# Chapter 40 – Pharmaceuticals in Temperature Controlled Containers

Many different pharmaceuticals are supplied worldwide, some requiring temperature controlled storage and distribution to maintain their efficacy and other properties.

Until fairly recently, long distance distribution of products was undertaken by air, but there has been a trend to move some of them by sea in refrigerated containers. Due to their sensitivity to the atmosphere and limited storage life, they are referred to as Time- and Temperature-Sensitive Pharmaceutical Products (TTSPP).

The carriage of pharmaceuticals and intermediaries is already established on many trade routes with different transit times. Two examples are Ventolin (an aid to breathing) carried at chilled temperatures and blood products moved as frozen cargoes.

Some cargoes create significant cold chain challenges if they are temperature sensitive or have a very high value. When both the sensitivity and high values of a pharmaceutical shipment combine, a careful and systematic approach to its planning and carriage must be undertaken. The consequences of a failure to do so can be serious. The damage to

cargo is one aspect that may lead to P&I claims, but timely delivery of pharmaceuticals may also be of critical importance for public health, eg during a pandemic.

## 40.1 Product Attributes and Challenges

Pharmaceutical product attributes have to be preserved through the cold chain to give the consignee the outturn expected after loading good quality product into the container. It is extremely helpful if shippers can explain the physical, chemical and biological attributes of sensitive products being carried. Products must have adequate storage lives for the transit phase and the next steps in the distribution chain to the patient or user.

Temperature control and times off refrigeration should be clearly specified and well controlled. Reefer containers are designed only to maintain the temperature and not to cool down any cargo. Shippers therefore need to ensure that appropriate procedures are followed prior to and during stuffing containers.

In the event of problems or claims concerning products whose characteristics are unknown, or not fully known, carriers/shipping lines should contact their P&I Club to identify experts to provide assistance.

## 40.2 Carriage Challenges

For the successful carriage of pharmaceuticals on long sea routes, carriers should ensure that:

- Cold chain requirements are met, using equipment that operates correctly
- procedures, information flows and operations are compatible and coordinated
- due diligence actions for quality control systems and security requirements are defined and followed
- careful work by trained personnel provides good quality control and assurance
- any ambiguity or lack of information is resolved prior to accepting a consignment.

Transport of pharmaceuticals in reefer container shipping is still relatively unusual and its requirements are less well understood. It may, therefore, be helpful to consider the features of an equivalent class of food product in transit.

However, many pharmaceuticals have a very much higher value than the equivalent volume of food products. They are also regulated by national or state medicines agencies that have several similar roles to foods standards agencies.

The World Health Organization (WHO) supports member States through the publication of international standards to ensure delivery of high quality finished products to the end user. Some examples are *Good Distribution Practices for Pharmaceutical Products* (Reference 62), *Guide to Good Storage Practices for Pharmaceuticals* (Reference 63) and *Supplement 13: Qualification of Shipping Containers* (Reference 64), a technical supplement to WHO Technical Report Series No. 961, *Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products*.

## 40.3 Management Issues

Carriers should define the extent to which they are prepared to carry cargoes of certain materials on different routes, as they can differ significantly in sensitivity, monetary values and the levels of control that are possible. The onus, however, remains with the shipper to declare the goods accurately and to specify any special carriage requirements. If the carrier discharges their duty of care as per the prescribed procedures and precautions, any losses may have to be picked up by the shipper and/or the consignee.

Pre-transit risk assessments should be made, to include discussions with the shippers (and consignees if necessary). Accepted cargoes should initially transit as trial shipments, with review after outturn. One approach is to limit risks by only accepting 20 ft container loads of particular products until the transits have been established. Corrective actions can be taken, if necessary, for further shipments, and in extreme circumstances bookings may be refused.

## 40.4 Commercial Issues

Additional insurance premiums may be payable, depending on the risk limits and previous experience in carrying similar products. Special rates may be necessary to cover the additional work in carrying the cargoes successfully and the extra precautions taken against the risks. Careful wording on B/Ls is also required.

## 40.5 Operational Issues

Shippers define the set point temperatures required for the cargo. Other carriage requirements must also be agreed with the carriers when the containers are booked. There may be a need for additional instructions and checks in transit, depending on product sensitivities and the routes. Clearance by the appropriate authorities in importing countries may be specified, as well as compliance with consignees' due diligence standards.

Shippers may include their own independent data loggers in the cargo space to measure product or air temperatures. A few data logger types are able to calculate mean kinetic temperatures (a defined form of weighted average), while others record shocks and vibrations. Relative humidity is measurable, but the accuracy of the data must be considered carefully and large variations allowed.

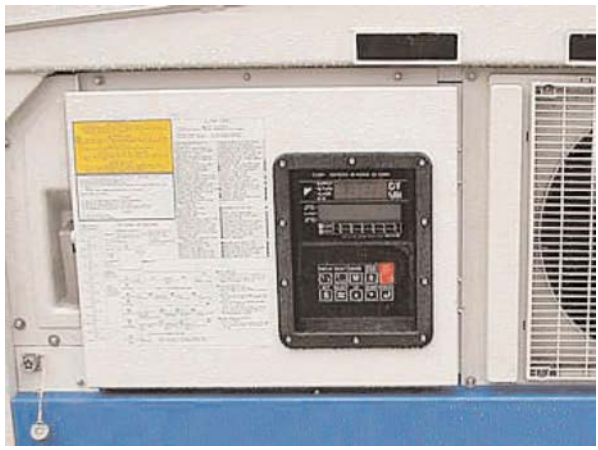


**Figure 40.1: Temperature/data recorder.**

## 40.6 Temperature

Pharmaceuticals should be carried in integral containers with good refrigeration capacity, high internal airflow rates and an ability to provide the required temperature control. Following the stuffing of the cargoes into containers, they require the capability to deal with the heat loads to which they may be subjected.

Warm cargo must never be shipped for cooling on board. All cargo must be pre-cooled to its temperature for carriage prior to stowing in a container, keeping in mind that reefer containers are only designed to maintain the temperature at which they are set.

Pharmaceuticals are often transported in reefer containers in nominated temperature zones. Many require an environment in the +2°C to +8°C range. These products must not freeze or become too warm in transit because this may impair their potency, or adversely affect colloidal suspension or other properties, potentially compromising product release. Pharmaceuticals vary in sensitivity, but the most sensitive could be considered somewhat similar to chilled meat for carriage. The container set point is normally in the +2°C to +8°C range, and +4°C or +5°C are often used.

Temperatures colder than minus 18°C (–18°C) are specified for some products. They are often sensitive to temperature fluctuations as well as needing a cold base temperature. A temperature set point of minus 25°C (–25°C) for containers is often requested. Serious thawing can often be observed by eye, but changes in protein structure or other changes caused by temperature fluctuations will require laboratory assessment. For example, frozen blood products could be compared to carrying a product with the combined properties of ice cream and individually quick frozen (IQF) prawns. Temperature fluctuations in ice cream can cause texture changes whilst prawns can incur protein denaturation and weld together. Ice crystals can form in both products. Similarly, blood products can suffer protein damage and separation if not stored correctly.

Temperatures cooler than +15°C or even +25°C are required for shelf stable products. Examples are powders, liquids and tablets. An equivalent food product is chocolate confectionery (usually carried with a set point of +10°C).

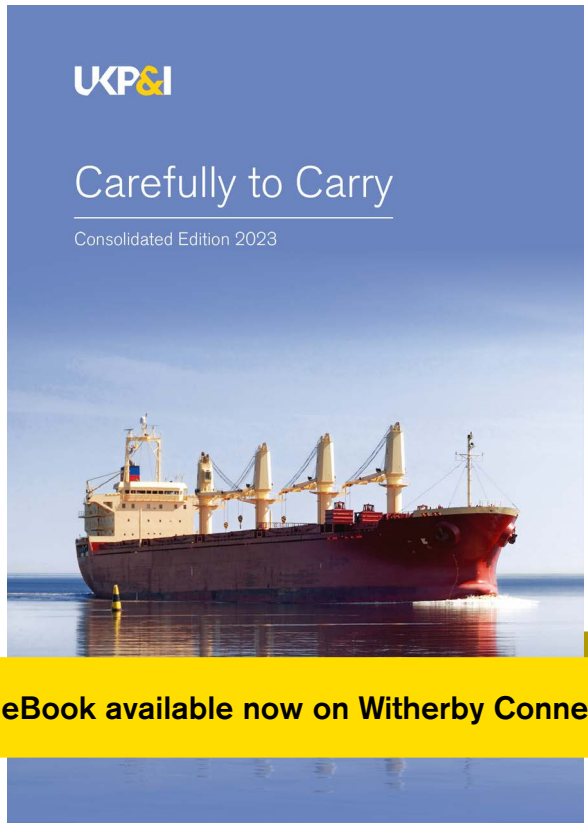
The shipper may specify individual container set points outside the above general ranges to meet a product requirement. If the carrier is uncertain as to the shipper's requests, independent expert advice should be sought.

The shipper may request relatively dry air to be circulated in the containers. Many modern containers are fitted with a dehumidifier to reduce the relative humidity (RH). The RH is measured and controlled by a probe in the refrigeration unit. It does not represent the actual RH throughout the cargo space, which is difficult to measure accurately, and a tolerance of at least ±5% over the available range should be expected.

Fresh air ventilation is not expected for chilled pharmaceutical cargoes, but the need for any such requirements should be checked before bookings are accepted. Ventilation volumes should be kept as low as is essential.

# Carefully to Carry

Consolidated Edition 2023




**Full eBook available now on Witherby Connect**

**Price: £95**

This comprehensive publication, compiled by the UK P&I Club, details best practice for the carriage, loading and storage requirements of a wide range of cargoes. It also contains essential information on draught surveys and preparing cargo plans.

Outlining and expanding on all major international cargo regulations and guidelines, it also includes detailed checklists, information on draught surveys and guides to preparing cargo plans. Cargoes covered include timber, gas, grain, steel and other metals, bulk goods and refrigerated goods.