Global validated cold chain transport (2°C–8°C) of clinical trials and drugs: challenge for the novel GDP guideline from 2013

Abstract

Many drugs have to be distributed by cold chain. In a climate chamber 3 packaging designs were assayed. The container RCW 25 (Dometic) with thermocouples (delta T) kept test drugs for 56 hours ≤ 8°C at 40°C outside and for 66 h $ 2°C at -10°C. Insulation systems are capable to fulfil the GDP (good distribution practice) guideline.

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Background

In Germany, there are currently about 6,500 different proprietary medicinal products according to the 'Red List' from 2013. Most of them are stored and transported in temperatures between 15°C to 25°C; about a third are subject to eventual cooling, and an estimated 250 products are subject to a cold-chain at 2°C–8°C throughout their entire existence from industrial production until administration to a patient. Based upon the 'Physicochemical stability of parenteral cytostatic, virustatic, and supporting drugs' most of these have to be stored and therefore also distributed according to this temperature interval in order to maintain maximum therapeutic effect [1]. For the whole pharmaceutical supply chain composed of the pharmaceutical industry, wholesale trade, as well as hospital or public pharmacies, the revised good distribution practice (GDP) policy [2] creates technical and logistical challenges. The surveillance authorities are additionally concerned since they have to supervise the realization of the novel guideline.

Methods

Three different passive cooling transport systems were treated with +4°C WHO-approved thermocouples of 200/400/1,000/3,000 mL volume:

(i) RCW25; Dometic Medical Systems, Hosingen, Luxembourg, see Figure 1a
(ii) BlueLine 30 L; delta T GmbH, Fernwald, Germany, see Figure 1b
(iii) PharmaCase 23 L; delta T GmbH, Fernwald, Germany, see Figure 1c

As test pharmaceuticals, 20 vials filled with water for infusion were used in the PharmaCase box; in the other two boxes (BlueLine and RCW25), 20 or 30 bags each filled with 250 mL of physiological NaCl were used. In each box, three calibrated temperature loggers (ThermoScan Messsonde –40 bis +80°C, delta T, see above) were placed: at the bottom left, in the centre, and in the upper right corner among the pre-cooled 5°C packaged goods. The boxes were incubated in parallel for 72 h at –10°C, +20°C, and +40°C, respectively, in a climate chamber (Beck-Messtechnik, Flein, Germany; accredited to EN ISO 17025:2005), see Figure 2; followed by an evaluation of the logger data (ThermoScan USB-Kit, delta T, see above).

Results

The differences between the logger positions were clearly detectable but not very large (after 72 h, Δ ≤ 2°C each). As expected, coldness had the most impact at the bottom measuring point (worst case), heat at the upper point (worst case), optimum buffering was given in the centre due to the most efficient insulation. The significantly shortest time to exceed or fall below the temperature limits for cold-chain active compounds were observed for the BlueLine box (~ 5 and ~ 6 h). This outcome is dependent on the limited insulation with only two thermocouples placed above and below the drugs due to the construction of the container. PharmaCase and RCW25 box

Figure 1: Passive insulation-based systems for the quality-assured transport of clinical trials and drugs (a: RCW25, Dometic; b: BlueLine, delta T; c: PharmaCase, delta T)

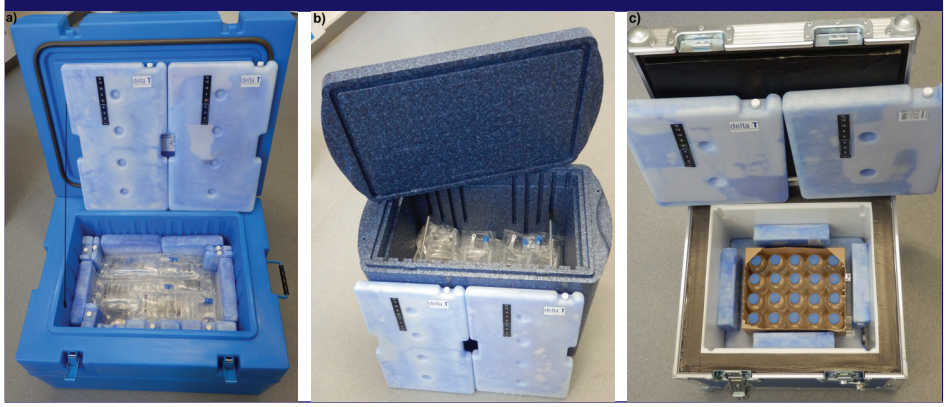

Table 1: Examination results of the three investigated tranportation systems with respect to the different outside incubation temperatures (–10°C, +20°C, +40°C)

Box	Surrounding temperature	Position of data logger	< 2°C after ~ [h]	> 8°C after ~ [h]
BlueLine	–10°C	bottom left corner	5.50	n.o.
BlueLine	–10°C	centre of goods	6.50	n.o.
BlueLine	–10°C	upper right corner	5.75*	n.o.
BlueLine	+20°C	bottom left corner	n.o.	10.50*
BlueLine	+20°C	centre of goods	n.o.	11.25
BlueLine	+20°C	upper right corner	n.o.	10.75
BlueLine	+40°C	bottom left corner	n.o.	4.75*
BlueLine	+40°C	centre of goods	n.o.	5.50
BlueLine	+40°C	upper right corner	n.o.	5.25
PharmaCase	–10°C	bottom left corner	41.50	n.o.
PharmaCase	–10°C	centre of goods	43.00	n.o.
PharmaCase	–10°C	upper right corner	40.75*	n.o.
PharmaCase	+20°C	bottom left corner	n.o.	> 72
PharmaCase	+20°C	centre of goods	n.o.	> 72
PharmaCase	+20°C	upper right corner	n.o.	> 72
PharmaCase	+40°C	bottom left corner	n.o.	35.25*
PharmaCase	+40°C	centre of goods	n.o.	37.25
PharmaCase	+40°C	upper right corner	n.o.	35.75
RCW25	–10°C	bottom left corner	66.75	n.o.
RCW25	–10°C	centre of goods	68.00	n.o.
RCW25	–10°C	upper right corner	65.75*	n.o.
RCW25	+20°C	bottom left corner	n.o.	> 72
RCW25	+20°C	centre of goods	n.o.	> 72
RCW25	+20°C	upper right corner	n.o.	> 72
RCW25	+40°C	bottom left corner	n.o.	56.25*
RCW25	+40°C	centre of goods	n.o.	58.50
RCW25	+40°C	upper right corner	n.o.	58.00

n.o.: not observed; *worst case.

with cubic arrangement of the thermoelements kept the drugs for 35 and 56 h ≤ 8°C (at +40°C outside incubation temperature), and for 41 and 66 h $ 2°C (at –10°C outside incubation temperature). At +20°C the maximum transport time increased both > 72 h, the end of the experimental incubation period, and even BlueLine achieved > 10 h.

Conclusion

Valid insulation-based systems are available for up to 2–3 days of cold chain transport of drugs and clinical trials, without the need of connectivity to a power supply [2–7]. Two of the investigated arrangements provided excellent results, which might be improvable by pre-cooling the box. Based upon these data, concerned substances, such as cytostatic drugs for infusion should be globally transportable in best quality by any part of the supply chain. Further studies should reveal whether parameters such as air pressure (e.g. below atmospheric pressure in the cargo space of an aircraft), humidity, shock (e.g. during the loading process), and vibration (e.g. caused by the engine of the car or van) could negatively affect the quality during transport and have to be taken into consideration in future. Influence has been demonstrated for low atmospheric pressure and vibration concerning red blood cell concentrates during the supply of military field hospitals as well as during humanitarian help in natural disaster scenarios.

Figure 2: Incubation design in order to store the three transport systems at –10°C, +20°C and +40°C, respectively, simulating transportation conditions in the climate chamber

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