



INSTALLATIONS INTRODUCTION

Mexichem Fluor has over thirty years' experience in the use of the packages and containers used for the transport and storage of liquefied gases (such as ZEPHEX® pharmaceutical propellant). This wide experience means that a comprehensive technical service can be offered to customers on these matters.

Information concerning storage installations and the delivery of propellant into these installations will nearly always be specific to the particular installation and the particular customer requirements. However, irrespective of whether the requirement is to link a drum or cylinder to a pilot installation or whether the requirement is the design of completely new bulk storage facilities Mexichem Fluor should be able to help.

Mexichem Fluor's Transport Engineering personnel have also been successfully involved in the conversion of existing CFC storage facilities to HFA duty. On all occasions these conversions (and also new installations) have been undertaken to the standards required by the leading regulatory bodies such as the US Food and Drugs Administration and the UK Medicines and Healthcare Products Regulatory Agency.

OPTIONS FOR STORAGE INSTALLATIONS

Three main options for ZEPHEX® propellant storage installations are viable, and are typically used. These are:

1. The construction of new stock tank/storage installations.
2. The use of an ISO tank container as a stock tank.
3. The conversion of existing CFC stock tanks.

Mexichem Fluor is keen to work with customers to ensure that storage installations and stock tanks are correctly specified, designed, commissioned, validated and correctly operated in routine use, irrespective of the option which is selected by the customer.

NEW STOCK TANK/STORAGE INSTALLATIONS

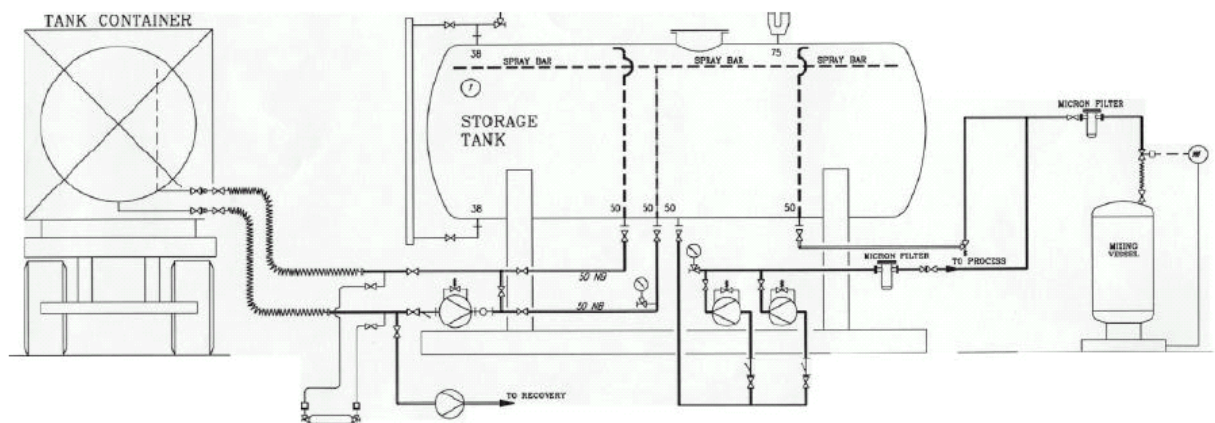
Introduction

Several aspects of well-designed delivery and storage installations are described below.

Although there will invariably need to be adjustments to a basic design to meet the requirements of a particular installation, the key features and the reasons for having them, remain. Moreover these key features are generic to both new build installations and the CFC stock tank conversion option and they should therefore be part of the consideration of any proposed conversion.

A diagram of the well designed, and well-connected, stock tank and delivery installation is given as Figure 1.

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



TYPICAL BULK STORAGE INSTALLATION

The Stock Tank

Obviously the starting point! In designing a new stock tank installation consideration will need to be given to the following:

- Tank capacity.
- Tank connections.
- The incorporation of spray bars.
- Ancillary equipment.

Capacity will in large part be determined by the downstream equipment for product formulation; it can however be pertinent to consider the capacity of the propellant delivery container and to consider aligning the capacity of one with multiples (or a proportion) of the other.

The inclusion of spray bars within the tank should be considered during the design process. Mexichem Fluor's view is that their inclusion will considerably facilitate the commissioning process, and can reduce the amount of propellant used, and therefore potentially discarded/downgraded.

The stock tank connections for linking to other equipment should be flanged in style.

The ancillary equipment associated with the stock tank will also need full consideration during the design process. Such equipment includes a level device indicator and relief valve mechanism for the tank as well as the connecting pipework.

Offloading Unit

The next key feature of a well-designed installation is the 'Offloading Unit' for the delivery container, usually an ISO tank container. This is itself comprised of a number of component parts:

- A dedicated offloading/recirculation pump; this eliminates the possibility of any cross contamination of the propellant.
- Flexible hoses for the connection of the delivery vehicle/container to the offloading pump.
- A sight flow indicator downstream of the pump. This assists in the offloading process by enabling visual detection of propellant flow, and also provides a visual check that no particulate matter has been introduced to the propellant during the offloading process.

The pipework, equipment and valves should be configured to enable recirculation of the contents of the delivery container. In normal operation sampling may be required prior to the offloading process; this recirculation ensures the homogeneity of the propellant sample.

Visit the customer zone of www.zephex.com for a full description of propellant sampling procedures.

Process Feed System

The 'Process Feed System' is used to deliver product from the stock tank(s) to the pharmaceutical product formulation equipment. Again this is comprised of a number of key component parts and considerations:

- Pumps, which are sized to give required flow rates and pressures.
- A filtration mechanism; this is viewed as a 'safeguard' filter to cover the eventuality of residual particulate matter remaining within the storage installation from commissioning or scheduled maintenance. Robust cleaning protocols should prevent such particulate matter being present, and the propellant itself is supplied free of particulate matter, but it is a valuable feature.

- Temperature/Pressure control; consideration should be given to the need for temperature and pressure control in the manufacture of the formulated pharmaceutical product. Temperature and pressure variations can affect the fill weights of formulation vessels and/or the finished medical aerosol product.
- Temperature and pressure control therefore need to be an integral part of design considerations for the process feed system.

Cleaning Protocols and Procedures

An important feature of the design and installation of a delivery and storage facility is the attention given to ensuring that the component parts are scrupulously clean prior to assembly and commissioning. All equipment needs to be the subject of rigorous cleaning in accordance with pre-defined protocols. The cleaning protocols need to identify detailed requirements, and include appropriate checks and certification mechanisms.

For tanks, pipework and fittings degreasing with an appropriate cleaning agent is usually needed. Pipework and tanks are also typically 'pickled' (treated with a dilute acid wash appropriate to the material of construction) and 'passivated' (neutralised with an appropriate passivating agent, often an inorganic salt solution). Pickling and passivating is usually followed by a demineralised water rinse.

Valves must be procured from the manufacturer degreased to 'oxygen standards' (i.e. no grease) and supplied in sealed bags. Any parts supplied in damaged bags should be rejected; this requirement which should be stipulated in the appropriate cleaning protocol.

Assembly and Leak Testing

Once the component parts of the installation have been confirmed as being clean the installation can be assembled and leak tested. As with cleaning, a protocol needs to be defined for the assembly and leak testing.

Such a protocol will specify steps to ensure that there is no ingress of contaminants to the cleaned component parts, as well as specifying the duration of leak tests. These will typically be at elevated pressure using dry nitrogen or air. The dryness of the installation is also checked at this point from dew point determinations of samples (typically -30 °C or cooler).

Commissioning

Once assembled and leak tested, the commissioning of the installation can be undertaken. This should be done in stages (offloading, stock tank, process feed system) with the detailed activities to be undertaken, and the detailed results to be obtained, specified by protocol.

Beginning with the stock tank and offloading systems a deep vacuum is created, and the vacuum then broken by the introduction of propellant. The

initial inclusion of spray bars within the stock tank itself reduces the inventory of propellant needed for the commissioning since they allow for a total wetting of the tank interior surfaces with considerably less propellant than a full tank. The introduced propellant is initially recirculated around the offloading system and sampled for analysis. When satisfactory results are obtained the propellant recirculation can be extended to the stock tank. It is however essential for Mexichem Fluor to be satisfied with the integrity and cleanliness of the offloading system/stock tank before recirculation back into the delivery tank would be acceptable. Once satisfactory results have been obtained for the offloading systems and stock tank, propellant can be fed forward to commission the feed system to the pharmaceutical formulation process. Analysis of the propellant samples will typically be to confirm the absence of moisture, greases and particulate matter, and will therefore indicate the suitability of the facility for use. The results obtained will indicate the next steps, with flushing the system with fresh the propellant (e.g. if it contains grease), drying the propellant (and thereby the stock tank) or using the propellant, all possibilities.

Commissioning protocols need to address the issue of the ultimate use of the propellant, which is used in this flushing procedure. In the event that propellant analysis shows that the stock tank, offloading and process feed systems are suitable for use, some pharmaceutical customers allow the material to be fed forward; others prefer to remove and dispose of the commissioning propellant.

Mexichem Fluor is prepared to discuss with pharmaceutical companies the possible return of commissioning quantities of propellant for downgrading to industrial applications. It must however be noted that Mexichem Fluor are unable to handle propellant which has in any way been contaminated with active pharmaceutical ingredients.

Upon completion of the commissioning of the stock tank, offloading and process feed systems; it is possible for the propellant to be fed forward, and for the commissioning and validation of the pharmaceutical product formulation process to be undertaken.

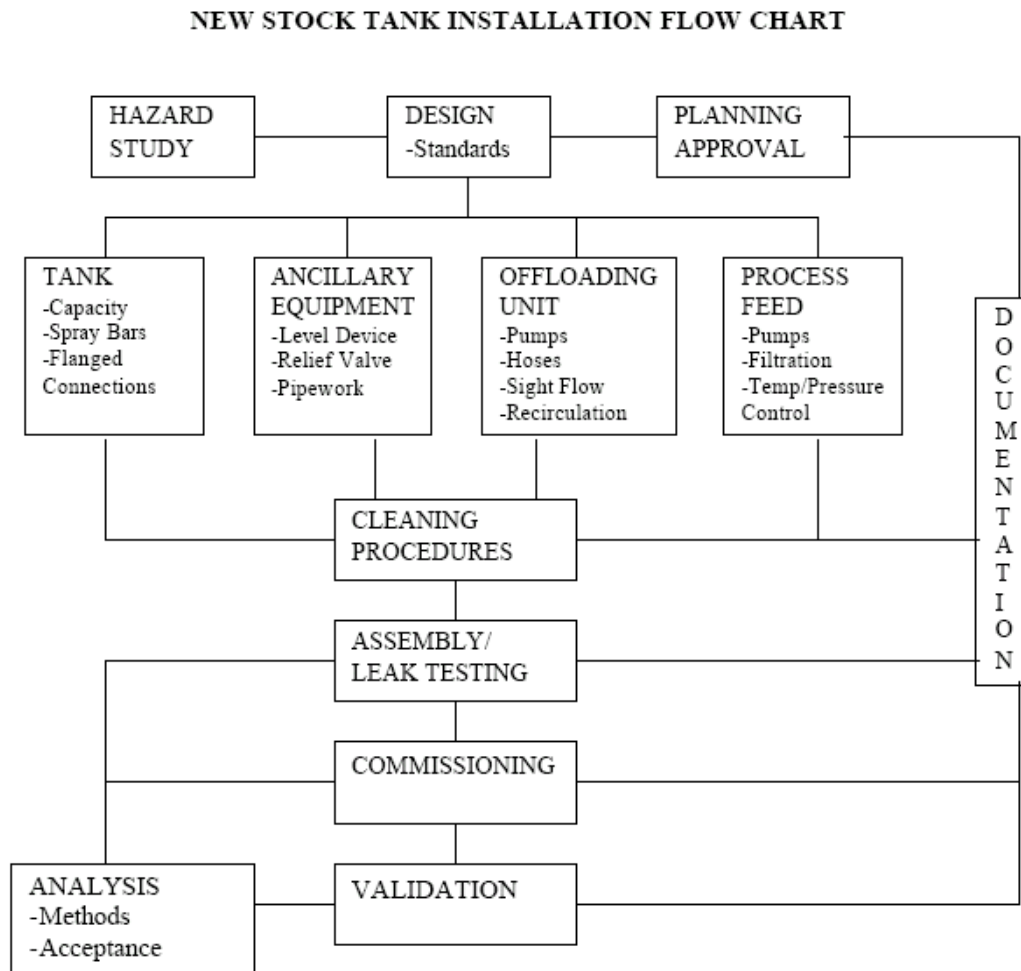
Mexichem Fluor: Always there to help

There are a number of ways in which Mexichem Fluor can help with the design, installation, commissioning and validation of new stock tank/storage installations:

- Input to design and commissioning.
- Definition of cleaning and validation requirements, including acceptance criteria.
- Site visits, before and during the commissioning process.
- Sampling procedures (see customer zone of www.zephex.com).
- Analytical methods.
- Analysis of samples at very competitive rates, by the Mexichem Fluor Medical Propellants Laboratory, located at Runcorn, UK.

- Pre-delivery visit, prior to first delivery.
- On site attendance during first delivery.

An installation flow chart is given below.



THE USE OF AN ISO TANK CONTAINER AS A STOCK TANK

Benefits

In some circumstances the use of an ISO tank container as a stock tank is the most appropriate option. Figure 2 shows the typical arrangements for an ISO tank container to be used in place of a fixed customer storage tank. This arrangement has the following key benefits:

- The customer does not have to invest in the cost of a storage tank, and the associated civil, electrical and pipework installation costs.
- The cleaning, commissioning and validation costs of a bulk storage installation are eliminated.

- The propellant will be transported and stored in stainless steel tank containers specifically designed for and dedicated to the transport of pharmaceutical grade products (as distinct from the industrial grade products).

Requirements

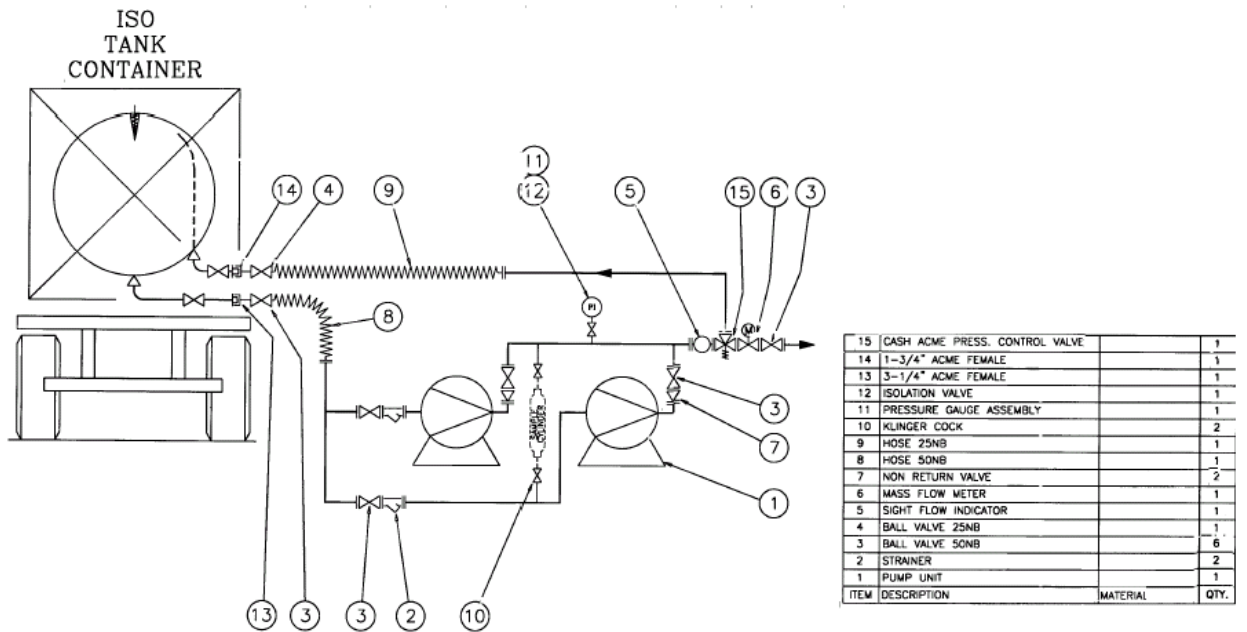
This arrangement does however have the following key requirements:

- Sufficient space is available to position an ISO tank container, possibly two, and a pumping unit. Figure 3 gives overall dimensions of a tank container mounted on a trailer. If it is possible to lift the container on to the ground then a crane capable of lifting 30 metric tonnes would be required.
- As there is a tamper proof seal arrangement on the outlets of the tank container to ensure the integrity of the product when it arrives on site, arrangements will need to be established to ensure that new seals are fitted when the tank is empty and leaves the site.
- A pumping system will be required which incorporates a number of features:
 - Two pumps, one standby and one spare.
 - A mass flow meter to determine usage, and to assist in controlling stock recorder levels.
 - A recirculation and sampling system to enable representative samples of the delivery tank to be taken [It is however essential for Mexichem Fluor to be satisfied with the integrity and cleanliness of the pumping system before recirculation back into the delivery tank would be acceptable].
 - Isolation valves fitted to the ends of the flexible hoses to the tanker connection point to minimise losses and the ingress of moisture and debris.

It is possible to utilise existing customer pumping equipment but it is recommended that the above features are incorporated.

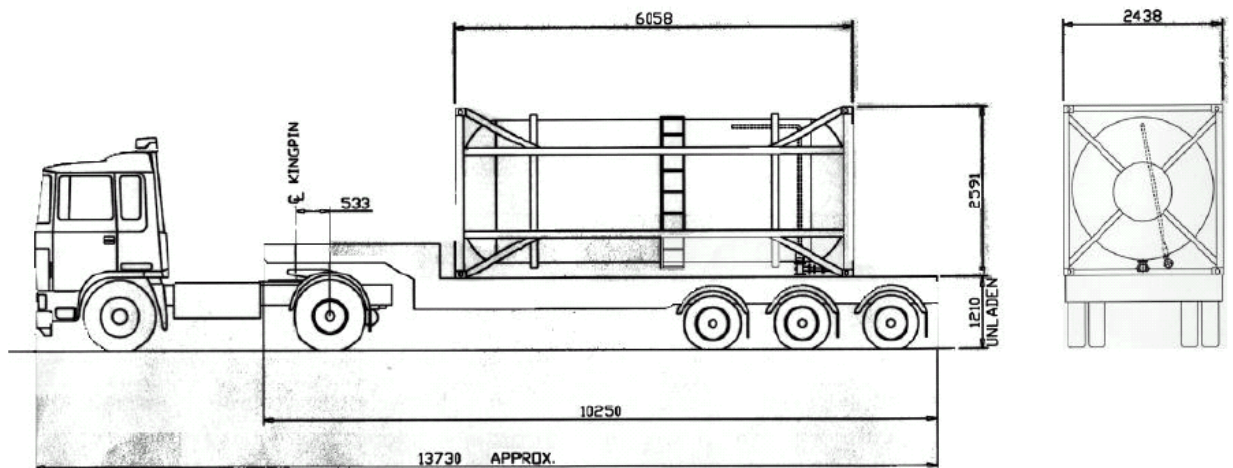
Although many of the significant capital costs associated with the construction of a new bulk storage facility would be avoided with this arrangement it does not come without costs.

Figure 2: Use of an ISO Tank Container as a Stock Tank



USE OF A TANK CONTAINER AS A STOCK TANK

Figure 3: Typical Arrangement and Dimensions of Tank Container mounted on Trailer



TYPICAL ARRANGEMENT OF TANK CONTAINER MOUNTED ON TRAILER

The cost of a trailer and ISO tank container hire is about \$75 per day, and the cost of a new pumping system, incorporating the features outlined above (and outlined in Figure 2) would cost around \$30K, excluding installation, cleaning and commissioning.

THE CONVERSION OPTION

Benefits

The conversion of existing stock tanks which have been previously used for the storage of CFC propellants is another aspect of product storage and handling with which Mexichem Fluor has considerable experience. Customers for ZEPHEX® propellants who have, or who are expecting to have, redundant CFC storage tanks may want to consider the option of converting them to either ZEPHEX®134a or ZEPHEX®227ea duty.

Stock tank conversion has its benefits. As might be expected it is cheaper than the cost of designing and building new storage facilities. Again as might be expected, a stock tank conversion is quicker than the new build option. A less obvious, although nonetheless important consideration is that the conversion processes recommended by Mexichem Fluor ensures that the loss of residual product is kept to an absolute minimum.

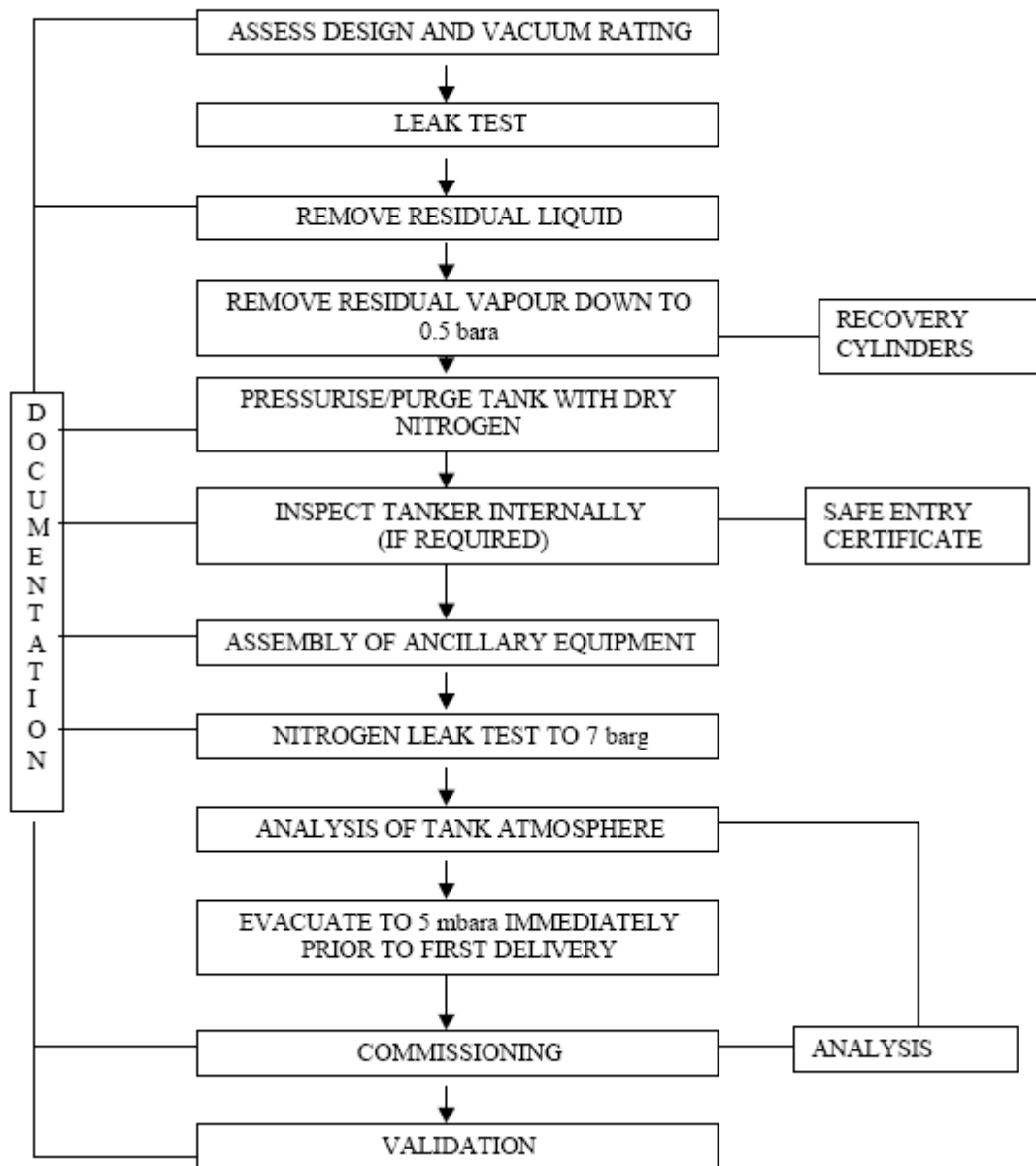
The Conversion Process

The stages in the process of converting CFC stock tanks to ZEPHEX® propellant duty is outlined in the flow chart below.

In stock tank conversions there are a number of other areas, in addition to the specific conversion steps, where Mexichem Fluor can help:

- Definition of the validation requirements, including acceptance criteria, and templates for the associated documentation.
- Input to any design or modifications needed to the offloading system.
- Site visits, before and during the conversion process.
- Sampling procedures (see customer zone of www.zephex.com).
- Analytical methods.
- Analysis of samples, at very competitive rates, by the Mexichem Fluor Medical Propellants Laboratory, located at Runcorn, UK.
- Pre-delivery inspection, prior to the first delivery into the converted stock tanks, or:
- On site attendance during the first delivery (in part to ensure that commissioning has been successfully achieved and that there is no possibility of any back flow into Mexichem Fluor's delivery tankers).

STOCK TANK CONVERSION FLOW CHART





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