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Maintaining the cold chain shipping environment for Phase I clinical trial distribution

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Abstract

The study aimed to demonstrate satisfactory inter-UK transit of cold storage clinical trial material. The product environment had to be maintained between 0 and 8 °C throughout transit until delivery. Straightforward, low cost and simplified shipping arrangements were sought that would be appropriate for small-scale Phase I clinical trial activities. A laboratory test defined an optimal three frozen gel pack configuration to maintain refrigerated environmental conditions for dummy product packs in a single type and size of insulated shipper. The internal environment was temperature monitored at 30-min intervals in all tests. Twelve Glasgow to London transits were then studied over 2 years to include all seasonal temperature variations. A configuration using three frozen gel packs and 4 h pre-chill of the transit container maintained the internal environment at 0–8 °C for up to 48 h during autumn, winter and spring. A modified four frozen gel pack configuration was suitable for summer transit. Thus cold shipment verification was successfully carried out for a small-scale distribution operation. It was proven that refrigerated shipping conditions could be maintained using a straightforward and cost effective 'passive' type system consisting of frozen gel packs and insulated transit containers.

Keywords: Phase I; Cold chain; Distribution

1. Introduction

Phase I clinical trials in Europe have significantly changed with the advent of the new European "Clinical Trials Directive". Article 13(3) of the 2001/20/EC directive for the implementation of Good Clinical Practice (GCP) in clinical trials formalizes the need for Good Manufacturing Practice (GMP) to be undertaken by Phase I clinical trial manufacturers and distributors (stated under Directive 2003/94/EC). At the core of the legislation is priority for patient safety, although equally there has been a desire to harmonize the trans-European approach to clinical trials and their conduct.

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The Cancer Research UK Formulation Unit is a Phase I/II unit founded in 1983 at the University of Strathclyde in Glasgow arising from their specialty in small volume parenteral production. Since its inception, the Formulation Unit has provided the charity Cancer Research Campaign, now operating as Cancer Research UK, with a small molecule pharmaceutical research, development and manufacturing facility for Phase I and II sponsored clinical trials in the UK (Beijnen et al., 1995; Elliott et al., 2002; Clamp et al., 2003; Jameson et al., 2003; Johnston et al., 2004).

Historically, the largest proportion of Phase I new chemical entities that have been formulated, manufactured and analyzed at the Formulation Unit ultimately have had a cold storage requirement. Transit arrangements must therefore demonstrate the ability to provide an appropriate environmental temperature for test materials being transferred from manufacturer to clinical centre (Taylor, 2001). The requirement for effective product transportation is detailed in Good Distribution Practice (GDP), lying at the interface of GMP and GCP (1994 Guidelines). However, the results of ineffective cold transportation are multi-factorial, ranging from patient safety concerns associated with potential product spoilage, to ethical issues surrounding loss of individual patient supplies leading to deferred or cancelled treatment, but also to include the financial loss associated with a defective product shipment.

We report here on a study relating to one aspect of the GMP GCP interface in the responsibility of the manufacturer to distribute medicines under appropriate environmental temperature conditions until received by the clinical centre. Cold chain shipment can be a complex undertaking to include application of active temperature control technology in wide distribution networks requiring refrigerated transit vehicles (Kayum, 2003). However, we sought to verify the shipping arrangements from +0 to +8 °C for cold storage products using a simplified, cost effective methodology that was achievable within a small Phase I units like our own.

2. Materials and methods

2.1. Transit container

A polystyrene shipper of exterior dimensions 45 cm × 45 cm × 45 cm enclosed in a white cardboard outer (Cool Logistics, Soulbury, Bedfordshire, UK) was used throughout all laboratory and actual transit studies. The shipper interior dimensions measured 32 cm × 32 cm × 24.5 cm.

2.2. Frozen gel packs

Icebrix® frozen gel packs (BDH Laboratory Supplies, Poole, Dorset, UK) of approximate dimensions 21 cm × 15 cm were frozen in a standard laboratory −20 °C freezer for a minimum of 24 h before use. Only gel packs that were frozen solid were used.

2.3. Temperature logging devices

Three Sergeant Temp temperature loggers (catalogue reference SGT Temp; Wessex Power Technology, Poole, Dorset, UK) were used to monitor the internal shipper temperature during the shipping trials. The logger serial numbers were MO6897, MO6982 and MO7972, with measurement capability in the range −40 to +70 °C with accuracy to 0.5 °C. The devices are returned to the supplying company for annual recalibration and certification. The Sergeant Temps were activated before packaging into the vial box dummy packs and set to record continuously at 30-min intervals. On return to the Unit, temperature logging was stopped by virtue of data download from each device. Data were graphed and analysed using the logging device software program.

2.4. Dummy product packs

Six white cardboard 10× 20 mL vial boxes with removable lids were each filled with 10 Type 1 clear glass vials (Adelphi Tubes Limited, Haywards Heath, West Sussex, UK). It must be noted that all glass vials used were empty of product as the study aimed to examine the environmental conditions experienced by product in transit, and not of the internal micro-product environment itself. A further three vial boxes had some internal card dividers removed to allow inclusion of a Sergeant Temp temperature logging device, with the remaining box space filled with empty glass vials.

The nine vial boxes were packed in three horizontal rows of three boxes, and stacked three boxes high. The bottom row had a temperature logger in the outer edge vial box, the middle row had the logger in the middle

vial box and the top row had the logger in the outer edge vial box (opposite to that in the bottom row). In this way a range of temperature positions would be able to be logged in the shipper internal environment. Before actual placement into the shipper, each row of filled vial boxes were wrapped in grip seal bags (as three boxes per bag), then all nine vial boxes were bubble wrapped as per usual Unit protocol intended to protect product in transit. Wrapped vial boxes in the shipper were surrounded by frozen gel packs placed in the chosen test configuration. Surrounding space was taken up by polystyrene chips to eliminate the possibility of excessive movement of the contents during transit.

2.5. Frozen gel pack laboratory tests

A laboratory test was set up to demonstrate the link between total number of frozen gel packs used and the ability to maintain a parcel internal refrigerated environment. Maximum shipper packing started with a total of 16 frozen gel packs placed as 2 on each of the vertical walls of the shipper, 4 on the shipper base, and 4 on top of the dummy product units packed into the shipper (the dummy product units contained the temperature loggers as previously described). The shipper was then closed and sealed for 24 h and the data downloaded. Further experimentation followed by reducing the frozen gel pack number firstly in half thereby using only eight frozen gel packs for 24 h followed by data download. This approach was then extended in separate experiments using four and then finally only three frozen gel packs. For the four frozen gel pack configuration, the packs were placed as one on each wall of the shipper with the dummy product packs in the centre. For the three frozen gel pack configuration, the packs were placed as one on each of two opposing walls of the shipper and one on top of the dummy product.

2.6. Shipping test

The shipper was packaged for transit with frozen gel packs, dummy product packs and temperature logging devices as previously described. The shipping box outer was then wrapped fully in brown paper before a consignee address label was attached. An additional red warning label applied to the box outer identified a cold transit trial in progress and alerted the recipient not to open the package. The shipper was uplifted from the Unit by courier, and request was made for next day delivery to the Cancer Research UK Drug Development Office in London. The recipient in London would turn around the parcel addressee label on arrival, and request return transit by the same courier to Glasgow. Transits were made in standard, non-refrigerated vehicles.

2.7. Seasonal definition

Transit tests were carried out throughout the year to examine the possible influence of external seasonally variant temperature on the internal test parcel environment. External logging of the parcel temperature was not possible. For the purposes of this study the seasons were defined as follows: spring as March, April and May, summer as June, July and August, autumn as September, October and November, and winter as December, January and February. These definitions were made from 21-year world temperature averages for Glasgow as follows (source data http://www.weatherbase.com); March, April, May averages 5, 7, 10 °C; June, July, August averages 13, 15, 14 °C; September, October, November averages 12, 8, 6 °C; and December, January, February averages 4, 3, 3 °C, respectively. The same data source detailed 18-year temperature averages for London as follows: March, April, May averages 6, 7, 11 °C; June, July, August averages 14, 16, 16 °C; September, October, November averages 13, 10, 6 °C; and December, January, February averages 5, 3, 3 °C.

3. Results

A laboratory test demonstrated the link between the total number of frozen gel packs used and the depth of chilling of the internal parcel environment (Table 1). Maximum shipper packing with 16 frozen gel packs maintained an internal frozen (sub-zero) environment for the entire 24 h duration of the test. This outcome was wholly undesirable for product with a refrigerated transit requirement, and so further experimentation followed by twice reducing the frozen gel pack number in half, as described in Section 2. Finally, the frozen gel pack number used was limited to only three. This had the effect of achieving an overall parcel internal average temperature of +2 °C over the 24 h of study (specification of +0 to +8 °C). Nonetheless, an exposure to slight

Table 1
Results from laboratory tests to determine the optimal gel pack configuration to be selected for refrigerated real time transit tests

No. of frozen gel packs per shipper	Overall average internal temperature (°C)	Absolute maximum internal temperature (°C)	Absolute minimum internal temperature (°C)
16	−7.5	−0.7	−18.8
8	−0.6	+0.9	−5.0
4	+0.8	+3.2	−6.1
3	+2.0	+3.2	−3.1

Data are reported from 24 h investigations.

freezing conditions was observed during the first 4 h of the test (Fig. 1). This freezing time period was linked to the maximum cooling phase for the frozen gel packs, having been removed directly from the freezer. Thus, to eliminate clinical product exposure to any slight freezing that may occur when packed simultaneously into the shipper with the frozen gel packs, the three frozen gel packs alone were placed into the shipping container 4 h in advance of final parcel packing with dummy product for a transit test (Fig. 2). This would also have the welcome 'side-effect' of pre-chilling the internal shipper environment. For transit of highly temperature sensitive materials handled by the Formulation Unit, specifically in relation to products sensitive to even slight freezing such as alhydrogel adsorbed vaccines, a 24 h pre-chill of the shipper with the frozen gel packs was also tested in an effort to avoid early phase internal parcel environment low temperature events (Fig. 3).

This approach of shipper 'pre-chill' with the frozen gel packs for either 4 or 24 h prior to packing the test product was then subjected to 12 individual transit tests from Glasgow to London over a time frame of 2 years. Successful results from ten of these 12 transits are shown in Table 2. Two specification failure transit tests occurred in the summer season (data not included in Table 2); one used the three frozen gel pack 4 h parcel pre-chill method, the other used the three frozen gel pack 24 h parcel pre-chill method. In the former test, the average temperature of each logger during transit ranged from +3.5 to +10.9 °C, whereas in the latter test, the average temperature of each logger ranged from +8.9 to +10.4 °C. This required a modification in approach to introduce more effective internal

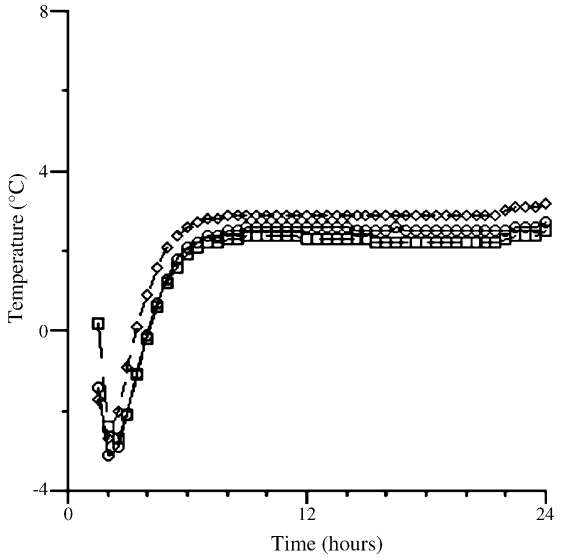

Fig. 1. Results from a laboratory test over 24 h using three frozen gel packs. Open circles, squares and diamonds represent data from each of the three loggers.

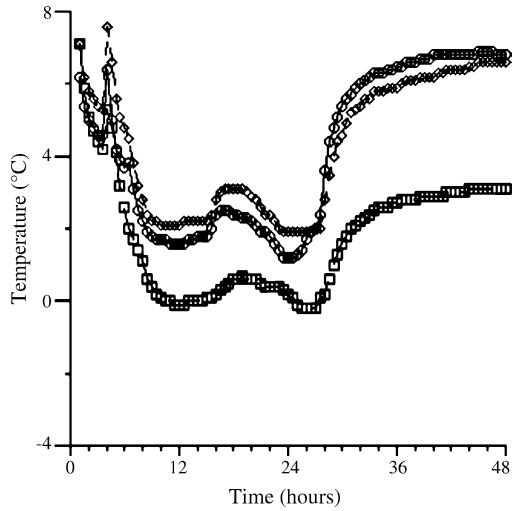

Fig. 2. Results from a 4 h pre-chill of the shipper with three frozen gel packs. The temperature loggers were cooled in the cold room for the 4 h that the parcel was being pre-chilled. At 4 h, the slight temperature rise is equivalent to the parcel packing phase.

Table 2
Evidence for a seasonally controlled internal parcel environment using either 4 h or 24 h parcel pre-chill

Season	Time for shipper pre-chill (h)	Average temperature of each logger[a] in °C during transit	Overall average temperature inside the parcel in °C during transit
Spring	4	4.1, 6.9, 7.5	6.2
	24	2.4, 5.5, 8.3	5.4
Summer[b]	4	2.6, 3.3, 5.2	3.7
	4	1.4, 2.3, 4.4	2.7
	24	1.2, 1.6, 6.8	3.2
	24	2.4, 4.4, 8.2	5.0
Autumn	4	3.9, 5.3, 6.6	5.3
	24	2.2, 2.6, 6.0	3.6
Winter	4	2.6, 5.2, 5.6	4.5
	24	2.0, 4.0, 4.7	3.6

[a] Each parcel contained three logging devices.
[b] For summer, four frozen gel packs were used. Three frozen gel packs were used for all other seasons.

environment parcel chilling for transit in summer. With reference to the laboratory tests, it was decided to use four frozen gel packs in place of three although the pre-chill times would be maintained. This modification brought about two further summer transit tests (one 4 h and one 24 h pre-chill), both passing the internal temperature requirements. A further two confirmatory summer transits were then carried out with all four results shown in Table 2 under "summer".

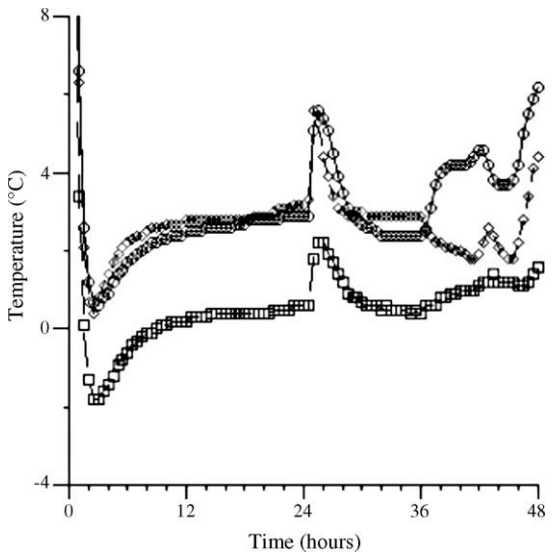

Fig. 3. Results from a 24 h pre-chill of the shipper with three frozen gel packs. The loggers were placed inside the parcel to record the internal environment over the 24 h that the parcel was being pre-chilled. At 24 h, the slight temperature rise is equivalent to the parcel packing phase.

This approach to cold chain shipping was proven to be effective, repeatable and seasonally robust (Table 2). Three repeats of a 4 h parcel pre-chill with three frozen gel packs and then shipment maintained the dummy product within +0 to +8 °C for overnight transit then delivery. Similarly, three repeats of the 24 h parcel pre-chill with three frozen gel packs and then shipment achieved the same pass specification outcome. For higher temperature months, all four of the frozen gel pack transit repeat tests, two with 4 h and two with 24 h pre-chill, achieved within specification results.

4. Discussion

The importance of satisfactory cold chain shipping arrangements is equally evident to regulators, manufacturers and distributors, and to patients themselves. Figures presented by a Medicines and Healthcare products Regulatory Agency (MHRA) inspector at a December 2001 meeting, stated that 22% of all serious deficiencies reported by inspections of wholesale distributors in 1999/2000 related to control and monitoring of transit temperatures. More recently, and in light of the new directive, a regulatory inspection visit sparked a cold transit audit by a hospital pharmacy department to establish protocols for transportation of products at the recommended cold storage temperatures (Jagani et al., 2004). Cold chain issues therefore affect all branches

of pharmaceutical practice from industry to hospital to academic trials.

A cold chain shipping format is here presented that has proven to be seasonally robust and repeatable, and that allows overnight cold transit of refrigerated materials being distributed as part of Phase I clinical trials. This verification study approach was simplified but highly effective and at the same time easily adaptable for small Phase I units.

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