

Preserving the cool chain

Mary Simpson, Edith Penxten and Elie Dechesne of Bristol-Meyers Squibb examine the logistical challenges facing the pharmaceutical industry when distributing temperature-sensitive products.

With new legislation in place, tighter regulatory controls and expansion of clinical trials to worldwide destinations, pharmaceutical companies are facing demanding logistical challenges when transferring temperature-sensitive investigational medicinal products (IMPs) from continent to continent. The industry must not only cope with legislation and quality standards, but may face substantial financial and ethical losses if the cold chain is broken. References to the cool chain process are found in legislation and guidelines, such as:

- The EU Guide to Good Manufacturing Practice, Annex 13
- The Guidelines on Good Distribution Practice (GDP) of Medicinal Products
- The Guide to good storage practice for pharmaceuticals
- Guidance notes for GDP for medicinal products, Health Sciences Authority (HSA)
- The Pharmaceutical Quality Group (PQG) monograph
- The US Code of Federal Regulations
- US and European Pharmacopoeia

A search of these sources reveals legislative documents requesting:

- Written dispatch and delivery procedures according to the nature of the product
- Packaging that ensures integrity of the product at intermediate destinations
- Transport by special means, with transit time kept to a minimum
- Container labelling regarding the storage conditions and recommending use of temperature-monitoring devices and the availability of monitoring records

The European Medicines Evaluation Agency (EMA) Committee for Proprietary Medicinal Products (CPMP) document, effective October 2003, requests specific reference to storage conditions on product labels and package leaflets to be consistent with those defined in the summary of product characteristics. In addition, it states that, 'The use of terms such as "room temperature" or "ambient conditions" is unacceptable'.

Surprisingly, temperature ranges from document to document are not always consistent. While 'room temperature' is listed as 15–30°C in the PQG monograph and the HSA guide, the European and US Pharmacopoeia define it as 15–25°C or up to 25°C.

Another discrepancy is the definition of 'cold': three documents list it as not exceeding 8°C; while the European Pharmacopoeia defines it as 8–15°C. Actual storage temperatures should be expressed quantitatively and not in general terms that are subject to different interpretations (see Table 1). There is certainly some room for harmonisation between various documents.

The need for uniform statements on storage conditions is confirmed in the Note for Guidance in the Declaration of Storage Conditions of IMPs, published by EMEA, which states: 'The purpose of this ... note is to set out uniform statements on storage conditions for inclusion in the labelling of medicinal products.'

Referring to the article 'Drug stability testing: classification of countries according to climatic zone', the shelf life of a medicinal product depends on the storage conditions. Climatic parameters are included in the testing conditions to obtain stability data. Stability studies take into account specific temperatures and relative humidity, representing not only conditions experienced in the distribution chain of the climatic zone, but also the expected seasonal excursions of temperature. To avoid multiple stability studies, countries have been classified in four different climatic zones, as follows:

- **Zone I:** temperate, less than 20°C – for example, Germany, Russia and Canada
- **Zone II:** sub-tropical, with possible high humidity, averaging 20.5°–24°C – for example, France, Peru, Australia and USA
- **Zone III:** hot and dry – for example, Botswana, Chad, Syria and Iraq
- **Zone IV:** hot and humid, averaging more than 24°C – for example, Taiwan, Singapore, India and parts of South America

Each country has been assigned to only one climatic zone even though several zones may be found within its borders (for example, Australia and the USA). The derived storage temperatures are defined accordingly.

Table 1. Reference to 'ambient' was not found in the source documents examined

Definition of terms/temperature ranges								
Source	Excessive heat	Warm	Room temperature (controlled)	Cool	Cold	Refrigerator	Freezer	Deep-freeze
Pharmaceutical Quality Group monograph N° 4 UK (1997)			Between 15 and 30°C	No higher than 15°C	Does not exceed 8°C	Thermostatically controlled between 2 and 8°C	Thermostatically controlled to not higher than -10°	
HSA Guide MQA-13-002 (2002)	Above 40°C	30–40°C	15–30°C	8–15°C	Does not exceed 8°C	Thermostatically controlled between 2 and 8°C	Thermostatically controlled between -20 and -10°C	
European Pharmacopoeia			15–25°C	8–15°C	8–15°C	2–8°C		Below -15°C
US Pharmacopoeia	Any temperature above 40°C	Any temperature between 30 and 40°C	'Controlled room temperature' or 'up to 25°C'	Any temperature between 8 and 15°C	Any temperature not exceeding 8°C	Thermostatically maintained between 2 and 8°C	Thermostatically maintained between -25 and -10°C	

Stability data

With regard to stability data, Table 2 features three sample products: A, B and C. The storage and shipping conditions for A and B are 2–8°C; and 15–25°C for product C. Temperature sensitivity is high for A, medium for B and low for C. This data is usually available. However, the permitted excursions per product are often not readily available to distribution staff, yet this excursion allowance will determine whether a product can be used or must be disposed of if the data recorded by the temperature-monitoring device exceeded the required shipping temperatures. Temperature excursions based on stability data for each product *must* be readily available to distribution staff. For instance, product A is high risk and must not freeze, although a 96-hour excursion at 15–25°C is acceptable. Product B (medium risk) may freeze and warm up for up to two weeks at 15–25°C. The low-risk product C accepts hot and cold excursions of up to two weeks.

Shipping risks

With regard to intercontinental shipping, IMPs are transferred from three main central distribution sites in North America and Europe to 62 countries – for example, to local warehouses, and from there to investigational sites. The local site shipment activities stress the need for a capable transporter and, even more importantly, local availability of adequate packing material.

The complex shipping routes are high risk for temperature-sensitive products, but so, too, are the numerous hand-offs from transporter to airlines, to customs and back to transporter.

When transferring IMPs, lead times from dispatch to arrival must be carefully calculated. Within Europe, a direct site shipment takes 24 hours. Keeping the cargo at the required temperature is relatively easy, providing

adequate packing material is used. Transit time to destinations outside the EU – for example, to Russia or Brazil – may take up to eight days. However, when the cargo passes customs and customs warehouses, there is no guarantee that temperature is controlled other than by the way the shipment is packed. In the worst-case scenario, in certain countries a consignment may be subject to a random lengthy clearance procedure, which may prolong the shipment lead time for up to 17 days. This can happen in Brazil and in a few other countries. End-to-end visibility via the transporter's shipment tracking system is essential.

An adequate choice of validated controlled-temperature packing material and monitoring devices is important

A shipment from a European warehouse to an European investigational site will change hands at least nine times, and be exposed to as many temperature fluctuations. The shipment goes from warehouse pick-up to a local station, gateway outbound, local hub, into the plane to gateway inbound to local station and into the delivery truck to the investigational site. The various hand-offs over a 24-hour period for a warehouse-to-site shipment within the EU underline the importance of using adequate packing material, tracking each shipment from dispatch to delivery and keeping metrics on lead times. Last but not least, using a transporter providing fast and reliable service minimises the risk for cool chain IMPs.

Table 2. Temperature excursions based on stability data for each product must be available

Temperature monitoring requirements based on stability data				
Product	Formulation	Storage/shipping conditions	Temperature sensitivity	Allowable excursions
Product A	Solution	2–8°C	High	<ul style="list-style-type: none"> Product must not freeze Warm excursions up to 96 hours at 15–25°C acceptable
Product B	Lyophilised vials	2–8°C	Medium	<ul style="list-style-type: none"> Extended excursions below freezing acceptable Warm excursions up to two weeks at 15–25°C acceptable
Product C	Tablets	15–25°C	Low	<ul style="list-style-type: none"> Hot excursions up to two weeks at 40–50°C acceptable Cold excursions up to two weeks at -20°C acceptable

Packing material

A wide range of packing material is on the market. Various options are possible, according to the characteristics of the shipment – for instance, the product's value and temperature sensitivity, the quantity to be shipped, the destination, the lead time and transportation. Transport containers are used mainly for large quantities and for continent-to-continent shipments, while one-way or reusable boxes with appropriate transit duration are preferred for site shipments.

However, sophisticated packing materials are not available worldwide. This results in the transfer of empty shippers, cool elements and monitoring devices to local country warehouses, leading to delays and increased costs. The use of non-standardised packing material across countries adds complexity and workload, due to the need for further verification, local purchase, and so on.

Cool chain distribution

When setting up cool chain distribution, detailed procedures as required by law are essential. Procedures should refer to:

- Obtaining stability data for each product to be shipped
- Shipping destinations, including climatic zones; shipping lead times; and emergency procedures in case of shipment loss
- Global availability of validated packing material; temperature-monitoring devices and transporter selection; and shipment tracking and taking metrics

Handling procedures at all levels need to be in place for sponsor, warehouses and investigators. Airlines and transporters should communicate their processes to the licence holders. Written agreements with third parties, such as independent local warehouses, should detail each of the outsourced activities.

What happens when temperature goes out of specification during transportation is a crucial question. Products denatured by exposure to

incorrect temperature, as indicated on the monitoring device, will be quarantined on arrival at a warehouse or investigational site. Product release can be obtained only if it can be proved that the temperature excursion was within the allowed temperature window. The product is lost when the temperature excursion is unacceptable, leading to re-supply costs and study delays.

Logistical challenges

The industry thus faces significant logistical challenges when distributing temperature-sensitive products. Awareness and respect of legislation and guidelines are essential, as is the availability of detailed specifications on temperature requirements and permitted excursions for each product. An adequate choice of validated controlled-temperature packing material and monitoring devices is important, together with the careful selection of a transporter providing safe, reliable and fast global service. Established contractual agreements with third parties, written procedures at all levels, and harmonisation and integration of sponsor procedures with those of third parties are necessary to provide access to a full shipment tracking system and metric collection that will ensure all discrepancies are quickly noted and alleviated so that optimisation of cool chain shipments may be achieved. ■

References can be obtained from the authors.

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