ABSTRACT
This article describes the shipping qualification process used for the international transport of a vaccine drug substance in flexible containers (FC) from the United States. The drug substance is produced in the US and dispensed into two-liter (2L) FCs. The FCs may subsequently be transported internationally for vaccine formulation and filling into syringes. Temperature control is required to be maintained at 2–8 ºC during transit and has been demonstrated through qualification via a combination of an insulated pallet shipper with refrigerated gel-sleeves and an active dry ice container controlled by a thermostat. Operational qualification (OQ) testing demonstrated the ability of the shipping system to control temperature in a controlled environment, while performance qualification (PQ) demonstrated the ability to control temperature through the transit process. OQ results indicated the shipper can tightly control temperature (between 2–8ºC) despite temperature extremes outside the shipper. PQ results indicated the shipper could maintain temperature between 5–7ºC during actual shipments. Based on the passing results of the OQ and PQ testing requirements, shipment conditions for drug substance 2L FCs at temperatures between 2–8ºC have been qualified for shipment from the US to an international location.

INTRODUCTION
Shipping qualification is an integral part of the validation process. The shipping process must be qualified as part of the overall validation program to consider uncertainties and variability associated with weather and external conditions (1).

Numerous guidance documents are available related to qualifying the shipping process. For instance, United States Pharmacopeia (USP) chapter <1079>, “Good Storage and Shipping Practices,” mentions “Operational and performance testing should be parts of a formal qualification protocol that may use controlled environments or actual field testing based on the projected transportation channel. These should reflect actual load configurations, conditions, and expected environmental extremes” (2). A more detailed summary of the expected qualification process is found in PDA Technical Report No. 39, Guidance for temperature controlled medicinal products; maintaining the quality of temperature-sensitive medicinal products through the transportation environment (3). This report summarizes the method of qualifying a shipping process, including design qualification (DQ), operational qualification (OQ), and performance qualification (PQ) as well as the quality systems supporting and monitoring the qualified system. This was one of the documents used to design the shipping qualification process discussed in this publication.

Qualification of shipping for vaccines has been reported previously. Most of the literature is focused on keeping vaccines from freezing in the cold chain prior to inoculation (4) and not the shipment of drug substance to formulation sites. A comprehensive qualification study was reported
for vaccines that should be kept frozen (i.e., live viral vaccines) and vaccines that only need to be maintained cold (e.g., greater than 0 °C and less than 8 °C) (5). Qualification involved both environmental chambers (equivalent to an OQ) and actual shipping of packages via commercial services (equivalent to a PQ). The environmental chambers tested the packaging containers, which ranged in size from 18 cm x 15 cm x 20 cm to 34 cm x 34 cm x 30 cm, from -20°C to 43°C. The “field” shipping studies were conducted in both summer and autumn as well as winter seasons, to simulate the extremes of weather that could affect the ability of the package to maintain temperature. The qualification study was designed to determine how the shipping condition affected the vaccine temperature versus designing and qualifying a packaging system to protect the vaccine within a designed shipping temperature. As expected, the location and number of gel packs affected the ability of the package to maintain its target temperature.

This paper discusses data and qualification and the vaccine shipping process. OQ and PQ testing was designed to provide documented evidence that the shipping process, when executed per the qualified procedures, would consistently maintain temperature requirements throughout transit. The OQ demonstrated the shipping system’s ability to withstand temperature extremes and the PQ confirmed that the developed process is effective, robust, and repeatable.

SHIPPING PROCESS DESCRIPTION
The 2L FCs containing drug substance are placed inside protective corrugated cartons and stored in a validated 2–8°C cold room. The insulated pallet shipper(s) using refrigerated gel-sleeves are prepared for the shipment of the 2 L FCs at a 2–8°C transit temperature. The cartons containing the 2L FCs are placed into the insulated pallet shipper inside the 2–8°C cold room. Qualified electronic temperature monitors placed both in the load and in the ambient environment record the temperature during shipment at eight-minute time intervals. The pallet shipper(s) is then placed inside the active dry ice container. Up to four pallet shippers can be placed into a single active dry ice container (Figure 1). The active dry ice container, containing from one to four pallet shippers, is loaded onto a temperature-controlled truck set at 15°C for transport and loading onto an airplane.

After the transatlantic flight, the pallet shipper is unloaded from the active dry ice container at the freight forwarder’s facility and loaded on a 2–8°C temperature-controlled truck for transport to its destination. Only one active dry ice container is transported per shipment due to the amount of

Figure 1: Loading of active dry ice container.
space required to be reserved in the cargo area of the aircraft. The transportation flow chart in Figure 2 depicts the process flow from the US to the international destination.

MATERIALS AND METHODS
The following describes the shipping components utilized for this process:

- **Active dry ice container shipping container.** The active dry ice container is an insulated container with a thermostat-controlled heat exchanger powered by 16 D-size alkaline batteries. The system uses a maximum of 300 kg (660 lbs.) of dry ice for cooling purposes only. The dimensions of the internal product loading space are approximately 99.8” x 81.3” x 55.9”. Figure 3 depicts the active dry ice container.

- **Insulated pallet shipper.** The insulated pallet shipper (Figure 4) consists of six panels of 2.5” polyurethane filled corrugated walls, and 20 corrugate sleeves containing four refrigerated gel bricks each. The assembled pallet container has an internal payload area of 37.00” x 29.00” x 35.00” and an external size of 48.00” x 40.00” x 51.00”.

- **Refrigerant sleeve.** The corrugate sleeves are made from board containing four chilled gel bricks per sleeve with an outer diameter of 34.125” x 9.00” x 2.00”. Each sleeve weighs 16.75 lbs. Twenty or twenty-three sleeves are used in each pack-out based on load size.

- **Dry ice.** Exact dry ice calculations are obtained on a shipment-by-shipment basis based on shipment weight and season from active dry ice container provider. Wrapped dry ice (no pellets) is used for the shipments.

During the selection and design of a shipping container suitable for transporting drug substance in 2L FCs, existing qualified shipping solutions across the Pfizer network were considered in order to maximize the efficiency of the qualification activity. The insulated pallet shipper and active dry ice container were previously qualified at the same temperature range (2–8°C), same shipment destination, and shipping space to ship drug substance FCs. Existing qualification data were thus leveraged for the insulated pallet shipper and active dry ice container solution for shipment of drug substance.
OPERATIONAL QUALIFICATION

The OQ runs were performed in a laboratory test chamber under simulated thermal conditions. OQ testing simulated worst-case time and temperature conditions anticipated during shipment representing both summer and winter seasons. A minimum of three runs was performed for both minimum and maximum loads tested under summer and winter ambient thermal profiles. During these runs a minimum and a maximum weight was established. Temperature monitors were used during testing to record the temperature surrounding the product inside the payload. OQ testing was not designed to be container or product specific, but was based on the potential payload mass inside the shipper. To accomplish this, the US to Europe and Australia temperature profiles were used to challenge the shipper to cover a broad area of origins and destinations. Qualification by weight allows other products, like that of the drug substance, to be leveraged using one confirmatory OQ run provided they fit inside the fixed payload area of the shipper, require the same temperature range, and will be shipped to a destination that has the same or similar thermal profile.

The following elements were considered when developing the thermal profiles:

- Originating site
- Receiving site
- Transit temperature requirements of the material being shipped
- Transportation mode (e.g., airplane, railcar, ocean container, truck)
- Node(s) (cities/ports)—the desired route of travel—especially important where ‘hand offs’ occur between various carriers and modes of transportation
- Estimated times of transport for each segment of the trip
- Estimated minimum and maximum ambient temperatures that may be encountered in each segment.

Figure 5 and Figure 6 depict the summer and winter ambient temperature profiles that the shipping system was subjected to during the OQ testing.

The following elements were considered prior to the OQ testing:

- Minimum and maximum product loads
- Summer (hot) and winter (cold) cycles
- Quantity and placement of refrigerants
- Conditioning of components (the process of bringing components such as shipping container and gel packs to a specified temperature before starting the packing process)
- Insulated shipping container interior configuration
- Placement of temperature monitors during shipping.

Minimum and maximum product weights within the payload area were selected based upon anticipated shipping configurations. Syringes were selected for the OQ loads because they represent the smallest volume of product having the greatest amount of container surface exposure packed into the shipper payload. Procedurally, all product shipped is conditioned to the shipping temperature prior to loading of the payload area. Therefore, the originating source of heat energy is from the outside of the shipper. The OQ is acceptable for other

**Figure 5:** 110 hours summer (external) temperature profile. At the completion of the 62-hour thermal profile, the dry ice bunker on the active dry ice container was replenished for one minimum and one maximum load run and the testing continued for an additional 48 hours or until the product temperatures were recorded out of the 2-8°C range.

**Figure 6:** 110 hours winter (external) temperature profile. At the completion of the 62-hour thermal profile, the dry ice bunker on the active dry ice container was replenished for one minimum and one maximum load run and the testing continued for an additional 48 hours or until the product temperatures were recorded out of the 2-8°C range.
products requiring the same shipping temperature when a palletized load fits inside the fixed payload of the insulated pallet shipper and meets the minimum and maximum weight requirements. The OQ using pre-filled syringes established a minimum and maximum weight requirement that is allowed to be placed inside the fixed payload area of the shipper. The minimum load contained in one pallet shipper is ≥ 47.07 lbs and the maximum load ≤ 221.40 lbs per pallet shipper with up to four shippers within an active dry ice container. In the case of the FCs, a minimum FC load per pallet weighs 67.2 lbs (consisting of one 2L FC, one 50mL FC, and dunnage) and a maximum load weighs 200.8 lbs (consisting of 30 2L FCs, three 3 50mL FCs, and dunnage). The minimum and maximum FC loads required to be shipped fits within the fixed payload area of the shipper, falls within the weight range established in the OQ, and is therefore acceptable with no additional OQ testing.

The summer OQ was executed successfully against the expected extreme summer thermal profile. The winter OQ testing revealed that the insulated pallet shipper and active dry ice container shipping system's limitation in maintaining product temperatures ≥ 2°C after being exposed to temperatures ≤ 0°C for approximately 15 hours. Consequently, exposure of product shipments, using the insulated pallet shipper and active dry ice container shipping combination, to ambient temperatures ≤ 0°C are recommended to be limited to less than 10 cumulative hours of exposure. There is a low risk of the shipment being exposed to ambient temperatures ≤ 0°C for greater than 10 hours. Routine measures are currently in place to minimize exposure to extreme ambient temperatures during the process steps where exposure is possible.

For each shipment, a temperature monitor is placed in the outside pouch of the active dry ice container to monitor ambient transit conditions. Temperature monitors located outside the shippers are for informational purposes only. Temperature excursions on monitors located outside the pallet shipper do not require an investigation, as long as all temperature monitors inside the shippers, representing product temperature, are within the specified range.

The qualification was designed so that the transit time may be extended, if necessary through the replenishment of dry ice. Therefore, no time specific transit duration limit is necessary.

**PERFORMANCE QUALIFICATION**

PQ testing was successfully performed to qualify the international shipment of drug substance in 2L FCs inside plastic corrugated cartons packed in insulated pallet shipper and active dry ice container transported by temperature controlled truck and airplane. The insulated pallet shipper and active dry ice container shipping system was previously qualified using 10L stainless steel cans shipped from the US to international destination through the performance of runs through the actual shipping process. Four PQ runs were executed qualifying two distribution lanes using ground and air transport; two minimum load runs and one maximum load run challenged the longest distribution lane and one minimum load run challenged the shorter distribution lane. The 10L can PQ was executed using both minimum and maximum product loads through the actual distribution process. Three minimum load runs and one maximum load run were executed from the US to international destination. Three runs were performed through the longest transit route using two minimum and one maximum load runs. One confirmation run was performed through the shortest route using a minimum load run. The minimum load runs consisted of three 10L cans and three 50mL falcon tubes. The maximum load run consisted of 24 10L cans and 24 50mL falcon tubes.

The 2L FCs were shipped using the same shipping system, packaging methods, and transit routes qualified for the 10L can shipments. The exception being the internal placement of the 2L FCs in cartons versus 10L cans inside the payload area of the shipper. One confirmation run with a minimum load of 2L flexible containers through the longest transit route was executed from the US to an international destination. The minimum load size was chosen as it represents worst case from a thermal perspective because the load is most responsive to ambient temperatures. The minimum load run was performed using one 2L FC and one 50mL FC.

Prior to packing the shipping container the temperature monitoring devices, FCs, insulated pallet shipper, refrigerant sleeves, and the active dry ice container were pre-conditioned to the desired shipping temperature range. Temperature monitors were used during shipment to record the environment surrounding the product. This is considered worst case as the air will respond more rapidly to temperature change than the product. A summary of high and low temperature monitoring locations recorded during both the summer and winter OQ test runs indicate the high and low temperature values occurred at the corners of the pallet. In general, high values occurred at the top corners and the low values occurred at the bottom corners. Based upon the OQ data, two temperature-monitoring devices will be placed inside
each pallet shipper regardless of the quantity of FCs being shipped. These devices will always be placed inside the cartons next to the FC on the bottom layer front left corner and the top layer back right corner. Placement in these locations will be used to monitor the temperature of the FCs during shipment. Both temperature monitoring devices must remain within 2–8°C during shipment. One device will be placed on top of each insulated pallet shipper and one device will be placed inside the document pouch on the outside of the active dry ice container. These devices monitor temperatures outside the pallet shipper and active dry ice container, respectively, and are not required to maintain 2–8°C during shipment.

Both the OQ and PQ testing were conducted with a surrogate. Water for injection (WFI) was used as the representative material for drug substance. WFI is an appropriate representative substitute for vaccine bulk as WFI and vaccine drug substance were demonstrated to have similar thermal and weight characteristics.

**RESULTS AND DISCUSSION**

**OQ Results**

Data in Table I show the minimum and maximum temperatures during the testing. Results indicated that when the shipping system is exposed to anticipated, extreme ambient summer or winter temperatures, the product would maintain temperature between 2–8°C with the following exception. The OQ revealed the system’s limitation in maintaining product temperatures ≥ 2°C after being exposed to temperatures ≤ 0°C continuously for at least 15 hours. Consequently, a 10-hour limit was chosen as the target time to limit exposure of the system to ambient temperatures ≤ 0°C. Based on the routes established in the PQ, there is a low

<table>
<thead>
<tr>
<th>Load description*</th>
<th># of runs</th>
<th>Ambient condition</th>
<th>Minimum temperature (°C)</th>
<th>Maximum temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 x 9 corrugate boxes containing 100 syringes per box (minimum load)</td>
<td>3</td>
<td>Summer</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>1 x 9 corrugate boxes containing 100 syringes per box (minimum load)</td>
<td>6</td>
<td>Winter</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>4 x 27 plastic corrugate boxes containing trays with 100 unlabeled syringes per tray (maximum load)</td>
<td>3</td>
<td>Summer</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>4 x 27 plastic corrugate boxes containing trays with 100 unlabeled syringes per tray (maximum load)</td>
<td>3</td>
<td>Winter</td>
<td>2</td>
<td>8</td>
</tr>
</tbody>
</table>

*OQ testing was not designed to be container or product specific; rather, the OQ was based on the potential payload mass inside the shipper. This is why the syringes are considered representative.

**Table II: Summarized results of PQ testing.**

<table>
<thead>
<tr>
<th>Run#</th>
<th>Load description a</th>
<th>Minimum internal temp (°C)</th>
<th>Maximum internal temp (°C)</th>
<th>Minimum external temp (°C)</th>
<th>Maximum external temp (°C)</th>
<th>Transit time (Hrs:Min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Max: (24) 10L cans and (24) 50mL falcon tubes</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>35</td>
<td>66:55</td>
</tr>
<tr>
<td>2</td>
<td>Min: (3) 10L cans and (3) 50mL falcon tubes</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>35</td>
<td>43:40</td>
</tr>
<tr>
<td>3a</td>
<td>Min: (3) 10L cans and (3) 50mL falcon tubes</td>
<td>5</td>
<td>6</td>
<td>3</td>
<td>36</td>
<td>61:00</td>
</tr>
<tr>
<td>4a</td>
<td>Min: (3) 10L cans and (3) 50mL falcon tubes</td>
<td>5</td>
<td>6</td>
<td>2</td>
<td>36</td>
<td>60:20</td>
</tr>
<tr>
<td>5a</td>
<td>Min: (1) 2L FC (1) 50mL FC</td>
<td>6</td>
<td>7</td>
<td>2</td>
<td>18</td>
<td>66:50</td>
</tr>
</tbody>
</table>

* The 2L FCs are shipped using the same shipping system, packaging methods, and transit routes qualified for the 10L can shipments (except for the internal placement of the 2L FCs in cartons inside the payload area of the shipper). One confirmation run with a minimum load of 2L flexible containers through the longest transit route was executed as part of the PQ.

b Route represents worst case route.
risk of the shipment being exposed to ambient temperatures below 0°C for greater than 10 hours. Routine measures are in place to minimize exposure to extreme ambient conditions during transit.

**PQ Results**

Data in Table II show the minimum and maximum temperatures of the temperature monitor placed next to the product during the testing. The temperature of the product was maintained between 2–8°C for the duration of the testing for all shipments. The PQ data in Table II show the environmental conditions as recorded by the ambient temperature monitor during each shipment. The results of all shipments were within the defined acceptance criteria.

**CONCLUSION**

Design and qualification of a shipping process were performed. During the OQ, the shipping system was exposed to both summer profiles, with temperature going as high as 50°C, and winter profiles, with temperatures as low as -5°C. During the PQ, the shipping system was exposed to ambient conditions as high as 35°C and as low as 2°C and was able to consistently meet the shipping criteria of 2–8°C. For our purposes and based on the passing results of the operational qualification and performance qualification requirements, shipment conditions for drug substance 2 L flexible containers at temperatures between 2–8°C are qualified for shipment from US to international locations.

**REFERENCES**


**ACKNOWLEDGMENT**

Thanks to Oumer Salim for his help with the design and performance of the OQ for syringes.

**ARTICLE ACRONYM LISTING**

- **DQ** Design Qualification
- **FC** Flexible Containers
- **OQ** Operational Qualification
- **PQ** Performance Qualification
- **USP** United States Pharmacopeia
- **WFI** Water for Injection

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