DAIKIN | Positively Innovative

SOLKANE™ 227 pharma

**PROPELLANTS**

# Breathe Easier with SOLKANE™ 227 pharma

Used in millions of inhalers, SOLKANE™ 227 pharma provides unique and unmatched properties in delivering respiratory drugs and respiratory therapy. You can breathe easier knowing SOLKANE™ 227 pharma is registered and approved for use worldwide, with full support and medical exemptions through 2036 and beyond under EU F-gas Regulation, the US AIM act and the Montreal Protocol.

# SOLKANE™ 227 pharma

## SOLKANE™ 227 pharma Special Pharmaceutical Grade

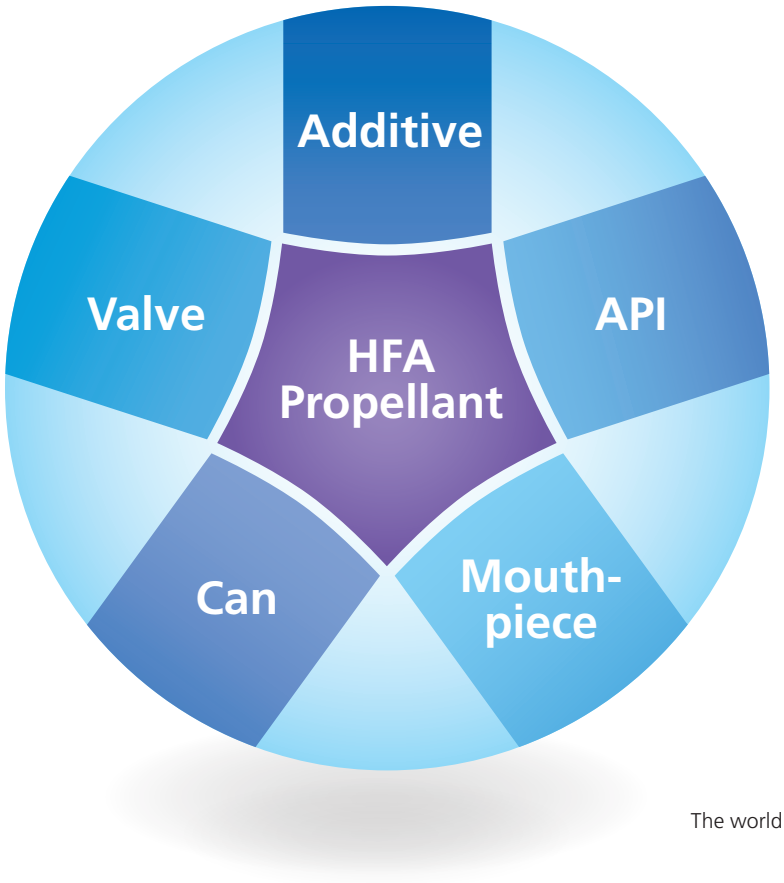
- Highest purity guaranteed by manufacture in dedicated facilities according to cGMP
- High-level quality control
- Specifically developed sophisticated analytical methods
- Worldwide Regulatory Affairs support in accordance with drug active substances

## HFA Propellants for Use in Medical Sprays

SOLKANE™ 227 pharma also known as HFA 227, HFC 227, Heptafluoropropane or apaflurane is used in medical sprays such as MDIs (Metered Dose Inhalers, also called asthma sprays or pharmaceutical aerosols inhaled by the patient), and other FDA-approved uses to propel the active ingredient which is dispersed or solubilized in the hydrofluoroalkane (hereinafter re-ferred to as HFA propellant). HFA 227 does not contain chlorine and is thus non-ozone depleting. Furthermore, it's non-flammable and chemically inert. This makes it (from a safety and toxicological point of view) an ideal candidate for use in medical products.

Moreover, HFA 227 has unique properties of low vapor pressure, which makes it ideal for packaging, and excellent solubility para-meters for respiratory drugs. It is the best solution for replacing last generation ozone-depleting substances especially in dual and triple drug formulations.

Daikin provides HFA 227, in a special phar-maceutical grade as SOLKANE™ 227 pharma, specifically for use in medical products.
It is produced in the highest quality as required by sensitive routes of administra-tion, such as via inhalation to the lung, as in the case of MDIs.




The world of pressurized Metered Dose Inhalers.

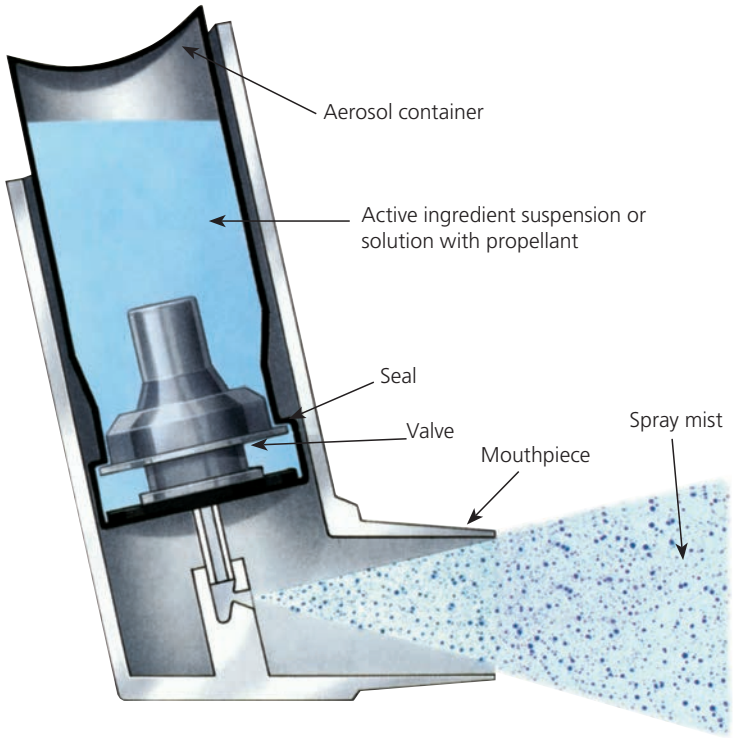
The main differences between pharma grade SOLKANE™ 227 pharma and ordinary "technical grade" (predominately used as a refrigerant and fire extinguishing agent) are:

- the higher purity obtained by additional manufacturing processes specifically developed and applied to meet the stringent specifications set out for pharmaceutical grade products,
- manufacturing in dedicated facilities according to the current good manufacturing practice guidelines,
- 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,
- registration of the manufacturing processes and quality control systems according to the standards for drug active substances, although HFA 227 is classed as an exipient.

## SOLKANE™ 227 pharma
## HFA Propellant for Medical Sprays

Uses:
- MDIs (Metered Dose Inhalers), also known as pharmaceutical aerosols or asthma sprays, for the treatment of: asthma, COPD (Chronic Obstructive Pulmonary Disorder) and respiratory infections
- other FDA approved uses

Proven by:
- 25 years of production, global supply chain and excellence of quality
- Daikin HFA 227 pharma has been used in millions of inhalers
- Security of availability through 2036 and beyond, under the US AIM Act and the EU F-Gas Regulation




Metered Dose Inhaler (MDI)

## History of the Pharmaceutical Propellants HFA 227 – 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 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 (International Pharmaceutical Aerosol Consortium for Toxicity Testing) 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.

### SOLKANE™ History of the Pharmaceutical Propellants HFA 227 – IPACT I, IPACT II

| | |
|---|---|
| 1989/1990 | Formation of two consortia:<br>IPACT I for the toxicological testing of HFA 134a<br>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 Hoechst, now Daikin-quality; specifications not disclosed |
| July 1998/April 2001 | CPMP reviews of the Solvay SOLKANE™ 227 pharma DMFs/Amendments |
| Dec. 1998/June 2001 | Final assessments and CPMP "approval" of all changes received with the final conclusion:<br>**"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."** [2] |

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 positive opinion for HFA 227 was similar similar to HFA 134a, 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." [1].

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 Solvay) support as the sole supplier of HFA 227. Daikin (formerly Solvay) submitted its Drug Master File for the manufacture and quality control of HFA 227 as part of the IPACT II dossier.

Since then, Daikin has optimized 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 Franfurt 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."*[3]

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.

Hereby Daikin fully complies with all specifications published by the CPMP[1, 4, 5] as mentioned above and the FDA[2].

The Daikin specifications for SOLKANE™ 227 pharma is listed as follows:

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

## Manufacture of SOLKANE™ 227 pharma by Daikin

The production of SOLKANE™ 227 pharma adheres to the stringent good 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 consign-ment 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 SOLKANE™ 227 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 (formally Solvay) has Drug Master Files in all countries for cross-reference to support drug applications containing SOLKANE™ 227 pharma.

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.

Visual inspection of dedicated pharma cylinders as part of Daikin's quality control.

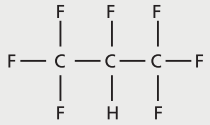
## SOLKANE™ pharma – Daikin's Center of Competence

- 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
- Highly qualified staff – continuous personnel training
- Traceability of each consignment via computer-controlled filling operations
- Manufacture of SOLKANE™ 227 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 working groups and the consortia for the establishment of harmonized test methods and specifications


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

# Physical Properties

## Nomenclature

| | SOLKANE™ 227 pharma |
|---|---|
| **Structural Formula** |  |
| **Molecular Formula** | $C_3HF_7$ |
| **Chemical Name** | 1,1,1,2,3,3,3-Heptafluoropropane |
| **Chemical Family** | Fluorinated Hydrocarbon |
| **ASHRAE* Nomenclature/** | HFA 227, HFA 227ea |
| **International Nonproprietary** | Apaflurane |
| **Brand Name:** | SOLKANE™ 227 pharma |

## Description

| | SOLKANE™ 227 pharma |
|---|---|
| **Physical Form at 25 °C** | Gaseous |
| **Colour** | Colourless |
| **Odor** | Faint ethereal odor |
| **Flammability** | Non-flammable |
| **Toxicity** | No appreciable toxic effect |
| **Ozone Depletion Potential (ODP)** | Zero |
| **Global Warming Potential (GWP)**[4] | 2,900 |
| related to $CO_2$ = 1.0 (100 years ITH*)<br>*ITH = integrated time horizon | |
| **Atmospheric Lifetime**[4] | 33 years |
| **Storage** | Liquefied gas under |

## Physical Data [SI Units]

| | | SOLKANE™ 227 pharma |
|---|---|---|
| **Chemical Name** | | 1,1,1,2,3,3,3- |
| **Chemical Formula** | | $CF_3–CFH–CF_3$ |
| **Molar Mass** | g/mol | 170.03 |
| **Boiling Point at 1.1013 bar** [5] | °C | –16.5 |
| **Freezing Point** [5] | °C | –131 |
| **Critical Data:** HFA 227 [7] | | |
| **Critical Temperature** | °C | 101.90 |
| **Critical Pressure** | bar | 29.52 |
| **Critical Density** | kg/l | 0.592 |
| **Critical Volume** | l/kg | 1.69 |

| **Temperature** | | 0 °C | 20 °C | 40 °C |
|---|---|---|---|---|
| **Pressure of the Vapor** | bar | 1.96 | 3.90 | 7.03 |
| **Density of the Liquid** | kg/dm³ | 1.482 | 1.408 | 1.322 |
| **Density of the Saturated Vapor** | kg/dm³ | 0.0159 | 0.0310 | 0.0564 |
| **Specific Heat Capacity of the Liquid** | kJ/(kg·K) | 1.096 | 1.148 | 1.222 |
| **Thermal Conductivity of the Liquid** | mW/(m·K) | 65.05 | 59.45 | 53.85 |
| **Dynamic Viscosity of the Liquid** | mPa·s | 0.346 | 0.267 | 0.210 |
| **Surface Tension of the Liquid** | mN/m | 9.31 | 6.96 | 4.80 |
| **Dielectric Constant Liquid Phase** HFA 227 [9]; HFA 134a [8] | 4.6 | 4.1 | 3.6 | 11.3 |

## Thermal Stability

| | SOLKANE™ 227 pharma |
|---|---|
| **Temperature Below Which no** | 475 °C [10] |

## Refractive Index

| | | SOLKANE™ 227 pharma |
|---|---|---|
| $n_{20\,°C}$ [11] | calculated value | 1.2207 |
| $n_{20\,°C}$ [12] | measured value | 1.2207 |

## Physical Data [US/UK Units]

| | | SOLKANE™ 227 pharma |
|---|---|---|
| **Chemical Name** | | 1,1,1,2,3,3,3- |
| **Chemical Formula** | | $CF_3–CFH–CF_3$ |
| **Molar Mass** | g/mol | 170.03 |
| **Boiling Point at 1 atm**[5] | °F | 3.9 |
| **Freezing Point**[5] | °F | –203.8 |
| **Critical Data:** HFA 227[7]; HFA 134a[6] | | |
| **Critical Temperature** | °F | 215.4 |
| **Critical Pressure** | psia | 424.7 |
| **Critical Density** | lb/ft³ | 38.77 |
| **Critical Volume** | ft³/lb | 0.026 |

| **Temperature** | | 32 °F | 68 °F | 104 °F |
|---|---|---|---|---|
| **Pressure of the Vapor** | psia | 28.43 | 56.56 | 101.96 |
| **Density of the Liquid** | lb/ft³ | 92.518 | 87.898 | 82.530 |
| **Density of the Saturated Vapor** | lb/ft³ | 0.993 | 1.935 | 3.521 |
| **Specific Heat Capacity of the Liquid** | Btu/lb °F | 0.262 | 0.274 | 0.292 |
| **Thermal Conductivity of the Liquid** | Btu/hr·ft °F | 0.0346 | 0.0316 | 0.0287 |
| **Dynamic Viscosity of the Liquid** | lbf/ft² | $2.3E^{-04}$ | $1.8E^{-04}$ | $1.3E^{-04}$ |
| **Surface Tension of the Liquid** | lbf/ft | $6.4E^{-04}$ | $4.8E^{-04}$ | $3.3E^{-04}$ |
| **Dielectric Constant Liquid Phase** HFA 227[9]; HFA 134a[8] | 4.6 | 4.1 | 3.6 | 11.3 |

## Thermal Stability

| | SOLKANE™ 227 pharma |
|---|---|
| **Temperature Below Which no** | 887 °F[10] |

## Refractive Index

| | | SOLKANE™ 227 pharma |
|---|---|---|
| $n_{20°C}$[11] | calculated value | 1.2207 |
| $n_{20°C}$[18] | measured value | 1.2207 |

## Vapor Table Wet Vapor Range SOLKANE™ 227 pharma [13] [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

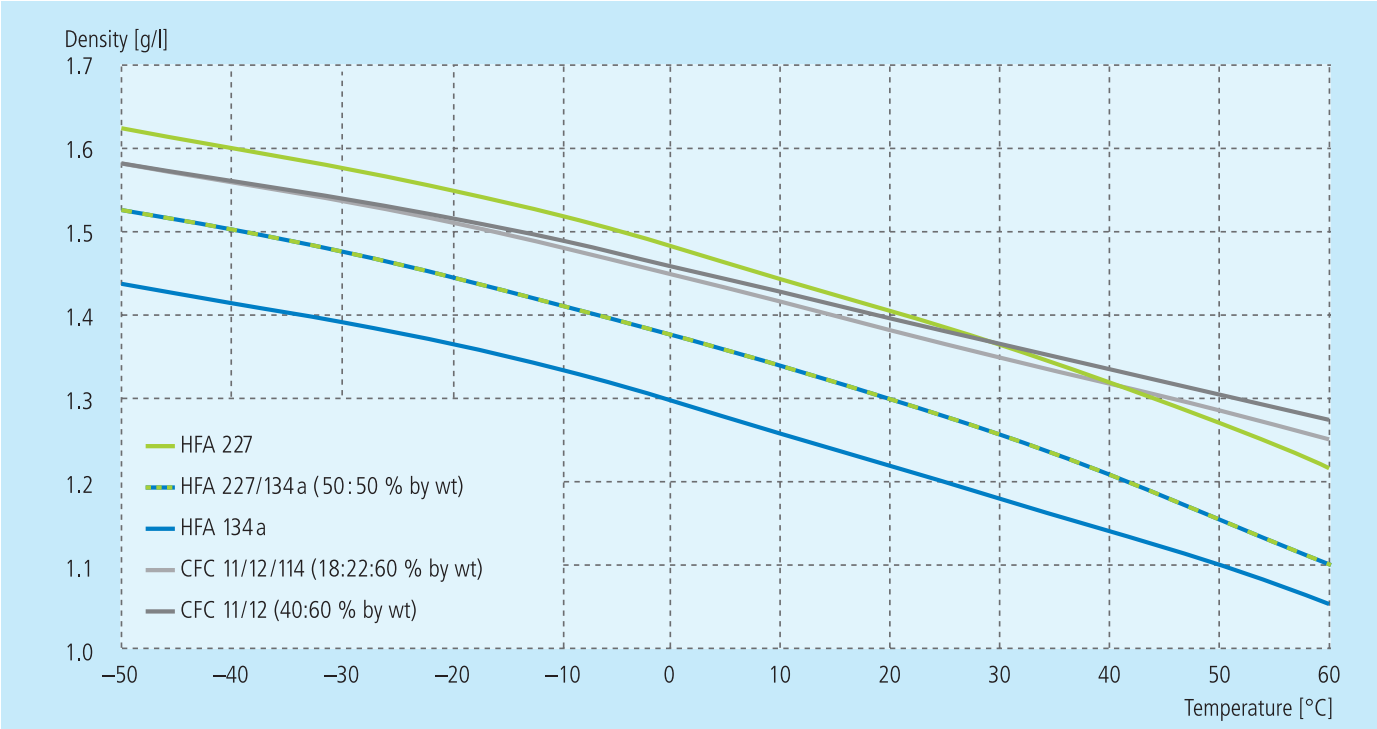



**Fig. 10:** Density of liquid of SOLKANE™ 227 pharma including a 50:50 blend depending on temperature in comparison to CFC blends (CFC 11/12 as 40:60 and CFC 11/12/114 as 18:22:60)[14]

## Vapor Pressure in bar

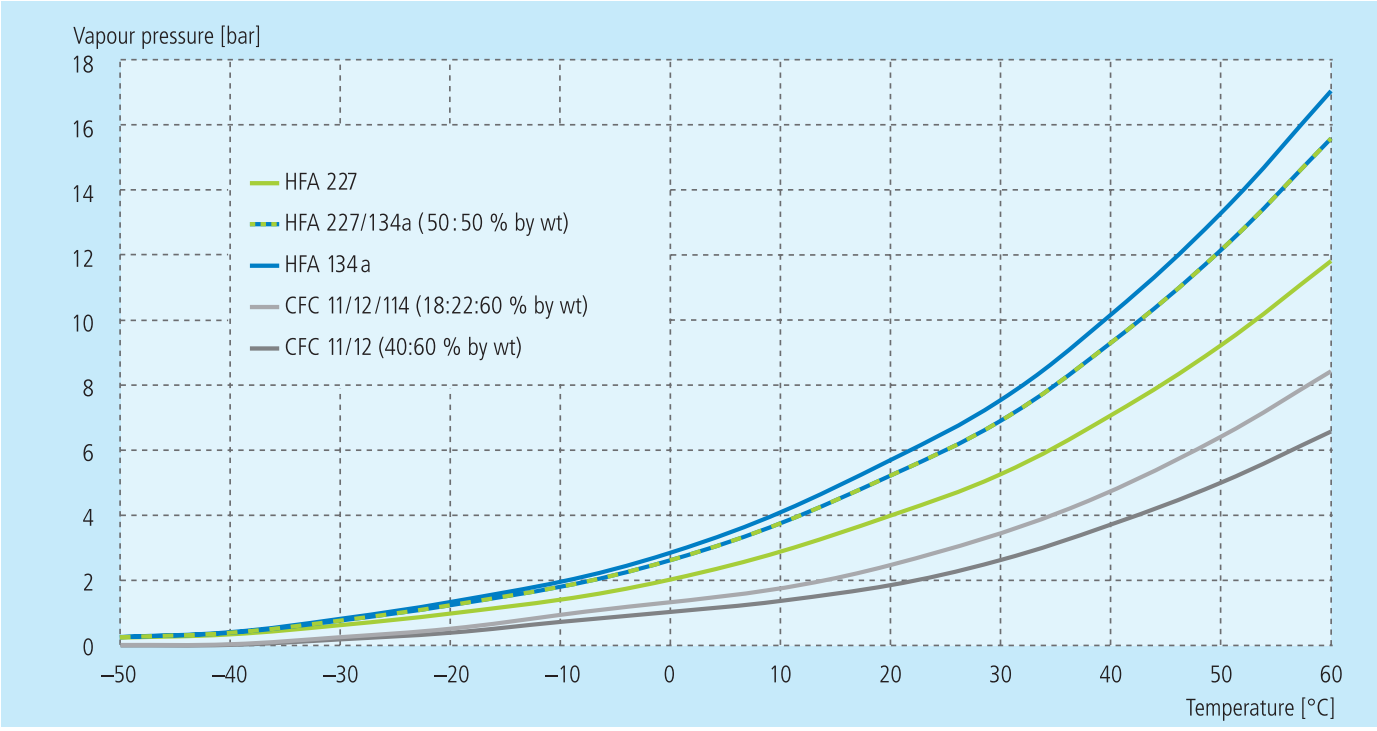



**Fig. 11:** Vapor pressure of SOLKANE™ pharma including a 50:50 blend depending on temperature in comparison to CFC blends (CFC 11/12 as 40:60 and CFC 11/12/114 as 18:22:60)[14]

## Vapor Table Wet Vapor Range SOLKANE™ 227 pharma [13] [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/ft$^3$

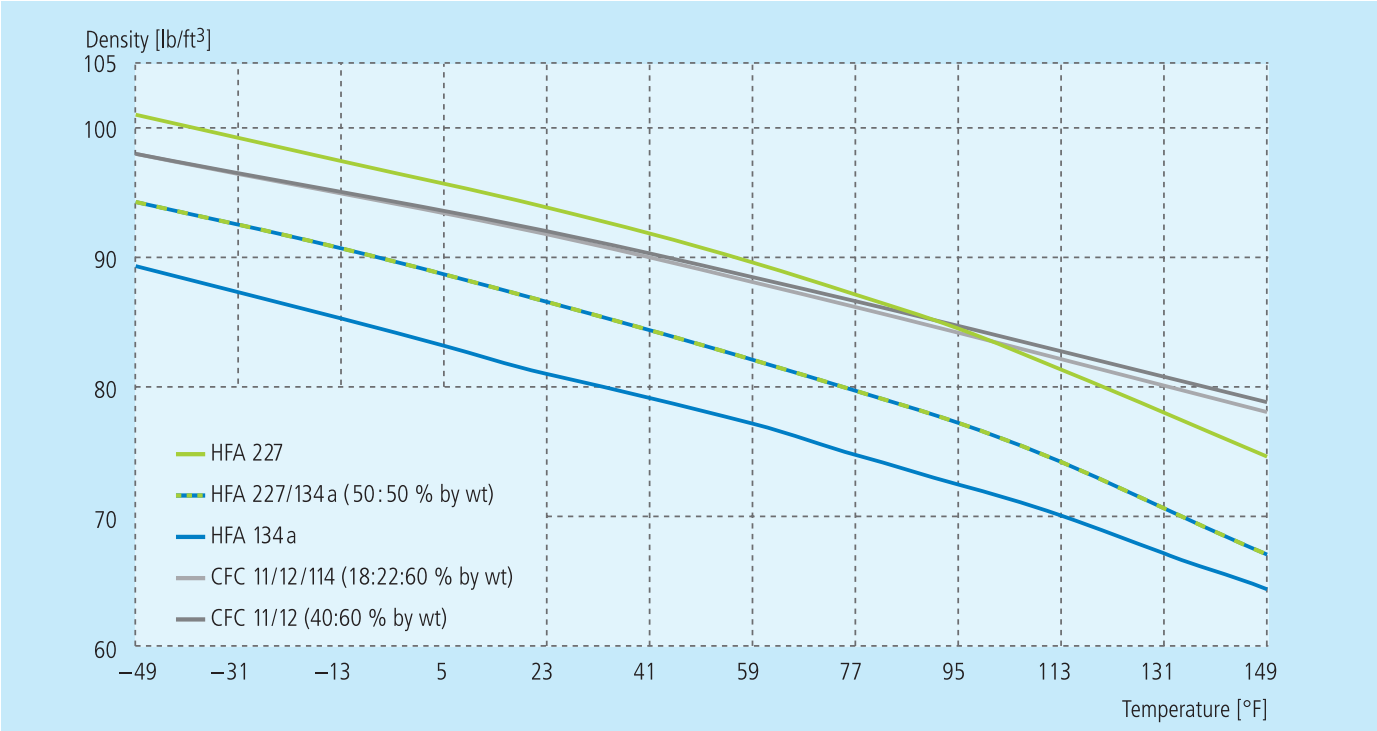



**Fig. 12:** Density of liquid SOLKANE™ 227 pharma including a 50:50 blend depending on temperature in comparison to CFC blends (CFC 11/12 as 40:60 and CFC 11/12/114 as 18:22:60)[14]

## Vapor Pressure in psia

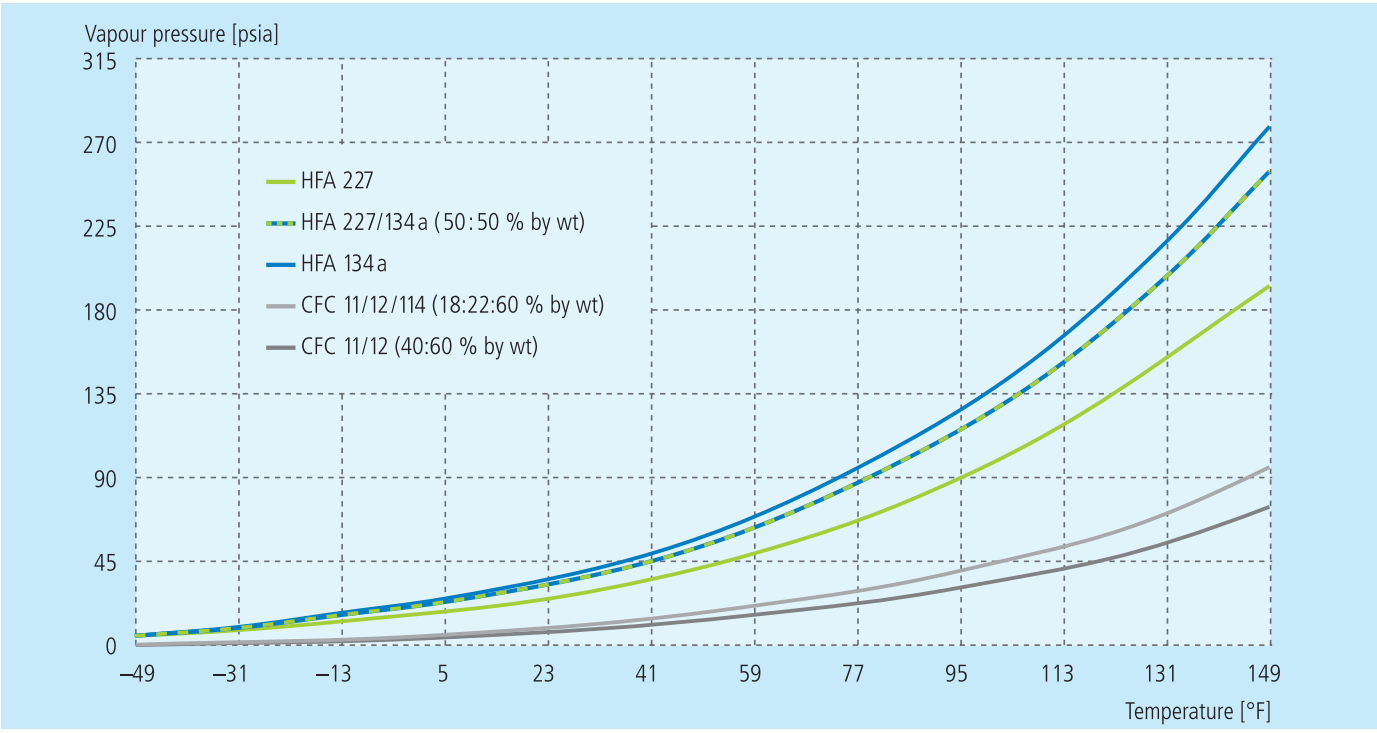



**Fig. 13:** Vapor pressure of SOLKANE™ 227 pharma including a 50:50 blend depending on temperature in comparson to CFC blends (CFC 11/12 as 40:60 and CFC 11/12/114 as 18:22:60)[14]

## Viscosity in mPa·s

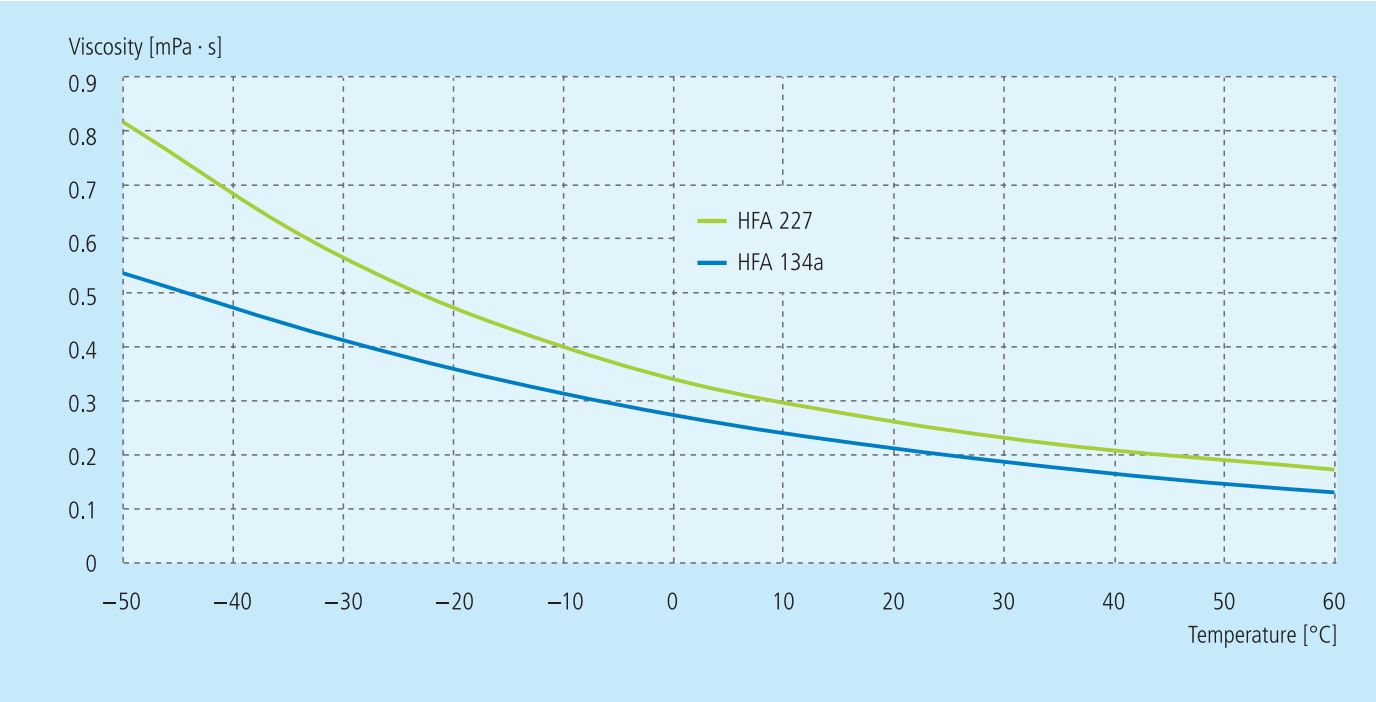



**Fig. 14:** Dynamic viscosity of liquid SOLKANE™ 227 pharma depending on temperature[13]

## Surface Tension in mN/m²

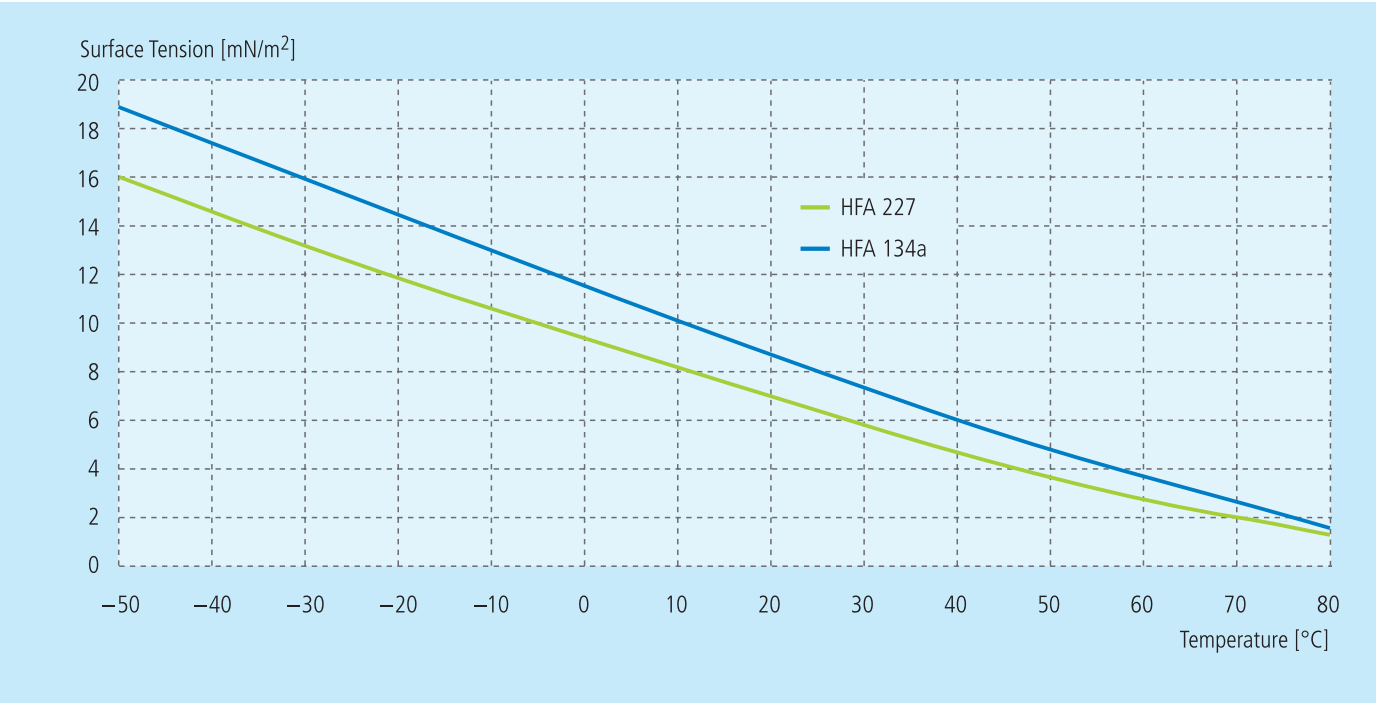



**Fig. 15:** Surface tension of SOLKANE™ 227 pharma depending on temperature[13]

# Solubility Parameters / Characteristics

## Solubility Values

| Solubility in | | | SOLKANE™ 227 pharma |
|---|---|---|---|
| **Water** [15] | at 20 °C, 68 °F | ppm | 58 |
| **Octanol** [15] | at 20 °C, 68 °F | ppm | 5.070 |

| Solubility in HFA 227 and HFA 134a of | | | |
|---|---|---|---|
| **Oxygen** [16] | at atmospheric conditions: | g/kg | approx. 0.08 |
| **Nitrogen** [17] | at atmospheric conditions: | g/kg | 0.55 |
| **Water** [15] | **Measured values at 25 °C** | **in liquid phase** | g/kg |
| | **Experimental results** | **in liquid phase at 25 °C** [18] | g/kg |
| **Ethanol** [15] | | | Miscible |
| **Silicone Oil** [19] | high viscosity oil (V1000) | ppm (wt.) | 149 |
| **Silicone Oil** [19] | low viscosity oil (V300) | ppm (wt.) | 585 |

## Solubility Characteristics

| | | |
|---|---|---|
| **Dipole Moment** measured value liquid phase | debye | 0.93 [9] |
| **Dipole Moment** calculated value gas phase [9] | debye | 1.46 |
| **Octanol-Water-Coefficient** [14] | log $P_{ow}$ | 2.05 |
| **Kauri-Butanol-Index** | | 13 [15] |
| **Solubility Parameter** calculated value [13] | | 5.4 |

## 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 [14]

| | |
|---|---|
| **HFA 227** | **1.46**; (0,93) [9] |
| CFC 114 | 0.66 |
| CFC 12 | 0.51 |
| CFC 11 | 0.45 |

## 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 behavior of the active substances

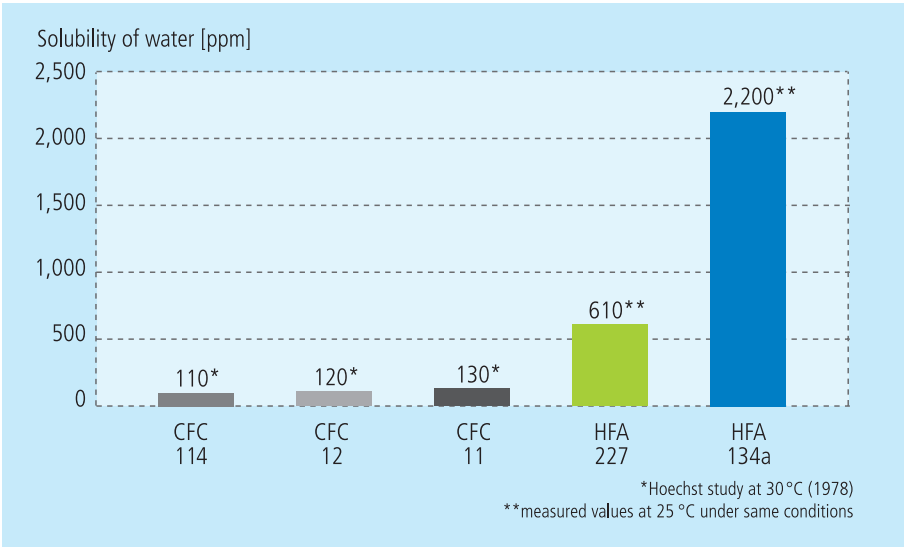



**Fig. 17:** Solubility of water in HFA compared to CFCs

## Solubility of Oxygen and Nitrogen

| | | SOLKANE™ 227 pharma Adsorption Number Q |
|---|---|---|
| **Oxygen**** | | |
| Experimental results converted to atmospheric conditions* in the liquid phase [16] | g/kg | approx. 0.08 |
| Experimental results converted to the conditions: partial pressure of $O_2$ = 1.0 bar, temperature 25 °C in the liquid phase | g/kg<br>g/kg | approx. 0.36 [16]],<br>0.21 [14] |
| **Nitrogen**** | | |
| Experimental results converted by linear fitting to the atmospheric conditions* (see illustration below) | g/kg<br>g/kg | n.d.<br>0.55 [14] |
| Experimental results at the conditions: partial pressure of $N_2$ = 1.0 bar, temperature 25 °C | g/kg<br>g/kg | n.d.<br>0.69 [14] |

* 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 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.
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).

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.

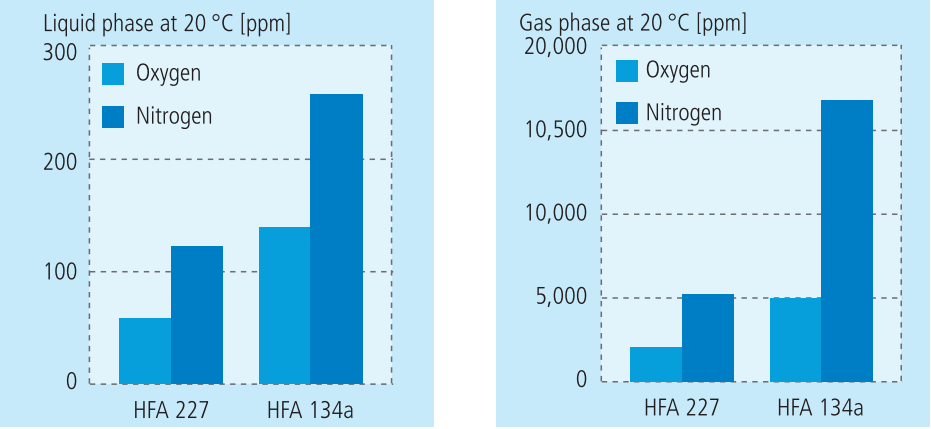



**Fig. 19/20:** Typical content of oxygen and nitrogen in SOLKANE™ 227 pharma

## Influence of Ethanol on HFA 227

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. 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).

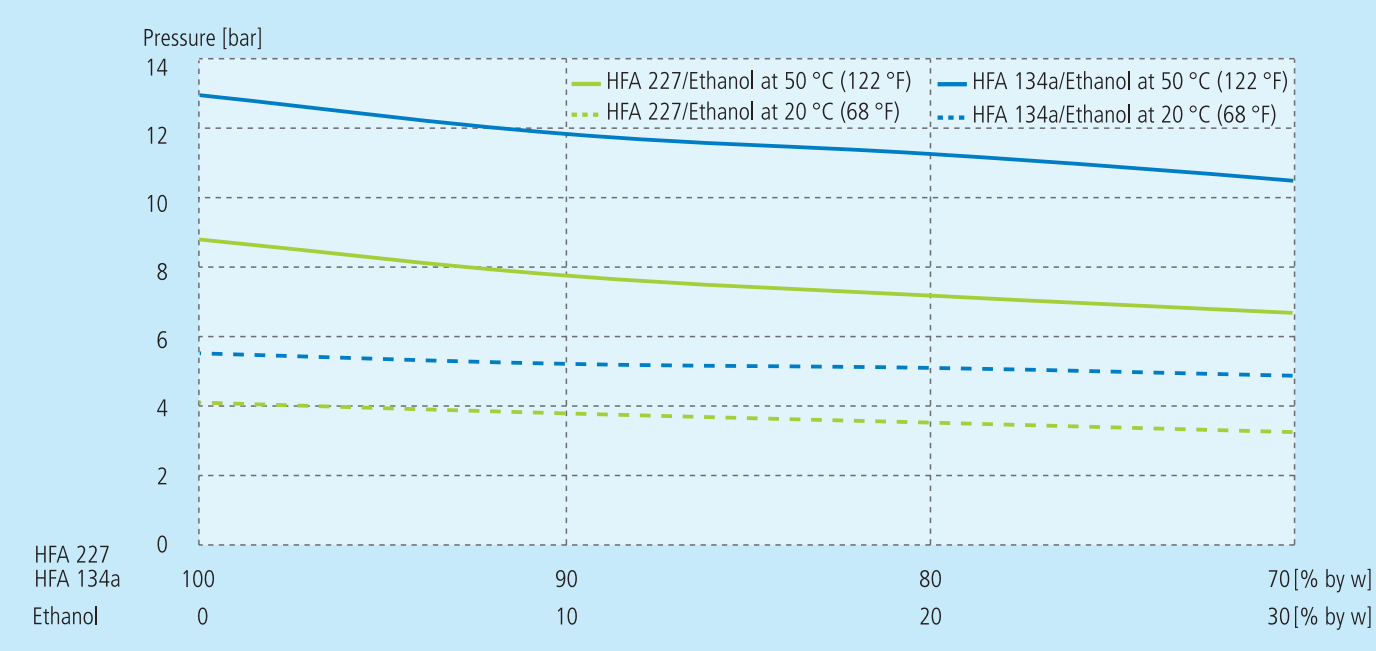



**Fig. 21:** Illustration of experimental results: pressure versus mixture curve of HFA 227 with ethanol 99.8 % [wt.]

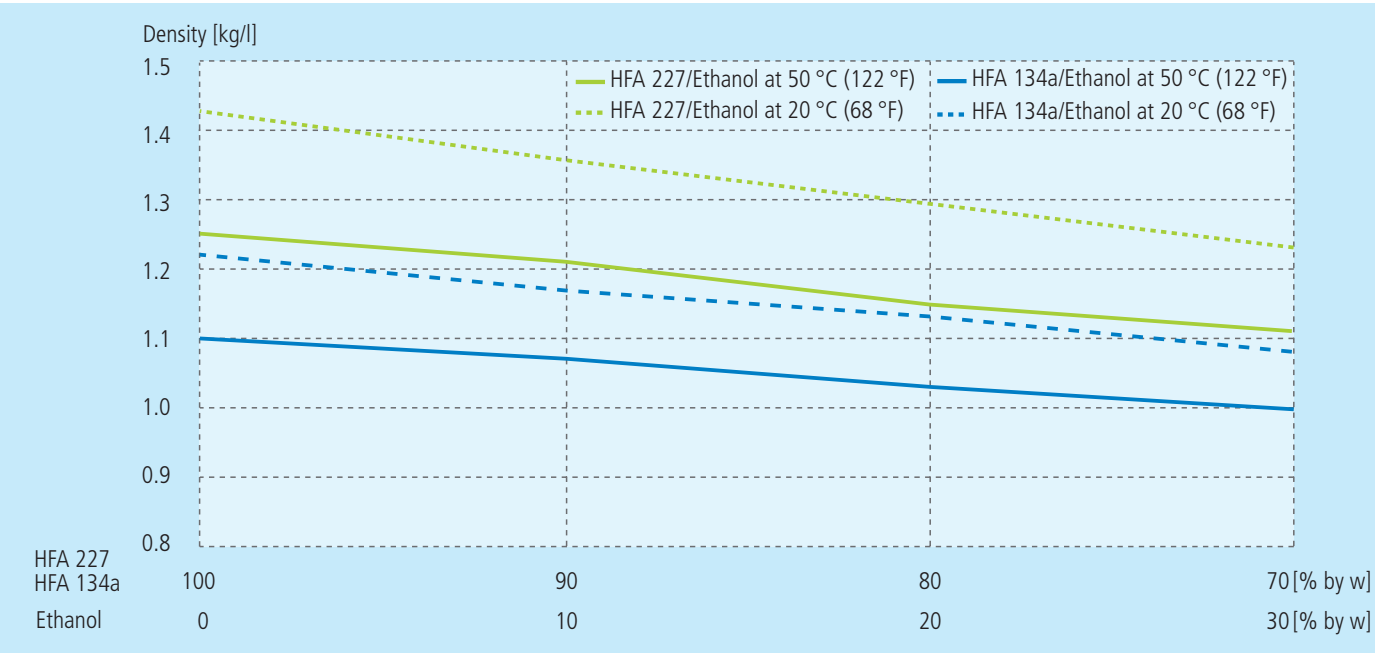



**Fig. 22:** Density of HFA 227 in mixtures with ethanol 99.8 % at 20 °C and 50 °C

# Chemical Behavior

## Material Compatibility

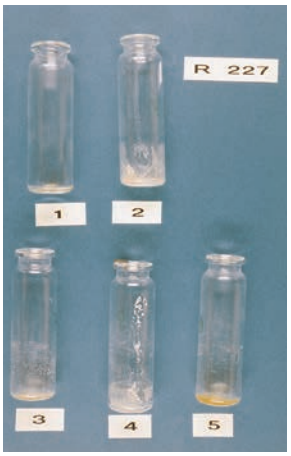
The material compatibility is tested to determine the specifications for materials suitable for the manufacture of pharmaceutical aerosols (e.g. composition of seals, metering chambers, gaskets, seats or stems).

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

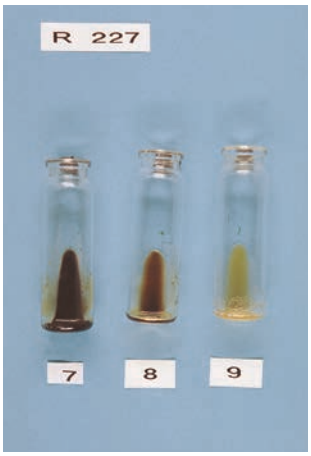
## Classification of Materials for Use in MDIs

| | HFA 227 |
|---|---|
| **Sealing Material** | CR, NBR, NR,EPDM (5), PVC (6), PCTFE (6), PA (6), PBT (6), PP (6), PTFE (6), IRR |
| **General Use** | NBR, IRR, POM, PTFE, PCTFE, PBT, PA, CR, NR |
| **Partly Use** | HNBR (4), FPM (1), PE (3) |

(1) Strong swelling behavior 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




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




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** |
|---|---|---|---|---|
| **1.** | **Metals/Valves/Fittings/ Vessels/Cans** | | HFA 227 is compatible with mild steel, stainless | |
| | Material ISO 1629 | Chemical | Trade name | Compability |
| **2.** | **Elastomers** [1] | | | |
| | Chlorobutadiene rubber | CR | Neoprene® | + |
| | Hydrated | HNBR | Perbunan® | + |
| | Natural rubber | NR | Dynaprene® | + |
| | Butyl rubber | IIR | Europrene® | + |
| | Fluorinated rubber | FPM | Viton®, Fluorel®, | – |
| | Acrylonitrile- | NBR | Perbunan® N | + |
| | Ethylene- | EPDM | Nordel® | + |
| **3.** | **Plastics** | | | |
| | Polytetrafluoroethylene | PTFE | Hostaflon® TFM, | + |
| | High density | HDPE | Alathon®, Eltex® | o |
| | Polyacetal | POM | Hostaform® C9021 | + |
| | Polyphenylene sulfide | PPS | Fortron®, Rylon® | * |
| | Liquid crystal polymers | LCP | Vectra® | * |
| | Polyester fibre | PET | Trevira®, | * |
| | Polyvinylchloride | PVC | Hostalit®, Solvin® | + |
| | Polychlorotrifluoro | PCTFE | | + |
| | Polyamide | PA | Isonamid® | + |
| | Polybutylene- | PBT | Celanex® X5002, | + |
| | Polypropylene | PP | Adell®, A-Fax®, | + |
| | Polystyrene | PS | Styron® | * |

[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 colorless gas with an ethereal odor at ambient temperature. If 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 [5] | 1,000 ml/m$^3$ |
| Acute inhalation toxicity $LC_{50}$* | 800,000 ppm [20] |
| Cardiac sensitisation LOAEL** | 100,000 ppm [20] |
| Effects on: pulse, blood pressure, ECG, lung function [21] 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 [5] | Non irritant |
| Degradation | Bio-transformed at very low rates to hexafluoroacetone trihydrate [22] |

* $LC_{50}$, 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 behavior of the offspring of exposed rats.

Different in vitro and in vivo mutagenicity tests were performed with HFA 227. No geneotoxic 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 ($LC_0$ fish = or > 30 mg/l; $EC_0$ bacterial activity = or > 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.

# Instructions

## Safety Instructions

SOLKANE™ 227 pharma is a liquefied compressed gas.

According to pressure vessel regulations, compressed gases are substances whose vapor 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 is a non-flammable gas. But, wherever it is handled, there must be no open flames or heat sources (e.g. hot metallic surfaces) or reactive products. The propellant 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 vapors 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 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 vapor 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 as a vapor have little or no effect on the skin or eyes. To avoid the cold irritation and frostbite from exposure to the liquid propellant, 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 is a non-flammable gas and does 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.

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

## SOLKANE™ 227 pharma

- **Hazardous Decomposition Products:**
  Hydrogen fluoride, fluorophosgene (HFA 227),
- **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 is polyvinylal-cohol)

### 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) is a liquefied compressed gases.

According to pressure vessel regulations, compressed gases are substances whose vapor 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 is a are non-flammable gas. 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.[23]

# Container Closure System

## Packaging

### Supply of SOLKANE™ 227 pharma

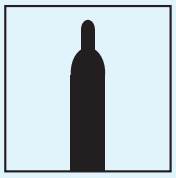
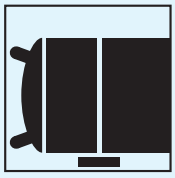
Global deliveries of SOLKANE 227 grades take place using dedicated ISO tank containers in quantities of 15,000 to 19,000 kg. SOLKANE pharma is also available in 10 l, 60 l or 900 l steel cylinders. All our cylinders have an additional safety device, which prevents the cylinders from accidental backflow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

### Applied Tests

All Daikin 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.


900 l container on a steel palette ready for transport.

## Returnable Cylinders

| | Unit |  |  |  |
|---|---|---|---|---|
| **SOLKANE™ 227 pharma** | **kg/lb** | **6/13** | **52/115** | **900/1,985** |
| **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**

## Classification and Transport Information

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

## International Standards for Valves, Connectors and Adapters

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

The valves, connectors and fittings used with HFA 227 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 SOLKANE™ 227 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**

- 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


Y-Valve adapter (red) liquid phase


Y-Valve adapter (blue) vapor phase

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. [24]

### Environmental Protection

The commitments of Daikin to protect people and the environment are demonstrated in many practical ways by SOLKANE™ 227 pharma

Environmental consulting includes responding to questions from customers and the public directed to Daikin as the producer of SOLKANE™ 227 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 vapor 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. [25]

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

# Daikin – Your Specialists for Fluorides

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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 cooperation with our customers.

Plant Frankfurt, Germany

# Bibliography


[1] CPMP/503/95 CPMP Results of the Co-ordinated Review of 1,1,1,2,3,3,3-Heptafluoropropane (HFA 227); London, 13 September, 1995

[2] FDA CDER October 1998 Draft Guidance for Industry - Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Products - Chemistry, Manufacturing, and Controls Documentation, November 05, 1998

[3] Final Assessment Report Part III on SOLKANE™ 227ea/P pharma (HFA 227), Federal Institute for Drugs and Medicinal Devices, (Bundesinstitut für Arzneimittel und Medizinprodukte; BfArM), Berlin, Germany, 4 December, 1998

[4] Intergovermental Panel on Climate Change (IPCC), Report, 2000

[5] Solvay Fluor und Derivate GmbH, Material Safety Data Sheet

[6] W. Scholten, Damptafel für Tetra-fluoroethan, Hoechst AG, R&D Chemicals

[7] G. Ernst, H. Wirbser, G. Bräuning, Hoechst AG, R&D Chemicals

[8] T. Barao et al., Dielec. Constant, Dielectric Virial Coefficients, and Dipole Moments of 1,1,1,2-Tetrafluoroethane, Journal of Chemical and Engineering Data, 40 (1995); data converted to the required tempera-tures by Solvay Fluor und Derivate GmbH, Hannover, Germany

[9] Schenk, Neubert, Kältemittel, Messung des Dipolmoments von H-FKW 227, Institut für Luft- und Kältetechnik, Dresden, 3.1.1991

[10] C. M. Invernizzi, Universita' degli Studi di Brescia, Itally

[11] R. C. Downing, Fluorocarbon Refrige-rants Handbook, 1998, p. 89-91

[12] M. Pittroff, Determination of the Refractive Index of SOLKANE™ 227ea/P pharma and SOLKANE™ 134a pharma, Drug Delivery to the Lungs XI, London 11.12.00 p. 147 -149

[13] Solvay Fluor und Derivate GmbH, Technical Data Program, Version 3.2

[14] REFPROP 6.0* (*REFPROP: Thermodynamic and Transport Properties of Refrigerants and Refrigerant Mixtures, NIST Standard Reference Database 23, Version 6.01, Copyright 1998)

[15] Solvay Fluor und Derivate GmbH, Hannover, Germany

[16] T. Schwarze, M. Pittroff, Solubility of Oxygen in SOLKANE™ 227ea/P pharma (Apaflurane) and SOLKANE™ 134a pharma (Norflurane) at Different Temperatures, Drug Delivery to the Lungs XI, London 11.12.00 p.143 -146

[17] R. Heide, Löslichkeit von Stickstoff in SOLKANE™ 134a, Institut für Luft- und Kältetechnik, Dresden, ILK-B-8/98-1715

[18] Control of Moisture and other Contaminants in Refrigerant Systems, ASHRAE Handbook-Refrigeration, 1998, chapter 6

[19] M. Pittroff, A. H. Pischtiak, T. Schwarze, Solubility of Silicone Oil in SOLKANE™ 227ea/P pharma and SOLKANE™ 134a pharma, Drug Delivery to the Lungs XI, London 11.12.00 p. 150-151

[20] S. R. Skaggs, T. A. Moore, R. E. Tapscott, Halon Replacements: Technology and Science, A. W. Miziolek, W. Tsang, Editors, Chap. 10, p. 99, American Chemical Society, Washington, DC (1995), source: S. Karecki et al., Use of Novel Hydrofluorocarbon and Jodofluorocarbon Chemistries for a high Aspect Ratio Via Etch in a High Density Plasma Etch Tool, J. Electrochem. Soc., Vol. 145, No.12, December 1998, p. 4305-4312

[21] H. H. Emmen et al., Human Safety Pharmacokinetics of the CFC Alternative Propellants HFC 134a and HFC 227 Following Whole-Body Exposure, Regulatory Toxicology and Pharmacology, 2000, Vol. 32, p. 22-35

[22] U. Köster et al., Biotransformation of the Aerosol Propellant 1,1,1,2,3,3,3-Heptafluoropropane (HFA-227): Lack of the Protein Binding of the Metabolite Hexafluoroacetone, Drug Metabolism and Disposition, 1996, Vol. 24, No. 8, p. 906-910

[23] M. A. Collins, HFC 134a: Acute Toxicity in Rats to Tetrafluoroethane, 1984, Unpublished Data from ICI, CTL, source: [22]

[24] Verband Chemischer Industrie (VCI) Brochure „Leitfaden Produktverantwortung"

[25] Christoph Meurer; Ewald Preisegger, Responsible Care Product Stewardship for Refrigerants; IIA Dubrofnik July 2001


**Formula Key**

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

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