Refrigerated medicinal products: what pharmacists need to know.

Patients and other healthcare professionals are entitled to expect that medicines sold or supplied from a pharmacy are fit for their intended purpose.
In this article, Steve Todd looks at preventing breaches in the cold chain.

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This article draws on some of the findings from inspections performed by the Medicines and Healthcare products Regulatory Agency's good distribution practice (GDP) inspectorate and focuses on the many issues relating to the storage and distribution of medicinal products that need to be maintained between 2 and 8C.

To ensure that medicines distributed to retail pharmacies and other persons entitled to sell products to the general public are of the appropriate quality, they must be manufactured in licensed facilities that comply with the principles and guidelines of good manufacturing practice (GMP). They must also be distributed through a network of licensed pharmaceutical wholesalers, who in turn, must comply with GDP.
The requirement for wholesalers to comply with the principles of GDP is stated in European Directive 92/25/EEC, which also provides that member states will perform inspections of their premises.

Distribution.
Following manufacture, some medicinal products need to be stored and shipped at lower than ambient temperatures to assure their quality and efficacy. These are often referred to as "cold chain products" or "fridge lines" and wholesale dealers are expected to store and distribute them in strict accordance with the product labelling requirements. (They cannot rely on stability data in the event of temperature deviations).

Some cold chain items, such as vaccines, insulin, biotech products and products derived from blood or plasma, can be classified as high risk because they are at risk from freezing as well as elevated temperatures. Other products, for example, chloramphenicol eye drops, may be labelled as requiring storage between 2 and 8C but a short deviation from this temperature range presents less of a danger to users.

Following dispatch from a manufacturing facility, the distribution chain for medicinal products can be complex, potentially involving a number of storage locations, wholesalers and modes of transport, before the delivery finally reaches the pharmacy.

The transportation arrangements from one location to another should be regarded as an extension of the storage activities and distributors are expected to treat each journey as unique with the length and complexity, as well as any seasonal variations, being considered when choosing the packing method and mode of distribution.
Cold chain products should be packed in such a way as to ensure that the required temperatures are maintained throughout the journey and the medicines are transported in accordance with their labelling requirements to prevent jeopardising their quality.

For small volumes of lower risk products, with short journey times of less than three hours, insulated containers are generally used. For extended journeys, gel or ice packs are added to the packaging to maintain appropriate temperatures throughout. The positioning of these packs within the consignment is extremely important and they must not be allowed into direct contact with the products being shipped.
Bespoke packaging with compartments for the gel or ice blocks are available, although securely encasing the blocks in some form of wrapping, such as bubble wrap, or installing some other form of a buffer can be equally as effective.
Larger volumes of refrigerated products will generally be shipped in refrigerated transport. This is particularly important if transportation times may be protracted or liable to delay.

Whatever method of transport is used, it is important to show that the required temperatures can be maintained for a stated time period. Wholesalers are therefore required to undertake validation studies of their distribution activities and may use, for example, temperature loggers in deliveries during the summer and winter months for the most difficult journeys.

Best practice in this area is the implementation of temperature monitoring as a matter of routine for all refrigerated deliveries, but especially within shipments of high risk products, where the temperature should be strictly controlled and monitored with calibrated temperature probes, to provide temperature data for the entire journey. Daily temperature monitoring and recording should also be carried out at all storage locations. Any recording devices should be calibrated annually against a certificated standard.

Distributors should review the temperature records or data for each consignment and there should be procedures in place for implementing corrective action in the case of adverse events. They should also ensure that consignments of refrigerated goods are clearly labelled with the required storage and transport conditions to be maintained. When wholesalers employ couriers, they must satisfy themselves that they also adhere to the above. To ensure this, some wholesalers will enter into a technical agreement with their chosen courier.

Receipt in the pharmacy.
When cold chain products are received at a pharmacy, it is important that they are promptly checked in and placed in a refrigerator. The person responsible for receiving the delivery must also satisfy themselves that the goods have been transported under appropriate conditions (e.g. there has been no direct contact between the products and gel or ice blocks).

If it cannot be confirmed that the products have been transported under appropriate conditions and there is concern that their quality may have been compromised, the delivery should be quarantined in a suitable refrigerator whilst enquiries of the supplier are made. Until the issue has been clarified to the pharmacist’s satisfaction the products in question should be considered as unsuitable and should not be supplied or sold to patients. If, following enquiries, there is still doubt as to the quality of the medicines received, the delivery should not be accepted and should be returned to the supplier.

As with any delivery, staff receiving goods should also be alert for the presence of counterfeit medicines.

Cold chain returns.
Returns of cold chain products is an area that receives a great deal of attention during a GDP inspection. MHRA have issued guidance on refrigerated returns which states that if a cold chain product is to be returned to the wholesaler, this must occur within 24 hours of the original dispatch. After this time, the returned product cannot be considered for resale and must be sent for disposal.
In practice however, because of the inherent dangers of returning cold chain products, many wholesale dealers will not consider them for subsequent resale in any event. All such returns are immediately stored in a dedicated and marked area awaiting collection by a licensed disposal company.
In the event of a wholesaler accepting a return of a refrigerated product, possibly because of its high monetary value, the product must be returned within 24 hours following dispatch, in an appropriate method of transport, with supporting documentation, such as a returns form. The returns form would normally include the reason for the return, contain details of the product and how it has been stored and should be signed by an authorised and identifiable signatory.
A trained person at the wholesalers will examine the returned product to check for tampering and to confirm that the return has been made within the stated 24 hours. If this examination cannot be undertaken immediately, the product should be stored in a dedicated and marked area in a refrigerator until the checks can be made. Provided the checks are satisfactory the product may be returned to saleable stock.

Storage in the pharmacy.

Domestic refrigerators.
Standard domestic refrigerators are not ideal for storing cold chain products for a number of reasons, including an uneven temperature distribution (as a result of minimal air circulation) and a normal operating range of between 0 and 10C. Opening and closing the fridge door can cause significant temperature fluctuations, making monitoring of the internal temperature difficult. There is also a risk that products could freeze if they come into contact with the chiller plate or coil at the back of the fridge.
During GDP inspections of pharmacies that also hold a wholesale dealer's licence there have been instances where the refrigerator is also being used by staff for the storage of milk and food as well as medicinal products.

Pharmaceutical refrigerators.
A purpose-built pharmaceutical refrigerator is recommended for the storage of cold chain products, especially those identified as high risk. The air within this type of refrigerator is circulated by a fan, which provides a uniform temperature profile and a rapid temperature pull down after the door has been opened. Temperature monitoring is usually by a calibrated electronic min/max thermometer, with an accuracy of ±0.5C, which can be read without opening the refrigerator door. Additional benefits are that these refridgerators can be locked and some have the option of either an audio or visual alarm system to alert staff in the event of temperature deviations. Many also

have glass fronted doors giving greater visibility to stock levels, aiding stock management and also deterring the storage of non-medicinal products, as mentioned above.

When purchasing a new refrigerator therefore, factors to consider might include how long the unit can maintain the recommended temperatures if the power is turned off and to what extent the cabinet temperature is affected by ambient temperature variation, for example, in hot spells.

Best practice.
Whatever type of refrigerator is used, products should be stored in an orderly fashion on shelves - not on the floor of the unit - to ensure air circulation and consistent temperatures throughout. Temperature monitoring probes should be sited in a central location within the refrigerator and, preferably, between the products. They should not be placed in the door.
The refrigerator should be cleaned regularly (as part of a general cleaning rota) and serviced at least annually. If fitted with an audible or visual alarm this should routinely tested to confirm correct operation.
The stock within the refrigerator should be subject to effective stock rotation based on first expiry, first out, and it should not be assumed that the most recent deliveries will have a longer expiry period.

Temperature monitoring.
As was applicable for transportation, products stored in a refrigerator should be subject to daily temperature monitoring.
Temperature records should identify any temperature deviations and give details of corrective actions taken as a result. For instances where there has been a temperature deviation, best practice would be to take a further reading later the same day, to ensure that it was a transient deviation and show that the temperature was now back within prescribed parameters.
Temperature records are especially important in the event of a problem with a product and may be required as evidence of appropriate storage. With this in mind, they should be free from alterations or corrections and the person responsible for taking the readings each day should have a trained deputy to cover for absences. Additionally, the records should be routinely reviewed by the Responsible Person.

Conclusion.
Maintenance of the cold chain throughout the licensed wholesale network is assessed by MHRA GDP inspectors and it is hoped that this article has heightened awareness of some of the issues that need to be considered surrounding the transportation, receipt and storage of cold chain products.
In recent years, UK wholesalers have generally been receptive to an increased inspection focus in these areas and there has been a noticeable improvement in standards.

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