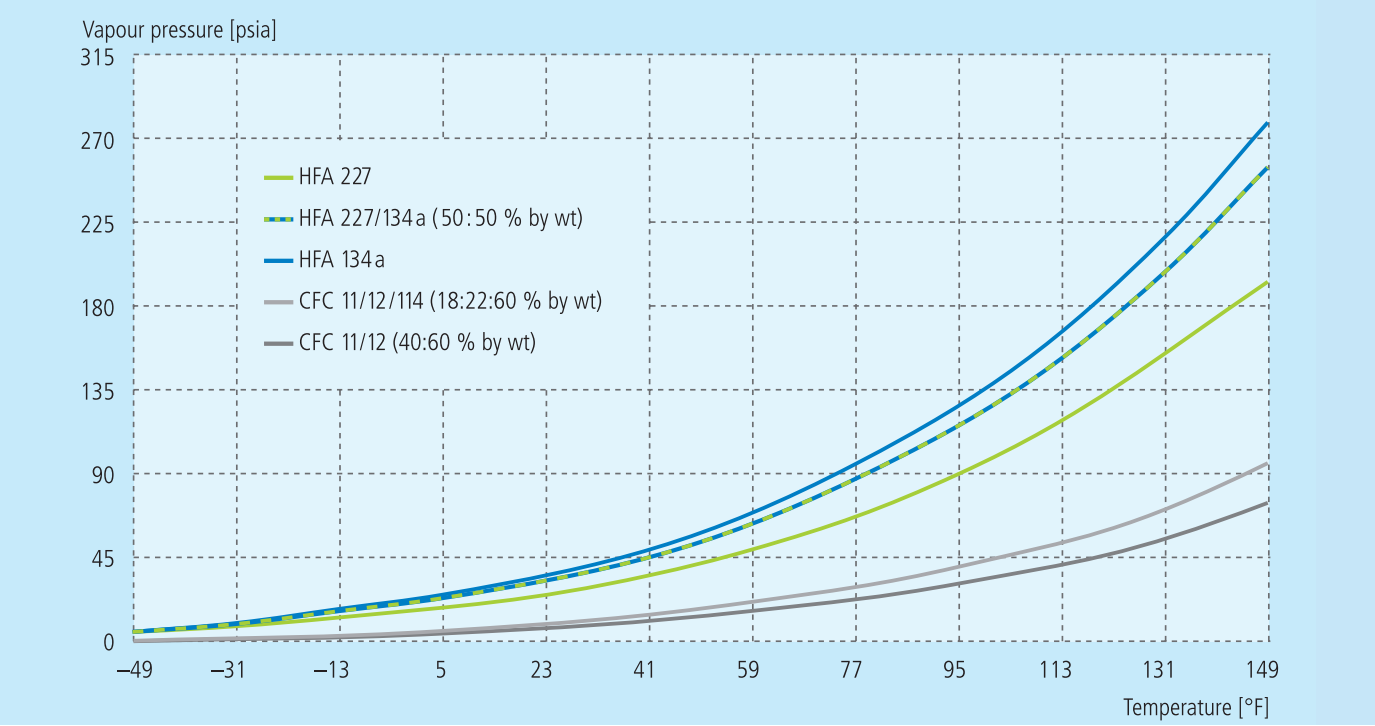


Fig. 13: Vapour pressure of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma [19] including a 50:50 blend depending on temperature in comparison to CFC blends (CFC 11/12 as 40:60 and CFC 11/12/114 as 18:22:60) [20]

Viscosity in mPa·s

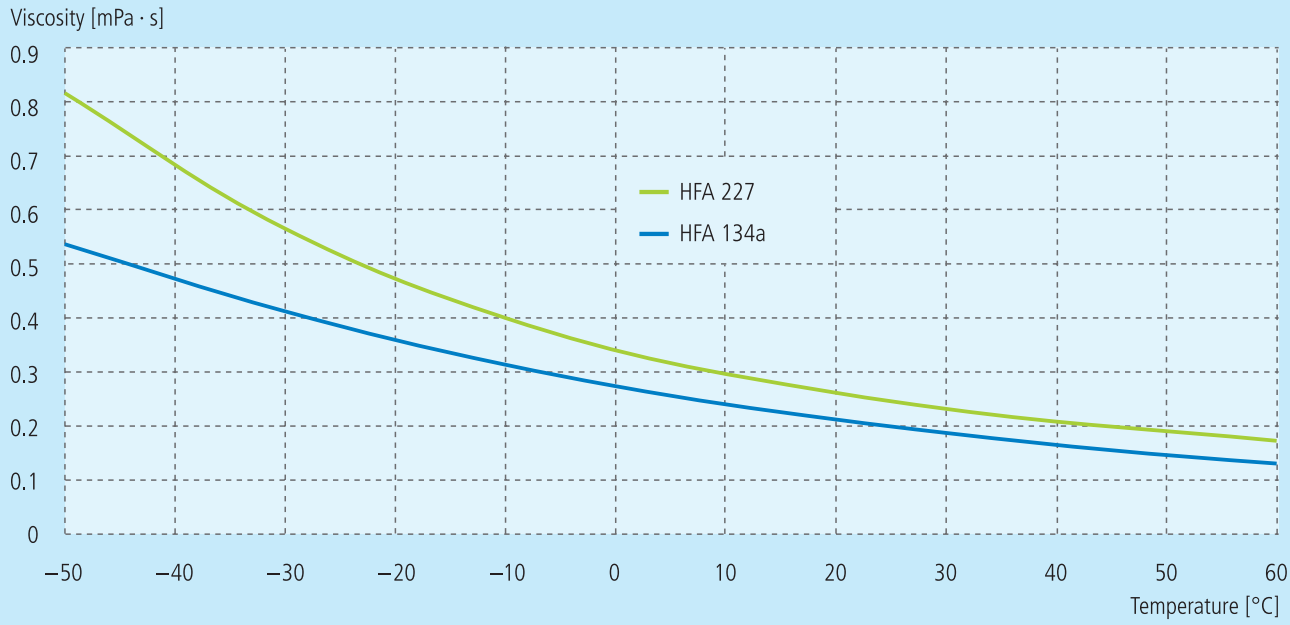


Fig. 14: Dynamic viscosity of liquid SOLKANE™ 227 pharma and SOLKANE™ 134a pharma depending on temperature[19]

Surface Tension in mN/m²

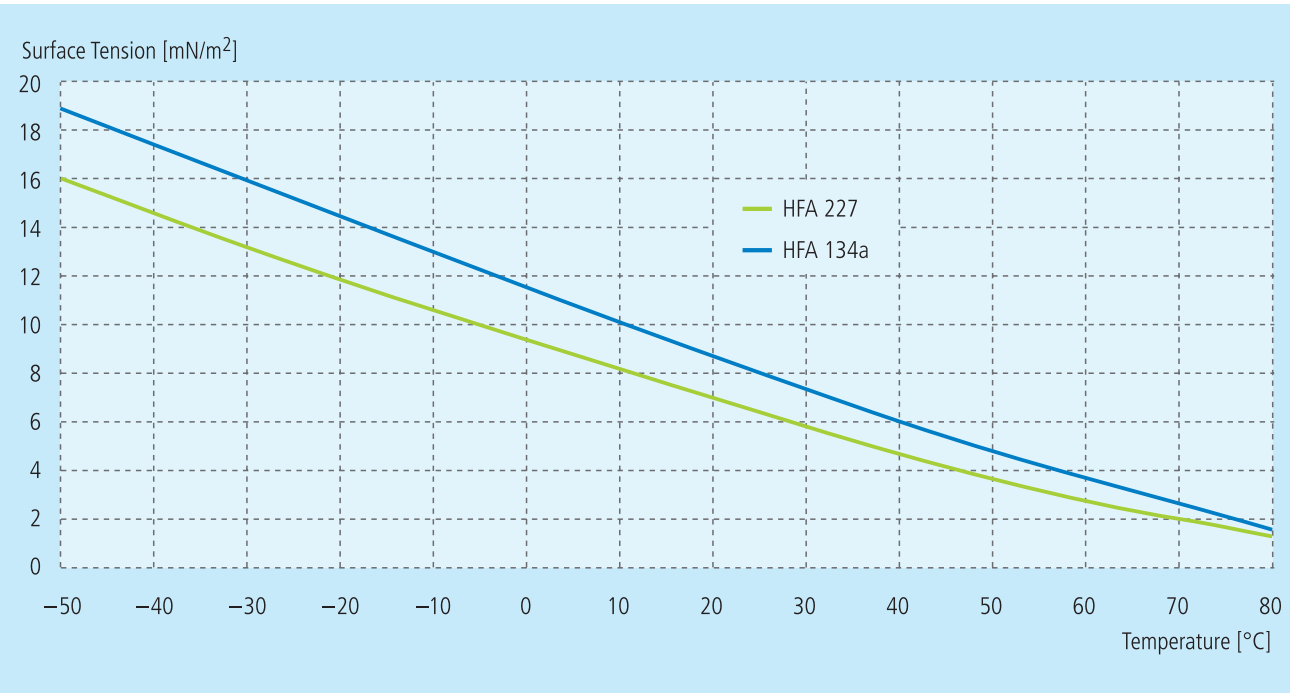


Fig. 15: Surface tension of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma depending on temperature[19]

Solubility Parameters / Characteristics

Solubility Values

Solubility in			SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
Water [21]	at 20 °C, 68 °F	ppm	58	193
Octanol [21]	at 20 °C, 68 °F	ppm	5.070	2.140
Solubility in HFA 227 and HFA 134a of				
Oxygen [22]	at atmospheric conditions: at 25 °C (77 °F), in liquid phase	g/kg	approx. 0.08	approx. 0.10
Nitrogen [23]	at atmospheric conditions: at 25 °C (77 °F), in liquid phase	g/kg	0.55	0.15
Water [21]	**Measured values at 25 °C in liquid phase**	g/kg	0.61	2.20
	Experimental results in liquid phase at 25 °C [24]	g/kg	n.d.	1.21
Ethanol [21]			Miscible	Miscible
Silicone Oil [25]	high viscosity oil (V1000)	ppm (wt.)	149	317
Silicone Oil [25]	low viscosity oil (V300)	ppm (wt.)	585	505

Solubility Characteristics

		SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
Dipole Moment measured value liquid phase	debye	0.93 [14]	2.058 [26]
Dipole Moment calculated value gas phase [14]	debye	1.46	n.d.
Octanol-Water-Coefficient [20]	log P_{ow}	2.05	1.06
Kauri-Butanol-Index		13 [21]	9.2 [27]
Solubility Parameter calculated value [19]		5.4	6.8

Solubility of Water

There is a notable difference in water solubility between HFA 227 and HFA 134a. As shown in Fig. 17, the moisture uptake of HFA 134a is six times higher compared to HFA 227 (measured values) due to its higher polarity. Therefore HFA 227 is preferred for formulations which might change due to water uptake during the MDI shelf life, e.g. for drugs such as sodium cromoglycate, cromoglycic acid, nedocromil sodium, nedocromil, ipratropium bromide, salbutamol sulfate, terbutaline hemisulfate or formoterol. In general, the HFAs are more polar than CFCs and thus more hygroscopic.

Dipole Moments [20]

HFA 134a	**2.06**
H_2O	1.85
Ethanol	1.68
HFA 227	**1.46**; (0,93) [14]
CFC 114	0.66
CFC 12	0.51
CFC 11	0.45

Water Solubility in HFA 134a

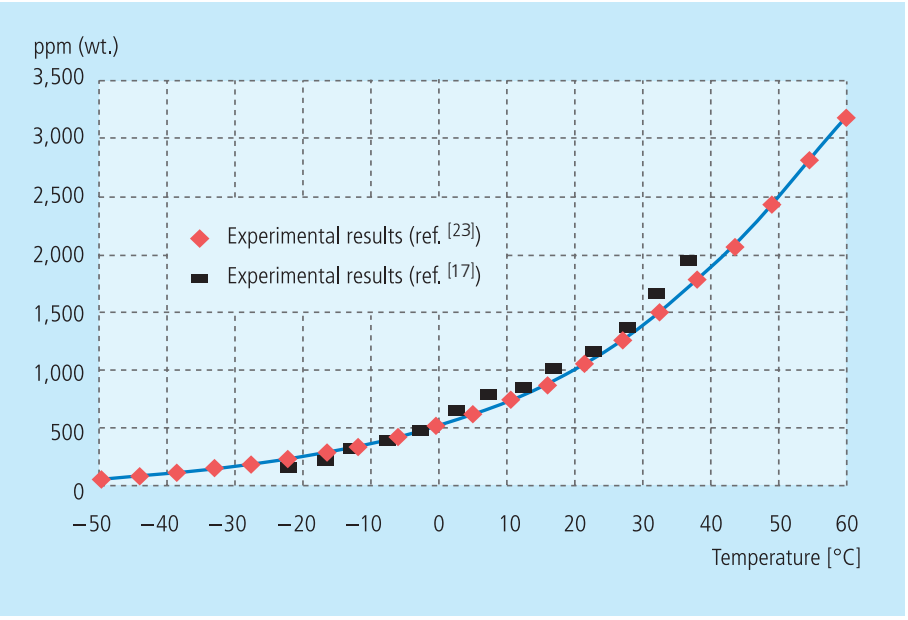


Fig. 16: Illustration of the experimental results for water solubility in HFA 134a in liquid phase [23, 17]

Moisture Uptake

Sources of Moisture Uptake in MDIs:

Due to partial pressure differences inside and outside of the MDI, moisture uptake takes place by diffusion.

Possible Effects of Moisture Uptake:

- Improves solubility of polar substances in the propellants
- Reduces the solubility of lipophile, hydrophobic substances
- Increases probability that sensitive substances become oxidised during shelf live
- Increases the corrosion risk of aluminium cans over the shelf life
- Agglomeration of suspended drug substances
- Influences the discharge behaviour of the active substances

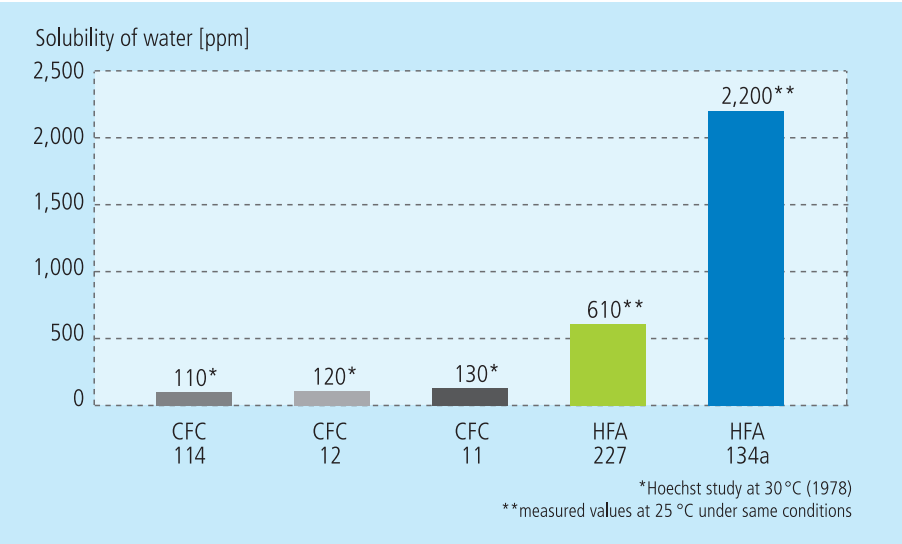


Fig. 17: Solubility of water in HFAs compared to CFCs

Solubility of Oxygen and Nitrogen

		SOLKANE™ 227 pharma Adsorption Number Q	SOLKANE™ 134a pharma Adsorption Number Q
Oxygen**			
Experimental results converted to atmospheric conditions* in the liquid phase [22]	g/kg	approx. 0.08	approx. 0.10
Experimental results converted to the conditions: partial pressure of O_2 = 1.0 bar, temperature 25 °C in the liquid phase	g/kg g/kg	approx. 0.36 [22] 0.21 [20]	approx. 0.70 [22] 0.34 [20]
Nitrogen**			
Experimental results converted by linear fitting to the atmospheric conditions* (see illustration below)	g/kg g/kg	n.d. 0.55 [20]	0.51 [23] 0.15 [20]
Experimental results at the conditions: partial pressure of N_2 = 1.0 bar, temperature 25 °C	g/kg g/kg	n.d. 0.69 [20]	0.63 [23] 0.19 [20]

* Atmospheric conditions: 25 °C, 1 bar, partial pressure of O_2 = 0.2 bar, partial pressure of N_2 = 0.8 bar
** All values are indicative values due to dependence on the filling factor (different distribution and equilibrium in gaseous and liquid phase)

Solubility of Nitrogen in HFA 134a

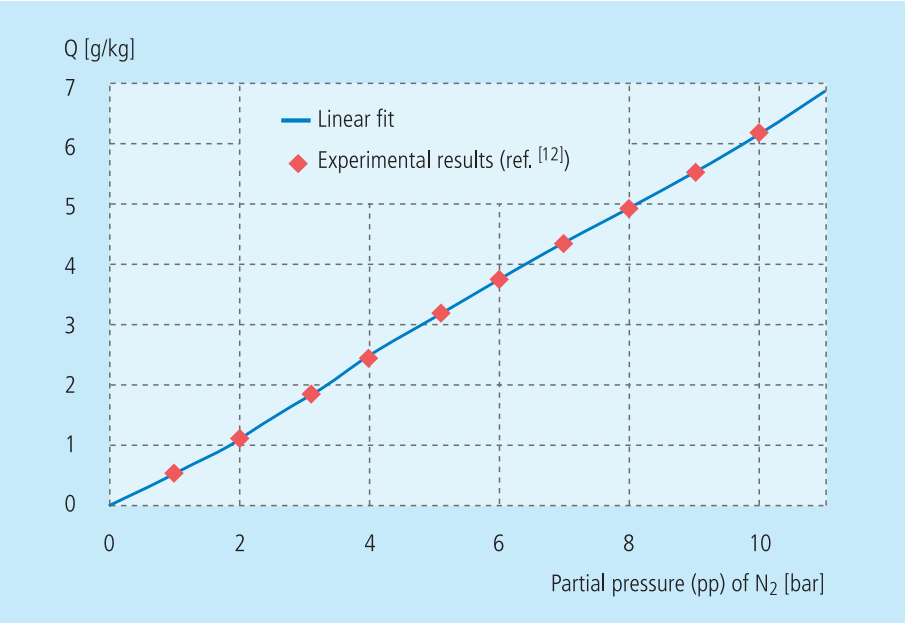


Fig. 18: Illustration of experimental results for solubility of N_2 in SOLKANE™ 134a pharma at 25 °C as a function of the partial pressure of nitrogen [23]

Solubility of Oxygen

During the manufacture of MDIs (metered dose inhalers), organic molecules (for example active substances e.g. sodium cromoglycate), tensides (e.g. oleic acid) and solubilisers (e.g. ethanol) are suspended or solubilised in HFA 227 and/or HFA 134a. Because organic molecules can be oxidised by oxygen, it is important for the manufacture of MDIs to know the solubility of oxygen in the propellant being used (such as SOLKANE™ 227 pharma and SOLKANE™ 134a pharma).

Gases like oxygen and nitrogen always form equilibria with pressurised liquefied gases in the gas phase and the liquid phase. These equilibria depend on temperature, filling factor and total pressure. Therefore, the figures show precisely determined values but only for one temperature, one filling factor and a specific amount of gas. The most important result is that there is a big difference between the oxygen and nitrogen content in the gas phase compared to the liquid phase.

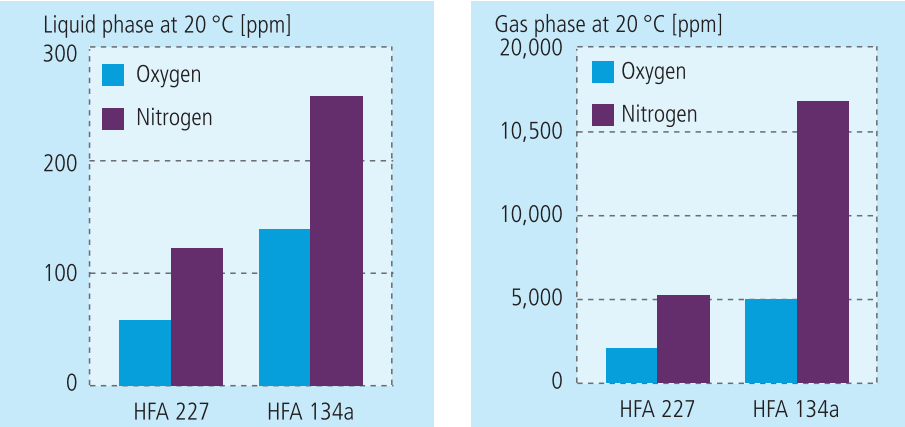


Fig. 19/20: Typical content of oxygen and nitrogen in SOLKANE™ 227 pharma and SOLKANE™ 134a pharma

Influence of Ethanol on HFA 227 and HFA 134a

Ethanol is widely used as an exipient in pharmaceutical formulations for MDIs because of its miscibility with the HFA propellant and the positive influence on the solubility of organic molecules due to the higher polarity. The addition of ethanol increases the polar/hydrophobic characteristics of a formulation. However, the addition of ethanol also increases the moisture uptake capacity of the MDI formulation which might have an impact on the shelf life. Furthermore, in the case of HFA 134a the addition of ethanol slightly reduces the pressure of the propellant.

Adding ethanol to a formulation also reduces the density of the mixture. The pressure versus mixture curves (Fig. 21) were derived from measured data (Hoechst 90/91).

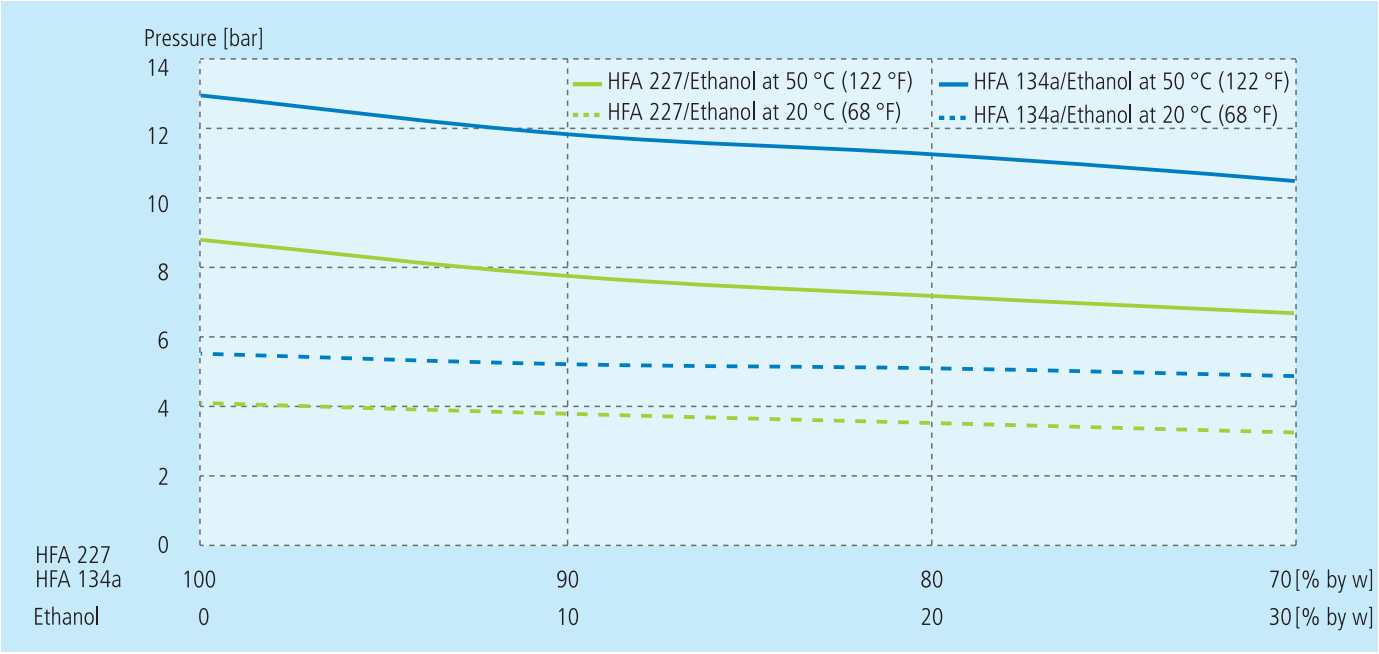


Fig. 21: Illustration of experimental results: pressure versus mixture curve of HFA 227 and HFA 134a with ethanol 99.8 % [wt.]

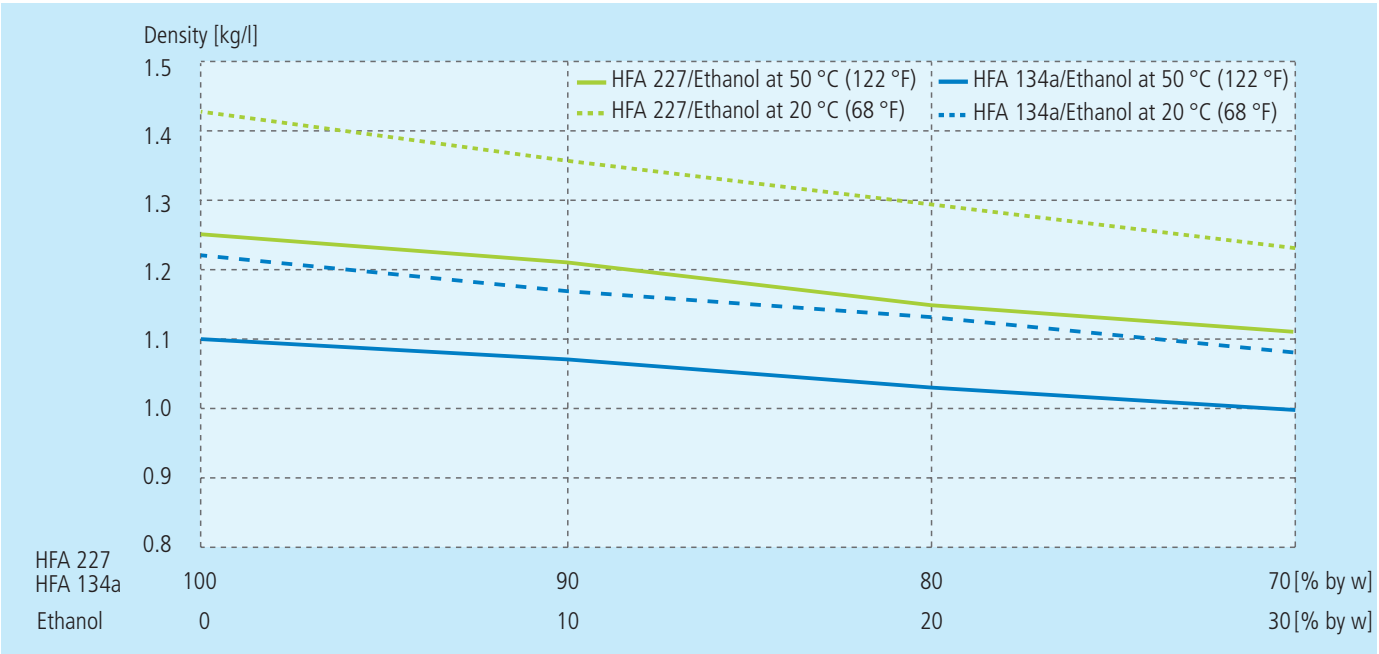


Fig. 22: Density of HFA 227 and HFA 134a in mixtures with ethanol 99.8 % at 20 °C and 50 °C

Chemical Behaviour

Material Compatibility

The material compatibility is tested to determine the specifications for materials suitable for the manufacture of pharmaceutical aerosols (e.g. composition of seals, metering chambers, gaskets, seats or stems).

Aspects analysed include changes in weight, volume, length, width, shore hardness, appearance (e.g. bubble formation), permeability of water and amount of extractables.

Classification of Materials for Use in MDIs

	HFA 227	HFA 227 and HFA 134a	HFA 134a
Sealing Material	CR, NBR, NR, EPDM (5), PVC (6), PCTFE (6), PA (6), PBT (6), PP (6)	PTFE (6), IRR	HNBR, POM, PET
General Use	NBR, IRR, POM	PTFE, PCTFE, PBT, PA, CR, NR	HNBR
Partly Use	HNBR (4)	FPM (1), PE (3)	NBR (2), EPDM (2)

(1) Strong swelling behaviour and presence of bubbles
(2) Permeability of water
(3) Bubble formation on material surface
(4) Strong swelling
(5) Recommended in the absence of mineral oil or alkyl benzene
(6) If technical specification designs allow, e.g. PTFE used in connection with metal joints

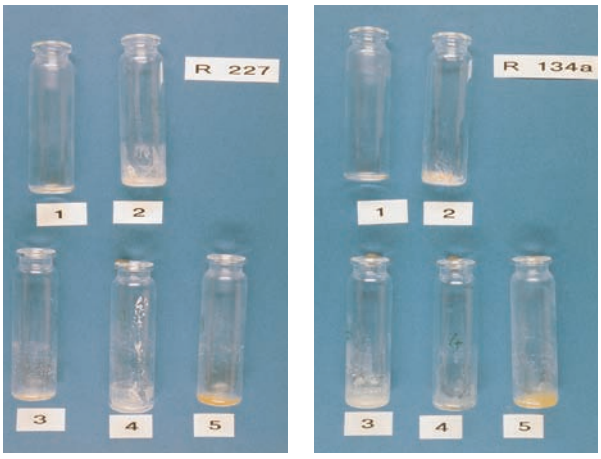


Fig. 23: Extractables from plastics:
1.) Polyethylene (PE),
2.) Polyamide 6.6 (PA),
3.) Polyacetal (POM),
4.) Poly(butylene terephthalate) (PBT), and
5.) Polypropylene (PP) after immersion in
HFA 227/5 wt % EtOH and HFA 134a/5 wt % EtOH
for 500 h at 80 °C;
Polytetrafluoroethylene (PTFE) produced zero extractables

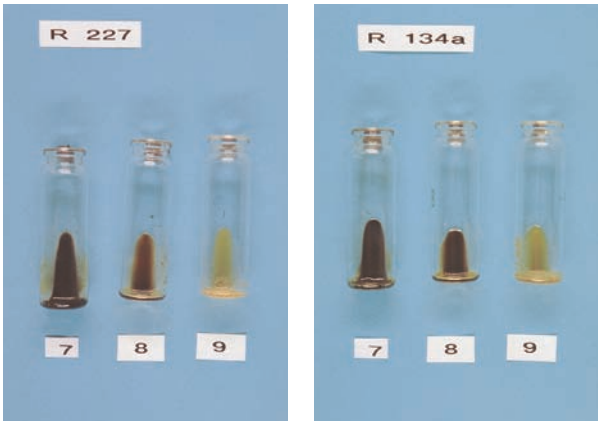


Fig. 24: Extractables from elastomers
7.) Acrylonitrile-butadiene rubber (NBR),
8.) Ethylene-propylene-diene rubber (EPDM) and
9.) Chloroprene rubber (CR)
after immersion in HFA 227/5 wt % EtOH and
HFA 134a/5 wt % EtOH for 500 h at 80 °C

Evaluation Criteria for Material Compatibility

There is a large range of elastomers and plastics on the market with different trade names which are made of similar raw materials and which are only distinguished by certain additives. These additives may affect the thermal and mechanical stability, the swelling properties, as well as the resistance to aging of elastomers and plastics.

When assessing complete systems, it is necessary to include the compability characteristics of the drug formulation.

			SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
1. Metals/Valves/Fittings/Vessels/Cans			HFA 227 and HFA 134a are compatible with mild steel, stainless steel, $CuBe_2$ membranes, brass and aluminium, black sheet iron, copper and galvanised sheet metal when the presence of water can be excluded. Water content might lead to an increase in corrosion, with the exception of 1.4551 V2A–steel.	
Material ISO 1629	Chemical Abbr.	Trade name	Compatibility	Compatibility
2. Elastomers [1]				
Chlorobutadiene rubber	CR	Neoprene®	+	+
Hydrated acrylonitrilene-butadiene rubber	HNBR	Perbunan® Bayprene® Tomac®	+	+
Natural rubber	NR	Dynaprene®	+	+
Butyl rubber	IIR	Europrene®	+	+
Fluorinated rubber	FPM	DAI-EL, Viton®, Fluorel® , Tecnoflon®	–	–
Acrylonitrile-butadiene rubber	NBR	Perbunan® N, Krynal®, Hycar®, Chemigum®	+	+
Ethylene-propylenediene rubber	EPDM	Nordel®	+	+
3. Plastics				
Polytetrafluoroethylene	PTFE	Polyflon, Hostaflon® TFM, Algoflon®	+	+
High density polyethylene	HDPE	Alathon®, Eltex®	o	o
Polyacetal	POM	Hostaform® C9021	+	+
Polyphenylene sulfide	PPS	Fortron®, Rylon®	*	+
Liquid crystal polymers	LCP	Vectra®	*	+
Polyester fibre	PET	Trevira®, Hostaplast®, Hostaphan®	*	+
Polyvinylchloride	PVC	Hostalit®, Solvin®	+	+
Polychlorotrifluoro ethylene	PCTFE	Neoflon	+	+
Polyamide	PA	Isonamid®	+	+
Polybutylene-terephtalate	PBT	Celanex® X5002, Valox®, Arnite®	+	+
Polypropylene	PP	Adell®, A-Fax®, Eltex P®, Hostalen®	+	+
Polystyrene	PS	Styron®	*	o

[1]According to ASTM D 1418-01

+ compatible / o borderline / – incompatible / *no information, tests required

Toxicological Profiles

Toxicological Profile of HFA 227

HFA 227 is a colourless gas with an ethereal odor at ambient temperature. It has a very low acute toxicity. No deaths occurred when rats and mice were exposed by inhalation once to 300,000 and 500,000 ppm respectively. Signs of narcosis were observed from 100,000 ppm.

HFA 227 released into the eyes of rabbits did not induce any sign of irritation. Long term exposure of the airways of different test species (rats, dogs) at experimentally high concentrations of HFA 227 caused no irritation nor any untoward effect on the integrity of the respiratory tract function.

HFA 227 can induce cardiac sensitisation in dogs at concentrations from 100,000 ppm (10% v/v) and higher after an exogenous epinephrine challenge.

In long term studies in which rats and dogs were exposed via inhalation to HFA 227 at concentrations up to 240,000 ppm (1 hour per day for 6 months), no treatment related effects of toxicological significance were observed.

Toxicity Test	HFA 227
Recommended workplace guide value [10]	1,000 ml/m³
Acute inhalation toxicity LC_{50}*	800,000 ppm [28]
Cardiac sensitisation LOAEL**	100,000 ppm [28]
Effects on: pulse, blood pressure, ECG, lung function [29] in human volunteers	No adverse effects after exposure levels up to 8,000 ppm
Reverse mutation assay	Non-mutagenic
Carcinogenicity	Non-carcinogenic
Teratogenicity	Non-teratogenic
Irritation of eyes, rabbit [10]	Non irritant
Degradation	Bio-transformed at very low rates to hexafluoroacetone trihydrate [30]

* LC_{50}, lethal concentration for 50 % of the population of rats, 4h exposure
** LOAEL: Lowest Observable Adverse Effect Level

In several fertility studies in male and female rats in which animals were exposed for 1 to 6 hours per day to HFA 227 concentrations up to 150,000 ppm, no effects of toxicological significance were observed when measured on the fertility and pregnancy index. Concentrations of up to 150,000 ppm HFA 227 had no embryotoxic nor fetotoxic effects in rats or rabbits. Similar concentrations had no significant effect on the development and behaviour of the offspring of exposed rats.

Different in vitro and in vivo mutagenicity tests were performed with HFA 227. No genotoxic potential was observed. The in vitro chromosomal aberration test performed on human lymphocytes showed effects that were considered to be related to oxygen deprivation in the test system.

When rats and mice were exposed by inhalation to concentrations of 0, 60,000, 120,000 and 240,000 ppm for 2 years at a regimen of 1 hour per day, no increased incidence of benign or malign neoplasms were observed when compared to controls.

Some alveolar histiocytosis was observed in the lungs of rats exposed to high doses of HFA 227. In view of its normal incidence in this strain of animals and its only very slightly increased severity compared to controls, this effect was considered of no biological significance.

In human volunteers exposed to concentrations up to 8,000 ppm for one hour, no treatment related effects on cardiac performance, pulse rate, blood pressure and lung function were observed when compared to air control and CFC-12 reference conditions.

Pharmacokinetic parameters indicated that blood levels of HFA 227 increased in an exposure related pattern. In males, blood levels were higher than in females.

HFA 227 showed a biphasic elimination from the body after exposure. (mean T1/2: approx. 6.5 minutes and 44.5 minutes). These values appeared to be independent of the exposure concentration.

Acute toxicity to aquatic organisms is very low (LC_0 (lethal concentration to 0% of test organisms) fish = or > 30 mg/l; EC_0 (effective concentration to 0% of test organisms) bacterial activity ≥ 173 mg/l). Although no significant biodegradation has been observed, the high volatility and low bio-accumulation potency makes any impact of heptafluoropropane on the aquatic environment highly unlikely.

Toxicological Profile of HFA 134a

HFA 134a is a non-flammable, colourless gas with a faint ethereal odor.

HFA 134a has a very low order of acute toxicity. Concentrations over 700,000 ppm in inhaled air are required to produce lethal effects. The symptoms of acute intoxication are characterised by central nervous system effects due to narcotic properties seen only at extremely high exposure concentrations.

When HFA 134a is in contact with cutaneous or ocular mucosal membranes it causes slight irritation possibly due to evaporation. It does not sensitise the skin.

HFA 134a can induce cardiac sensitisation in dogs at levels of 80,000 ppm (8% v/v) and higher following exogenous epinephrine challenge.

The chronic toxicity of HFA 134a was studied in rats at inhalation exposure levels up to 50,000 ppm. No significant toxicological effects were observed in these studies.

Toxicity Test	HFA 134a
Recommended workplace guide value [8]	1,000 ml/m³
Acute inhalation toxicity LC_{50}*	500,000 ppm [31]
Cardiac sensitisation LOAEL**	80,000 ppm [32]
Effects on: pulse, blood pressure, ECG, lung function [29] in human volunteers	No adverse effects after exposure levels up to 8,000 ppm
Reverse mutation assay	Non-mutagenic
Carcinogenicity	Non-carcinogenic
Teratogenicity	Non-teratogenic
Irritation of eyes, rabbit [10]	Slightly irritant
Degradation	Degradation in troposphere to trifluoroacetic, formic and hydrofluoric acid and carbon dioxide [29]

* LC_{50}, lethal concentration for 50 % of the population of rats, 4h exposure
** LOAEL: Lowest Observable Adverse Effect Level

HFA 134a showed no adverse effects on fertility in mice. It was not teratogenic in rats or rabbits. Only non-specific effects on fetal maturation, in the form of delayed fetal ossification in rats were observed at 50,000 ppm and above.

HFA 134a was not genotoxic in vitro or in vivo as shown in a large variety of studies, including all important end points.

In a limited study in rats involving daily oral administration of 300 mg/kg body weight HFA 134a dissolved in corn oil over a period of 1 year, and a 16 month post-treatment observation phase, no tumorigenic effects were seen.

In a two year inhalation study with exposures up to 50,000 ppm, HFA 134a only produced some benign changes in the testes of rats exposed to the highest concentrations. These changes are considered of limited relevance to humans.

In human volunteers exposed to concentrations up to 8,000 ppm for one hour, no treatment related effects on cardiac performance, pulse rate, blood pressure and lung function were observed when compared to air control and CFC-12 reference conditions.

Pharmacokinetic parameters indicated that blood levels of HFA 134a increased in an exposure related pattern. In males, blood levels were higher than in females. HFA 134a showed biphasic elimination from the body after the end of exposure. (T1/2: approx. 10 minutes and 43 minutes). These values appeared to be independent of the exposure concentration.

Acute toxicity to aquatic organisms is very low. Although no significant biodegradation has been observed, the high volatility and low bio-accumulation potency makes any impact on the aquatic environment highly unlikely.

Instructions

Safety Instructions

SOLKANE™ 227 pharma and SOLKANE™ 134a pharma are liquefied compressed gases.

According to pressure vessel regulations, compressed gases are substances whose vapour pressure at 50 °C is above 3 bar. In line with the regulations governing pressure vessels, these may only be transferred to approved and labelled gas-tight gas cylinders or containers.

Recommended Safety Procedure

HFA 227 and HFA 134a are non-flammable gases. But, wherever they are handled, there must be no open flames or heat sources (e.g. hot metallic surfaces) or reactive products. The propellants can decompose and the decomposition products are corrosive, irritate the mucous membranes and are poisonous when inhaled.

The decomposition compound, hydrogen fluoride, is highly toxic. However, it is easily recognised by its odor. Even small amounts, below the danger limit for humans, are noticeable in the ambient air. Also, the decomposition product vapours should be prevented from contacting hot spots and electric arcs (welding). Containers that have been exposed to fire should not be approached until sufficiently cooled (e.g. by large quantities of water).

HFA 227 and HFA 134a should only be used with the equipment and materials which are compatible with the products. Contact with alkaline and alkaline-earth metals may provoke violent reactions or explosions.

Storage and work areas must be well ventilated. In particular, ventilation must be effective at ground level because the propellant vapour is heavier than air and displaces available oxygen.

Recommended Working Conditions

When inhaled at high concentrations (for inhalation limits see page 28), there is a danger of narcosis, cardiac arrhythmia or asphyxia through lack of oxygen. Therefore, all products should be handled in a ventilated, cool area. An important precondition is strict adherence to the threshold limit value (TLV).

Respiratory Protection:

- Minimal need if the local exhaust ventilation is adequate
- Self-contained breathing apparatus should be used when insufficient oxygen is present (large uncontrolled emissions) and in all circumstances when the mask and cartridge do not give adequate protection
- Use only respiratory protection that conforms to international and/or national standards

HFA 227 and HFA 134a as vapours have little or no effect on the skin or eyes. To avoid the cold irritation and frostbite from exposure to the liquid propellants, certain precautions have to be followed during handling. Skin frequently exposed to the propellant can become dry and chapped and there is a risk of developing chronic dermatitis.

Severe eye irritation, watering, redness and swelling of the eyelids, burns (frostbite) can occur as a result of contact with liquefied propellant.

Flammability

HFA 227 and HFA 134a are non-flammable gases and do not form explosive mixtures with air at any mixing ratio under ambient temperature and atmospheric pressure. However, all propellants containing hydrogen may form explosive mixtures with air under certain conditions.

HFA 134a vapour may form explosive mixtures with air under increased pressure. At atmospheric pressure, an HFA 134a pharma vapour/air mixture is not explosive at temperatures below 280 °C [33]. The pressure limit for the formation of explosive mixtures in air is dependent on the temperature.

During leak detection or pressure testing, compressed gas must never be used with propellants which contain hydrogen.

SOLKANE™ 227 pharma and SOLKANE™ 134a pharma

- **Hazardous Decomposition Products:**
  Hydrogen fluoride, fluorophosgene (HFA 227), carbon monoxide (HFA 134a)
- **Packaging Material:**
  Ordinary steel, aluminium
- **Flammability Limits in Air at Normal Conditions:**
  None

Skin Protection:

- Handle only with impervious apron/ boots if there is a risk of splashing
- Gloves, overalls and boots should be double layered (protection against cold)

Hand Protection:

- Protective gloves (recommended material for HFA 227 and HFA 134a is polyvinylalcohol)

Eye Protection:

- Wear protective goggles for all industrial operations
- If risk of splashing: chemical-proof goggles/face shield are required

Handling and Storage Instructions

SOLKANE™ 227 pharma (HFA 227) and SOLKANE™ 134a pharma (HFA 134a) are liquefied compressed gases.

According to pressure vessel regulations, compressed gases are substances whose vapour pressure at 50 °C is above 3 bar. In line with the regulations governing pressure vessels these may only be transferred to approved and labelled gas-tight gas cylinders or containers. HFA 227 and HFA 134a are non-flammable gases. But, wherever they are handled, there must be no open flames or heat sources (e.g. hot metallic surfaces) or reactive products.

An important precondition is strict adherence to the threshold limit value (TLV).

Handling

Be sure to close all cylinder valves when not in use. The valves of empty cylinders should also be closed.

Ensure that gas cylinders are transported so that they do not tip, fall or roll. Gas cylinders should be secured to the cylinder trucks or carts. Regulators should be removed and valve protection caps should be secured in place before moving cylinders.

Also, cylinder valves should be closed before moving cylinders.

Appropriate lifting devices, such as cradles or nets, must be used when using a crane, hoist or derrick to transport gas cylinders. Do not use magnets or slings to lift gas cylinders. Do not use the valve protection cap to lift a gas cylinder.

It is necessary to take precautions to prevent gas cylinders being dropped or striking each other or other objects. Dropping or striking may damage the cylinder valve, which could turn the cylinder into a dangerous torpedo with the potential to destroy property and/or injure personnel.

Storage

Gas cylinders should be properly secured at all times to prevent tipping, falling or rolling. They can be secured with straps or chains connected to a wall bracket or other fixed surface, or by using a cylinder stand. **Store cylinders in a cool, dry, well-ventilated, fire-resistant area in accordance with local regulations.**

A cylinder storage area should be located in an area where the cylinders will not be knocked over or damaged by falling objects. When a cylinder is not being used, the valve should be closed and the valve protector secured in place.

Inspection

Gas cylinders should be visually inspected to ensure that they are in a safe condition. If necessary, a cylinder can be tested ultrasonically for hidden defects. Leaking regulators, cylinder valves or other equipment should be taken out of service. A cylinder's contents should be identified at all times. Cylinder status should also be identified; for example, whether the cylinder is full, empty or in service.

Emptying

The safest and best way to empty larger amounts of HFAs from a container, e.g. one tonne cylinder, is to use an oil-free pump.

MSDS

Consult the appropriate MSDS for detailed information on the chemical contained in the gas cylinder. Specific chemical handling and storage precautions will be outlined in the MSDS. The MSDS will also have specifications for appropriate personal protective equipment for worker protection. [31]

Container Closure System

Packaging

Supply of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma

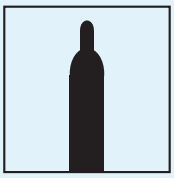
Global deliveries of SOLKANE™ 227 pharma grades and SOLKANE™ 134a pharma grades take place using dedicated ISO tank containers in quantities of 15,000 to 19,000 kg. Both SOLKANE™ pharma qualities are also available in 10 l, 60 l or 900 l steel cylinders. All our cylinders have an additional safety device, which prevents the cylinders from accidental backflow of the material.

Applied Tests

All Daikin Refrigerants Europe GmbH pressure containers (steel cylinders, ISO containers) are tested by the local authority before they are released for use. Steel cylinders have to be re-certified every ten years.

Fig. 25: ISO Tank Container for supply of Solkane propellants

Returnable Cylinders

	Unit			
SOLKANE™ 227 pharma	**kg/lb**	**12/26**	**70/154**	**1,050/2,314**
SOLKANE™ 134a pharma	**kg/lb**	**10/22**	**60/132**	**900/1,984**
Capacity approx.	l	10	61	910
Height incl. protection cap approx.	cm	100	106	–
Height excl. protection cap approx.	cm	81	92.5	–
Length approx.	cm	–	–	223
Diameter across beads approx.	cm	14	32	86
Tare weight approx.	kg	13	30	500 – 550
Test pressure	bar (abs)	300	43	44

ISO Tank Containers

ISO Tank Container

SOLKANE™ 227 pharma: approx. 17,000 kg/37,478 lb

SOLKANE™ 134a pharma: approx. 16,500 kg/36,333 lb

Classification and Transport Information

	SOLKANE™ 227 pharma	SOLKANE™ 134a pharma
Chemical Name	1,1,1,2,3,3,3,-Heptafluoropropane	1,1,1,2-Tetrafluoroethane
Chemical Formula	$CF_3–CFH–CF_3$	$CF_3–CH_2F$
CAS-No.	431-89-0	811-97-2
EG-No. (EINSEC)	207-079-2	212-377-0
UN No.	3296	3159
Hazardous good Label	Compressed gas, non-flammable, Class 2, Figure 2	Compressed gas, non-flammable Class 2, Figure 2
GHS-Label	Gas cylinder, GHS04	Gas cylinder, GHS04

International Standards for Valves, Connectors and Adapters

Cylinders for SOLKANE™ 227 pharma or SOLKANE™ 134a pharma are equipped with a Y-valve including a dip tube for product withdrawal as vapour or liquid depending on the side adapter used (Connector No. 6, according to DIN 477).

The valves, connectors and fittings used with HFA 227 or HFA 134a should be manufactured in brass or stainless steel. Seals and gaskets are tested as described on pages 20/27.

The adapters listed below are suitable for both SOLKANE™ 227 pharma and SOLKANE™ 134a pharma

Possible Side Adapters depending on the Standards:

Cylinder Valves

- meeting the DIN (Deutsches Institut für Normen) Standard DIN 477 Part 1; connector No. 6, thread size W 21.8 x 1/14", side adapter A, valve screw in hole 28.8 or 19.8
- meeting the CGA (Compressed Gas Association) Standard; connector CGA No. 660, thread size 1.030", 14 threads per inch, right handed external thread
- meeting the BS (British Standard) BS 341 No. 6 (BS6); thread size G 5/8", right handed external thread

900 l Cylinder Cylinder Valves

- meeting the DIN Standard DIN 4676; thread size W 1¼", 31.8 ° 7

Adapter for ISO Container:

- Leakage-free dry Arta® coupling system, sterile connection elements are used, male and female, material 1.4435 electropolished, available in the following nominal diameters: DN 25, DN 40, DN 50, DN 80, DN 100, DN 150

Fig. 26: Y-Valve adapter (red) liquid phase

Fig. 27: Y-Valve adapter (blue) vapour phase

Fig. 28: Arta® coupling for bulk off-loading

Product Stewardship

Chemical manufacturers have a duty to minimise any health, safety and environmental risks related to their products. At the same time, they must meet the needs of their customers and the public for safely usable and environmentally compatible products. In the framework of the Responsible Care initiative, the concept of Product Stewardship has become an important building block in the attainment of sustainable development. [34]

Environmental Protection

The commitments of Daikin Refrigerants Europe GmbH to protect people and the environment are demonstrated in many practical ways by SOLKANE™ 227 pharma and SOLKANE™ 134a pharma.

Environmental consulting includes responding to questions from customers and the public directed to Daikin Refrigerants Europe GmbH as the producer of SOLKANE™ 227 pharma and SOLKANE™ 134a pharma.

Recovery/Reclamation

Recovery is performed when a system requires maintenance. There are several recovery devices on the market. These devices contain a compressor and a condenser, and may be used for liquid and vapour recovery.

The pharmaceutical propellants are included in a reclamation programme, however, reclaimed propellants can never be reused in pharmaceutical products or manufacture.

Recycling

The producer guarantees to take back and reutilize used single component propellants, commercial blends and mixtures of different propellants. The procedure is called secondary recycling and enables valuable raw materials for the chemical industry (hydrofluoric acid and hydrochloric acid) to be reprocessed from either CFC, HCFC or HFC propellants by thermal decomposition. These substances are reused as raw materials in chemical production or other applications.

Propellants containing active pharmaceutical ingredients undergo secondary recycling.

The decomposition products are reused in other processes. Solid wastes for landfill disposal and toxic waste gases are avoided. At the heart of the process, an H_2/O_2 flame with a temperature of 2,000 °C thermally decomposes CFCs, HCFCs and HFCs. The degree of separation under the given conditions was found to be greater than 99.99 %. Using O_2 instead of air to feed the flame avoids forming additional nitrous oxides. [35]

Fig. 31: Reprocessing of HF and HCl from CFCs, HCFCs and HFCs by thermal decomposition

Daikin – Your Specialists for Fluorochemicals

Daikin

For more than 80 years, Daikin has been involved in the research and production of fluorochemicals, and is one of the world's foremost manufacturers of fluorochemical products today. Daikin's unique expertise is essential to a variety of industrial fields: With world-class technology, Daikin offers a wide range of high quality products featuring advanced properties such as heat resistance, chemical resistance, water and oil repellency, and lubricity, with applications in automobiles, consumer cookware, wire and cable, textile and fabric treatment, paper and packaging, optics and displays, coatings and more. Daikin has a global presence with more than 210 sites and almost 60,000 employees worldwide.

Professional Fluorochemistry

We're in it for the long haul. Being the only company in the world dedicated to manufacturing both air conditioning systems and refrigerants, Daikin's deep-rooted commitment to fluorine chemistry is essential to sustain our global #1 market position in air conditioning. We remain fully invested in the research and development required to meet the ever changing needs of your markets. Our professional team of experienced chemists, sales and customer service staff is committed to taking on any challenge and to solving problems in close co-operation with our customers.

Fig. 32 Plant Frankfurt, Germany

Product Range

Hydrofluorocarbons

- SOLKANE™ 227 pharma
- SOLKANE™ 134 a pharma
- SOLKANE™ 134 a
- SOLKANE™ 404A
- SOLKANE™ 407C
- SOLKANE™ 410A
- SOLKANE™ 507
- R32
- R407A
- R407H
- R417A
- R417B

Fluoroplastics

- POLYFLON PTFE
- NEOFLON PFA
- NEOFLON FEP
- NEOFLON ETFE
- NEOFLON PCTFE
- NEOFLON EFEP
- NEOFLON CPT
- POLYFLON MPA
- POLYFLON PTFE Low Polymer

Fluoroelastomers

- DAI-EL
- DAI-EL F-TPV

Additives

- PPA

Surface Modification Technologies

- UNIDYNE
- OPTOOL
- ZEFFLE
- ZEFFLE infrared reflective coating
- FTONE
- DAIFREE
- DEMNUM
- DAIFLOIL

Etching agents for semiconductors

- Hydrofluoric acid

Materials for Lithium Ion Batteries

- Electrolytes

Organic Intermediates

- Fluorinated alcohols
- Fluorinated methacrylate monomers
- Fluorination technology
- Synthesis of aliphatic fluorine intermediates

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Formula Key

t	= Temperature
p	= Pressure
v'	= Specific volume, liquid
v''	= Specific volume, vapour
rho'	= Density, liquid
rho''	= Density, vapour
h'	= Enthalpy, liquid
h''	= Enthalpy, vapour
r	= Enthalpy of the evaporation
s'	= Entropy, liquid
s''	= Entropy, vapour

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