HFA propellants

Manufacture, storage and use. Avoiding the problems

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Mexichem FLUOR

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Mexichem Introduction

Mexichem

- One of Latin America's biggest chemical companies
  - 2008 sales of $2.83bn
  - Leading Global supplier of fluorspar and HF
  - Exports to 70 countries worldwide
  - Growing very rapidly
  - Bought refrigerants & medical propellants business from INEOS in 2010

Mexichem Fluor Medical Products

The Medical Products business contains:

- Inhalation grade of 134a (ZEPHEX 134a)
- Inhalation grade of 227ea (ZEPHEX 227ea)
- Other speciality 134a & HFA grades
- ZEPHEX is the Mexichem brand name for medical excipients
- ZEPHEX medical HFAs are used in around 78% of worldwide MDI production. (GSK, CIPLA, Norton/Teva…over 60 enterprises supplied)

- TD Torgsin are Mexichem's Russian HFA distributors

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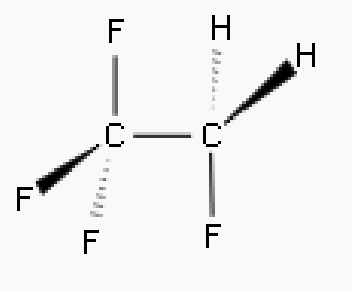
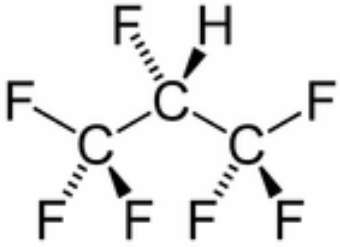
What are the HFAs?

HFAs are…..

- Simple C1 – C3 alkanes, which are partially fluorinated.
- The name: **H**ydro**f**luoro**a**lkane
- They have boiling points in the range –45C to +20C
- Do not affect ozone layer
- Several are non flammable, non-toxic
- Two in particular are useful for Metered Dose Inhalers (MDIs)
  - 134a (95%)
  - 227ea (5%)
  - Tox programmes in 1994-6 established minimum safe specifications (IPACT-1 & 2)

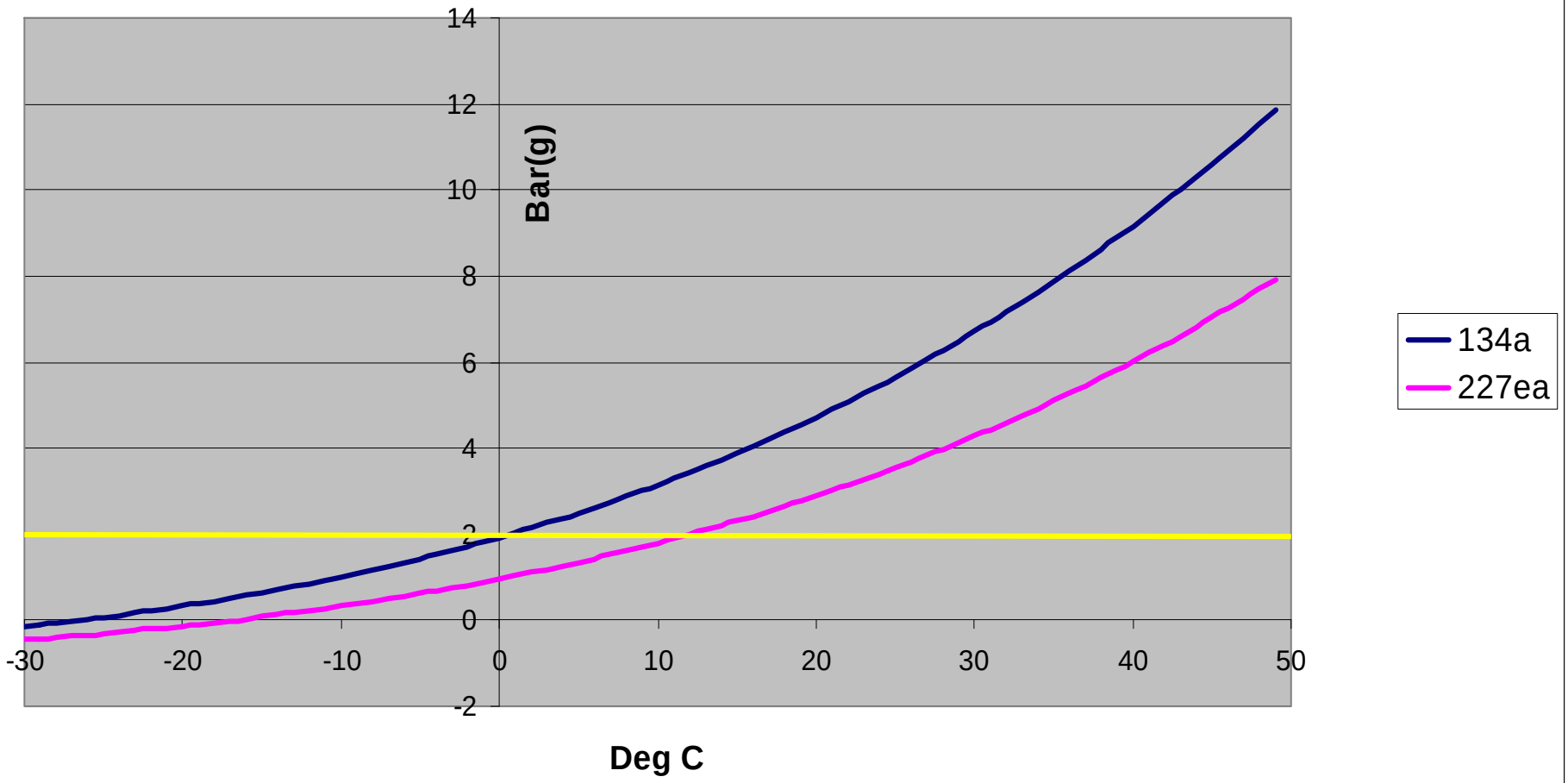
Medical HFAs

	ZEPHEX 134a	ZEPHEX 227ea
Full name	1,1,1,2 - Tetrafluoroethane	1,1,1,2,3,3,3- heptafluoropropane
Formula	CF_3CFH_2	CF_3CFHCF_3
Structure		

Medical HFAs - Physical properties

	ZEPHEX 134a	ZEPHEX 227ea	CFC11/12 (30/70)
Density **(g/cc)**	1.21	1.39	1.35
Flammability	none	none	none
B.P **(°C)**	-26	-17	~-5
Solvency	'alcohol –like' Polar	'Weak CFC like' Non-polar	Strong Non-polar
ODP	0	0	1

Vapour Pressue of ZEPHEX 134a and 227ea



Which HFA?

- 134a used in ~ 95% of MDIs
- 227ea costly, niche, and should be avoided
- Advances in valve technology has made use of 227ea no longer necessary

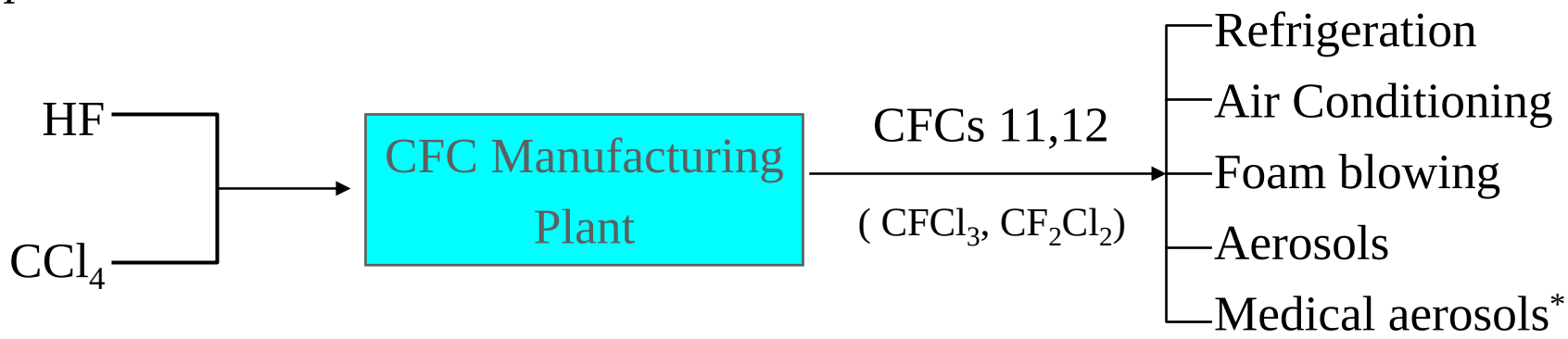
3

HFA Manufacture & Quality

Propellant manufacture
CFCs (Historical)

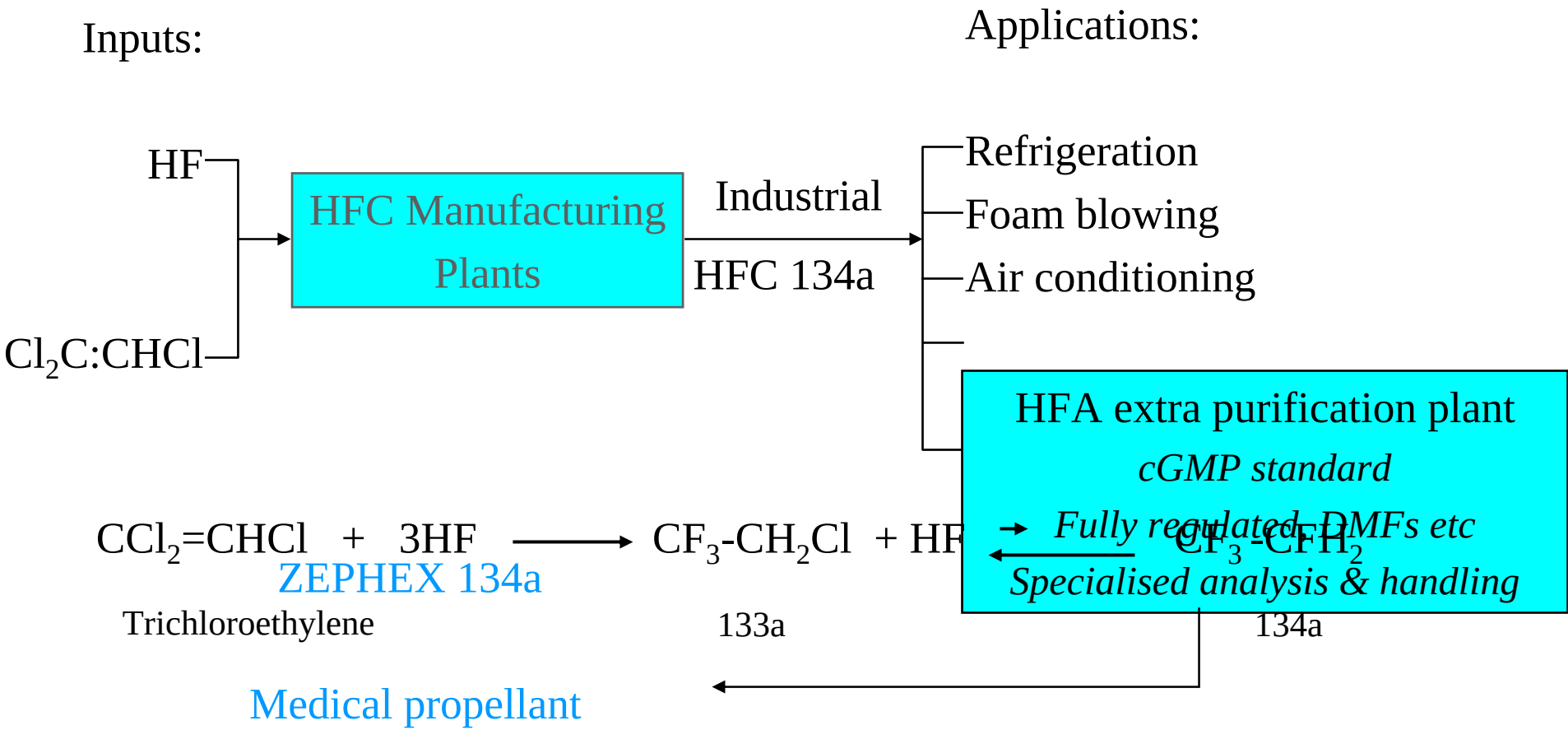
Inputs:

Applications:



* Extra analysis sometimes carried out

Propellant Manufacture
ZEPHEX 134a



Production of ZEPHEX 134a

St. Gabriel, USA

Mihara, Jpn

Medical plant
Runcorn, UK

Bulk customers

Pack customers

Medical HFA Manufacture– quality & compliance

- International HFAs for inhalation are
  - Purified to high levels
  - Controlled to full cGMP – treated like active ingredients
- Mexichem support this, and aim to lead on purity and GMP control.

- Why? ("It's only an excipient…")
  - The gas
    - Comes from difficult chemistry
    - *Some* unpurified industrial grades *can* have medically unacceptable impurities
  - The patient
    - 85-99.9% of inhaled dose is HFA
    - It is delivered to a diseased organ
    - Rapid uptake by bloodstream possible
    - ~ 60mg taken up to 4 times a day – for life…..

I hope you've got this right……I'm trusting you

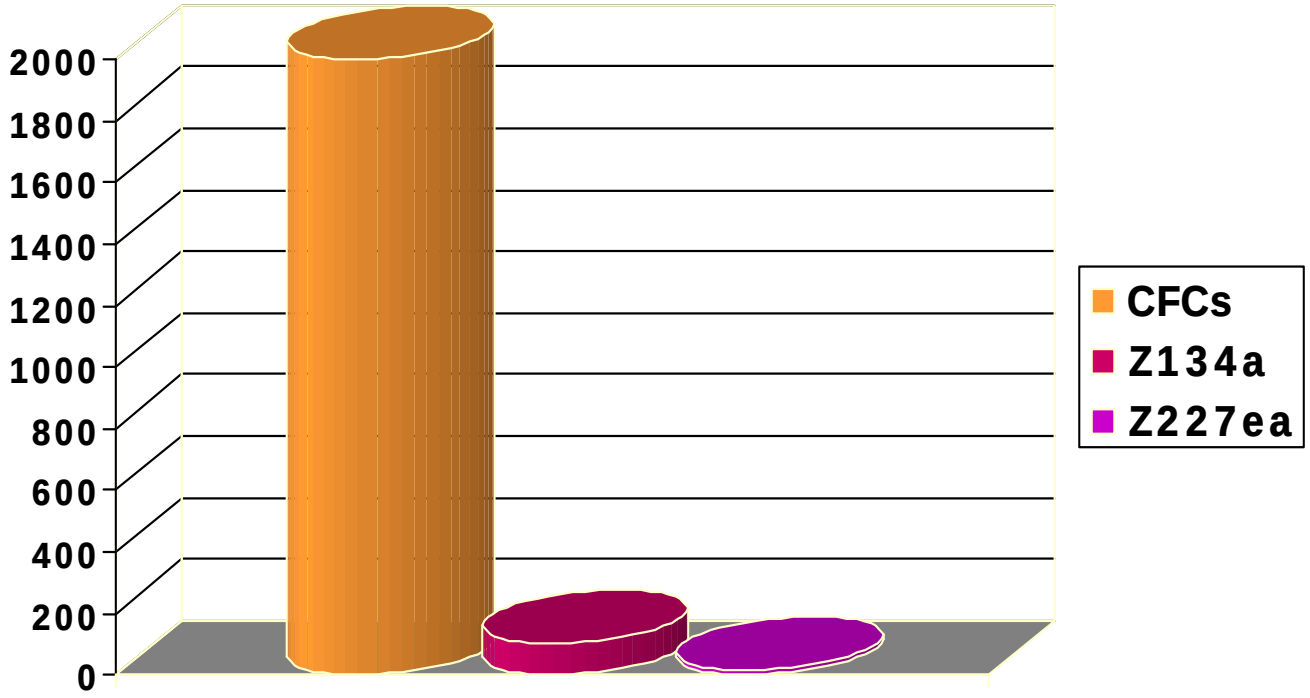

CCRU 432010 9
22T8
CAPACITY 21570 Litres
5698 U.S. Gall
NET 29410 kg
64838 lb
zephex
zephex
medical propellants
pure quality
SUTTONS
Y711
GFM

HFAs- 21st Century Medical Propellants

- The control required for this demanding application is achieved by:
  - Ultra-tight specifications
  - Rigorous analysis
  - Very high GMP compliance
  - Independent inspection by government health bodies

CFC and ZEPHEX purities compared

Specification total impurities ppm



QC Laboratory


DELL

Regulatory Scrutiny

- ZEPHEX 134a is controlled by regulators:
  - US DMF/ Inspections system. Z 134a is approved for and used in the USA.
  - UK MHRA (MCA) regular inspections ever 2 years (voluntary)
  - Perhaps 20 audits per year from customers

  A very high standard of cGMP is maintained

4 HFA delivery and storage

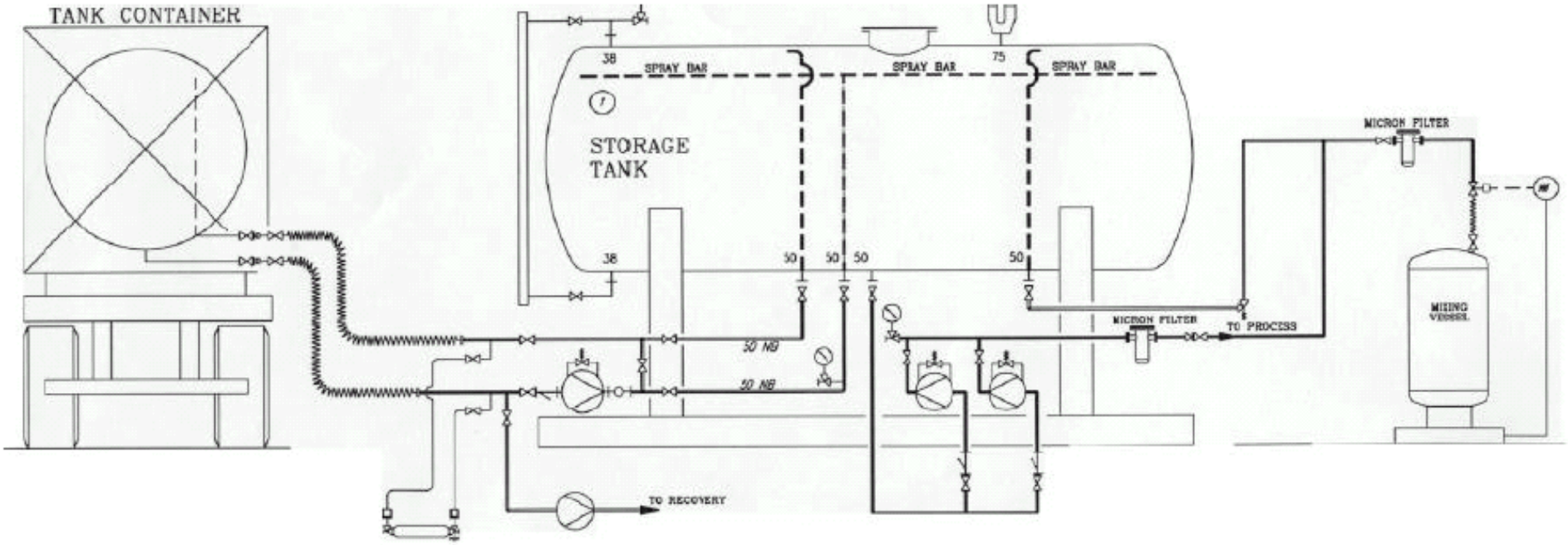
Shipment size & packages

ZEPHEX propellants can be delivered in

- Bulk loads of 10- 20 Tes
  - Unload to stock tank
  - Run from Isotank
- Returnable drums of ~ 1 tes capacity
- Cylinders of ~ 60 Kg capacity (usually for R&D work)

Typical Bulk installation

Figure 1: Typical Stock Tank and Delivery Installation (the 'Well Connected' Stock Tank)



TYPICAL BULK STORAGE INSTALLATION

Isotanks

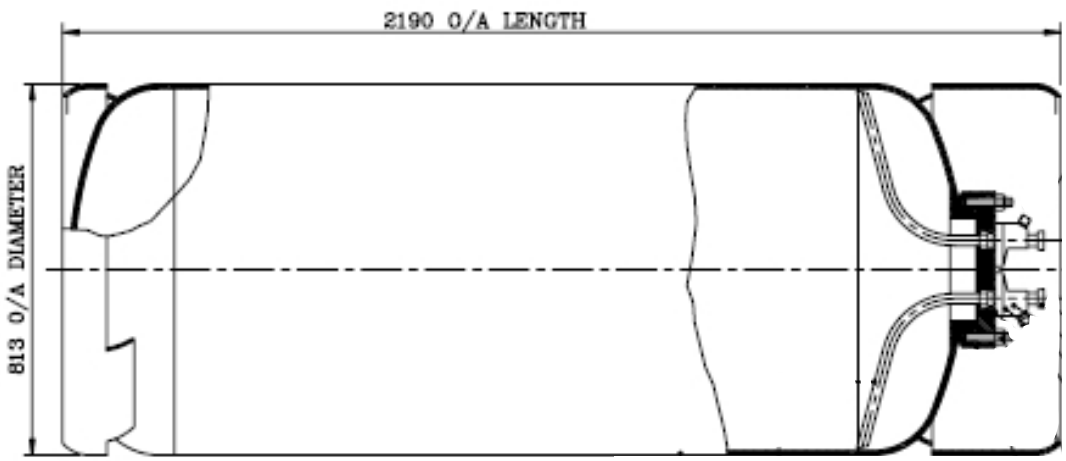
10 – 20 Tes loads in stainless steel isotanks

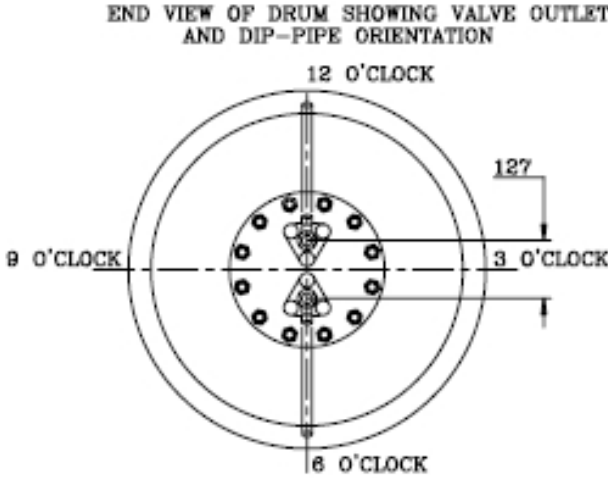
ZEPHEX - packages

57Kg Nett weight cylinders

935 Kg ‘roll’ drums

Typical HFA returnable ton drum





Useful drum handling Trolley

How can we help?

- Consultancy & Website customer zone
- Analytical methods
- Propellant handling expertise
- Propellant Engineering expertise

Consultancy

- Since Mexichem has worked with most of the HFA MDI development projects in the world, we know where most of the problems and traps are!
- We offer free consultancy, not only relating to the propellants, but to a wide range of MDI problems
  - Moisture gain
  - Poor stability
  - Bad taste
  - Decreasing respirable dose
  - Static
- Also give advice on formulation design – ethanol, our best friend and occasional enemy…
- Website customer zone – www.zephex.com

Analytical methods

Customers usually decide to set up one or two of the analytical methods:

- Identity testing for incoming raw material acceptance
- Moisture for in-process work (not needed?)
  All methods are available on the ZEPHEX website, and Mexichem analysts will assist customers to implement the methods as required.

Analytical methods – Available on website

Analytical Methods For ZEPHEX 134a	View Page	PDF
Interactive Certificate of Analysis	view	
Identity check by infra-red spectrometry		
Identity check by gas chromatography		
Determination of related organic impurity levels by gas chromatography	view	
Determination of non-condensable gases in the vapour phase by gas chromatography		
Determination of water content by Karl Fischer coulometer		
Determination of residual acidity		
Determination of high boiling impurities		
Assessment of appearance		
Detection of halide ion		
Determination of non-volatile residue		
Detection of malodour		

Identity by IR

A simple method using a standard IR machine. A specialised cell is needed.

Engineering and propellant handling Support

- Mexichem has engineers who are expert at working on customer HFA installations
- Can provide advice on:
  - Best layout for propellant storage facilities
  - Validation protocols for propellant storage and handling
  - Validation testing
- Package diagrams, procedures, advice on website ……and moisture resisting designs

Summary

A few key points

- HFA propellants behave differently to CFCs
- Treated more like drugs, controlled to a very high level. Extremely safe.
- Advice available from Mexichem to cover all aspects of use of HFAs to make MDIs
- HFA MDIs very well understood – possibly better than the old CFC ones