GDP Qualification of Equipment with Temperature Controlled Unit for the Transport of Pharmaceutical Products

Pharma Containers

TK 61362-11-MS Revision 1 (Print Date: May 27, 2016)

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This document is only valid in conjunction with the GDP validated equipment certificate and on compliance of the qualification process

Units covered:	
ColdCube™ Pharma containers	
ColdCube™ 140L	
ColdCube™ 330L	
ColdCube™ 915L	
Kit Pharma Solutions ColdCube	706782
For further information, refer to:	
ColdCube Operators Manual	TK 60942-11-OP

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Sale of product shown in this manual is subject to Thermo King's terms and conditions including, but not limited to, the Thermo King Limited Express Warranty. Such terms and conditions are available upon request. Thermo King (Ingersoll Rand) warranty will not apply to any equipment which has been so repaired or altered outside the manufacturer's plants as, in the manufacturer's judgment, to affect its stability.

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Recover Refrigerant

At Thermo King, we recognize the need to preserve the environment and limit the potential harm to the ozone layer that can result from allowing refrigerant to escape into the atmosphere.

We strictly adhere to a policy that promotes the recovery and limits the loss of refrigerant into the atmosphere.

In addition, service personnel must be aware of Federal regulations concerning the use of refrigerants and the certification of technicians. For additional information on regulations and technician certification programs, contact your local THERMO KING dealer.

1. About This Manual

Purpose

The information in this manual is provided to assist owners, operators and service people for GDP qualification of equipment with temperature controlled unit for the transport of pharmaceutical products.

This GDP Qualification Documentation is in line with the EU guideline of Good Distribution Practices of medical products for human usage (GDP) and annex 15 “Qualification and Validation” of the Good Manufacturing Practice for Medicinal products for Human and Veterinary Use (GMP).

Units covered in this manual are: Thermo King ColdCube™ Pharma containers: ColdCube ™ 140L, ColdCube ™ 330L and ColdCube ™ 915L.

CAUTION: This document is only valid in conjunction with the GDP validated equipment certificate and is validated on completion of the qualification process. This Certificate should be stored in the supplied pouch at the front of this manual along with the GDP Approval letters by Independent pharmaceutical company.

Contents

GDP qualification documentation

Transport equipment with Thermo King temperature controlled unit for the transport of pharmaceutical products.

This manual is organized into the following chapters:

Chapter	Purpose
Certificate of the equipment qualified GDP compliant	Validation of the Installation Certification for specific equipment. ***NOTE: To be inserted in pouch provided at the front of this Manual.***
GDP Approval letter by Independent pharmaceutical company	• Validation of Thermo King GDP Protocol • Qualification and Validation of standard equipment. ***NOTE: To be inserted in pouch provided at the front of this Manual.***
Qualification Plan	Summarizes the minimum information that is included in this qualification report, Purpose, User Requirements Specifications, stages of qualification, qualification method and responsibilities.
Risk Assessment	Identifies sensible measures to control the risks during the transport of pharmaceutical products with temperature controlled equipment.
Design Qualification	Lists equipment specifications and provides a documented verification that the proposed design of the equipment is suitable for the intended purpose.

Chapter	Purpose
Installation Qualification	Confirms that the equipment is installed and conforms to the approved design qualification and the manufacturer's recommendations.
Operational Qualification	Confirms that the equipment performs as intended throughout the anticipated operating ranges and provides operating guidance.
Performance Qualification	Provides temperature mapping test results that prove that the equipment can perform effectively and reproducibly, based on the approved process method and product specification.
Certification	Certificate of Approval of Ingersoll Rand Quality Management system.

Contacting Thermo King Service

Before you call Thermo King Service, have the following information on hand (for exact data see serial plate on your unit):

- Unit type (commonly typed on serial plate after code DESC).
- System or Model number (commonly coded on serial plate after code ITEM).
    - System number has usually six digits format (example 901902).
    - Model number is the same as System number with M letter at the end (example 901902M).
- Serial number.

Who to call: your Thermo King Dealer Representative or Thermo King Service Centre.

Blank Pages

This manual may contain blank pages at the end of chapters. This is normal. There is no information missing from the manual.

2. Table of Contents

3. List of Figures

4. Qualification Plan

4.1. Purpose

This qualification plan describes the procedure for qualifying a temperature controlled portable cooling and heating containers (ColdCube™ 140L, ColdCube™ 330L, ColdCube™ 915L), that have better insulation than ATP standards (0.4 W/m2.K or better insulation).

The qualification provides the documented proof of the fact that the respective refrigerated equipment fulfils the user requirements (URS), GDP and GMP requirements for the transport of medicines. This document specifies the responsibilities and activities that are to be carried out for the qualification. The specific activities and criteria are described and documented in the various test cases.

4.2. User Requirements Specifications (URS)

The equipment is designed to ensure that pre-temperature-controlled goods maintain an adjustable set temperature both for low and high ambient temperatures (winter -30°C and summer +45°C). It must be possible to operate the equipment within the following temperature ranges:

- Temperature below -20°C
- Temperature between +2°C and +8°C
- Temperature between +15°C and +25°C

4.3. Design Qualification (DQ)

The equipment mentioned below, **temperature controlled portable cooling and heating containers**, have been designed and qualified to meet the specific desired temperature ranges for the transport of pharmaceutical products.

- ColdCube™ 140L: 0.35 W/m².K
- ColdCube™ 330L: 0.29 W/m².K
- ColdCube™ 915L: 0.28W/m².K

Please refer to the document **GDP-TK-DQ_ColdCube**.

4.4. Installation Qualification (IQ)

The specific equipment has been installed successfully and was proved to comply with the design qualification and installation qualification of the sample-type equipment.

Please refer to the document **GDP-TK-IQ_ColdCube**.

4.5. Operational Qualification (OQ)

The specific equipment has been proven to perform according to the sample-type equipment. Operating guidance and planned maintenance schedule has been provided to ensure a correct use of the equipment during its lifetime.

The conditions of the performance test of the sample-type were defined.

Please refer to the document **GDP-TK-OQ_ColdCube**.

4.6. Performance Qualification (PQ)

A basic Performance qualification was performed on the sample-type equipment. The tests were performed according to the test cases defined in the Operational Qualification in order to simulate most common real life conditions. Tests were performed in accordance with ATP standards and test method NFX 15-140. The tests were successfully completed.

As a result of the test, some recommendations have been provided to ensure an optimal use of the equipment in the different operational modes.

Please refer to the document **GDP-TK-PQ_ColdCube**.

4.7. Qualification with a Sample-Type Approach

Thermo King did use a sample-type approach for the qualification of transport equipment. The sample-type approach consists of performing an initial full qualification on one equipment using the worst case scenario (including thermal mapping in extreme ambient conditions) and all new or existing equipment of the same design specifications are also qualified once IQ and OQ is completed successfully.

- A basic PQ for one member of each sample-type, selected as the most critical or challenging application in the family. Basic PQs are empty load temperature mapping performed in temperature-controlled chamber to better simulate worst case conditions.
- For each new and existing unit, an IQ and OQ have to be completed successfully at a Thermo King authorised workshop location. The verification is conducted by a Thermo King trained technician. The verification includes, above all, the equipment's design specifications and set point verification, sensor calibration and equipment performance check.

4.8. Responsibility

The qualification activities will be organised by the qualification team:

Organisation	Activity
Thermo King Pharma Team	Define GDP Protocol for transport equipment Define GDP qualification per sample-type Create and update GDP qualification documentation
	Create GDP certificate for each new or existing equipment proven GDP qualified
Ingersoll Rand Engineering Center	Conduct thermal mapping tests of selected transport Equipment in line with GDP Provide results of thermal mapping tests performed
External pharmaceutical consultant company	Provide the approval of the sample-type GDP qualification
	Sign GDP certificate for each new or existing equipment proven GDP qualified
Thermo King authorised dealers	For each new or existing equipment, perform IQ and OQ check

4.9. Qualification Facility

The qualification tests will be performed at the Ingersoll-Rand Equipment Manufacturing Engineering and Technology Center, Prague, Czech Republic. This organisation is an accredited ATP-test-station and has the ISO 17025 and ISO-9001 certifications.

5. Risk Assessment

5.1. Risk Assessment Thermo King

The transport process is defined as a closed temperature controlled storage box on wheels. This box can be used in a single temperature mode and set at three different temperature ranges (frozen, cool and ambient).

The risk assessment based on the Failure Mode and Effects Analysis (FMEA) methodology has been conducted in order to ensure that potential problems during the process of distributing pharmaceutical products have been considered and addressed before the first use of the transport temperature controlled equipment.

5.2. Risk Reporting Matrix

Thermo King used the risk reporting matrix (see below figure) to identify and classify potential problems while using the specific transport equipment with a refrigerated mobile container type ColdCube Pharma (140L, 330L, 915L) with better insulation than ATP (FRC) standards (0.4 W/m².K) for the transport of medicinal products.

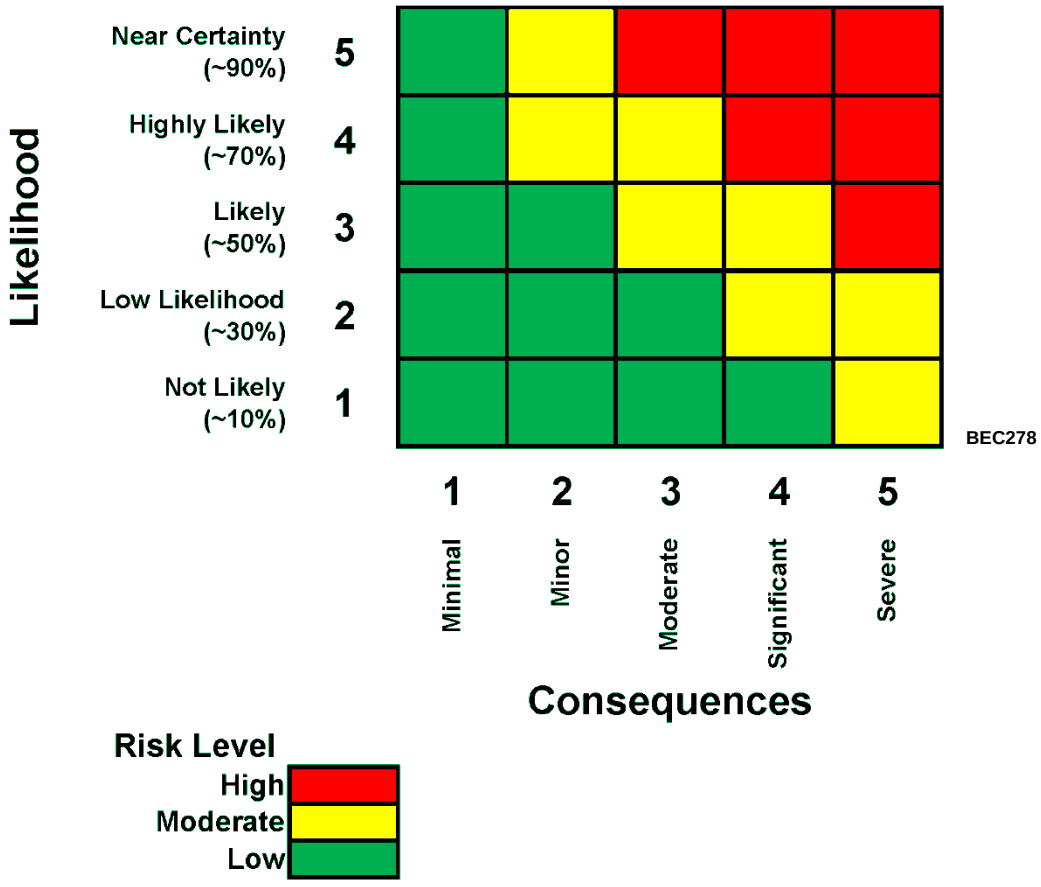

Figure 1: Risk reporting matrix

5.3. Identified Risks and Preventive Actions

5.3.1. Closed Box

Process	Defining the possible process problem	Likely-hood	Con-sequence	Risk	Preventive Action
Poor design of the transport equipment	Equipment not equivalent to sample-type equipment fully GDP qualified Poor quality finishes (example: bad insulation, door not sealed, body damage) The unit has been damaged on the body during use or installation	2	4	8 (Moderate)	At IQ, Check that the equipment design specifications are similar to sample-type equipment fully GDP qualified. At IQ, check that the body is sufficiently and tightly insulated At IQ, Check that the refrigeration machine only uses approved refrigerant and is labelled according to Refrigerant: R404A or R134a. Installation Qualification to be conducted and checked by Thermo King authorized and trained technician.
Temperature excursion	Unexplained temperature excursion There are installations obstructing the discharge air flow. Transport equipment not pre-cooled before loading goods Products not loaded at correct temperature.	3	4	12 (Moderate)	Datalogger and/or monitoring system should be installed on the transport equipment. Correctly check design specifications of the equipment at point of sales. Pre-cool the transport equipment to the set - temperature before loading the products. Implement correct loading/unloading practices. Where possible, an air circulation gap of 50 mm around the cargo should be kept.
Settings of the refrigerated unit	Incorrect settings of set points for the temperature range to be maintained	3	4	12 (Moderate)	To maintain the best temperature management within the load-space in winter and summer time, Thermo King recommends to operate with the following set-point temperatures: o +22°C or lower setpoint for temp. range +15°C to +25°C o +4°C setpoint for temp. range +2°C to +8°C o for temperature below -20°C; -21°C setpoint for ColdCubes 140L, 330L -24°C setpoint for ColdCube 915L In extreme ambient temp. conditions at -30°C, we recommend offsetting the controller of the ColdCube 915L by -3°C.

5.3.2. Environment

Process	Defining the possible process problem	Likely-hood	Con-sequence	Risk	Preventive Action
Temperature Europe	Ambient temperature in the regions can go up to extremes. Risk of temperature excursion due to high delta difference with inside temperature.	3	3	9 (Moderate)	Full Qualification of sample-type equipment (temperature mapping) has been successfully performed at extreme temperatures (-30°C and +45°C). For temperature below -20°C, GDP qualified at a max. ambient temperature of +30°C.
Solar radiation	In summer time, the effect of solar radiation can have a negative impact on the surface temperature of the equipment. The darker the body colour, the higher temperature increase.	2	3	6 (Moderate)	In DQ, recommended body to be white in colour or with a max. 20% decal coverage.
Door opening at non temperature controlled storage location	Depending on: - duration of the opening - temperature in the carrier and outside temperature - switch on/off of the cooling unit during opening doors	3	4	12 (Moderate)	All ColdCubes are fitted with an Air curtain to prevent temperature excursion. At IQ, check that it is correctly installed. Minimize door opening time where possible. Load and unload the transport equipment at temperature controlled loading docks of storage location. Driver training on best loading/unloading practices should be conducted.

5.3.3. Process / Operational Qualification

Process	Defining the possible process problem	Likely-hood	Con-sequence	Risk	Preventive Action
Calibration temperature loggers	Invalid temperature registration	2	4	8 (Moderate)	At IQ check Process, all sensors that are used for temperature control and monitoring are to be checked. A proof of calibration check of each sensor as part of IQ Process. Yearly calibration check of all sensors that are used for temperature control and monitoring. Minimum sensor requirements and location should be in accordance with equipment manufacturer's recommendations. The calibration process should be in line with the EN12830.
Breakdown / damage of the equipment	No regular maintenance of the transport equipment Maintenance not done correctly. No use of genuine parts	2	4	8 (Moderate)	A maintenance contract with Thermo King or authorized Thermo King dealer should be in place. If no maintenance contract, the user of the equipment should prove that he has the right schedule maintenance, repair procedures, genuine parts, breakdown risk assessment, and training in place. The user should be open to regular audits. All replacement parts are to be from genuine manufacturer's parts.
Lack of hygiene	Risk of contamination of Pharmaceutical products	3	3	9 (Moderate)	A Cleaning Procedure should be in place. The internal space is easily accessible for cleaning. The internal surfaces of the refrigeration body are corrosion-resistant and comply with hygiene regulations. Pharmaceutical products should not be transported in a mixed load with food products.
Drivers' operating mode	Transport equipment not used appropriately Lack of knowledge on how to use the refrigerated unit	3	4	12 (Moderate)	Thermo King provides an Operational manual to use efficiently the transport equipment. Conduct Training of drivers on GDP and how to use the refrigerated unit.

6. Design Qualification

6.1. Design Qualification

Thermo King designs and builds temperature controlled portable cooling and heating containers.

These types of equipment can be qualified for a specific desired temperature range for the transport of pharmaceutical products.

- Temperature below -20°C
- Temperature between +2°C and +8°C
- Temperature between +15°C and +25°C

To ensure total flexibility the qualification is to be performed at all stated ranges from above.

The scope of the qualification work will be done to the temperature controlled for the transportation, under temperature restrictions, of medicines.

A standard configuration is defined for each group.

6.1.1. Specifications

- 3 insulated portable containers with different capacity
  - 140L
  - 330L
  - 915L
- A K factor respective to the container volume. A K factor that is better is also permissible
  - ColdCube™ 140L: 0.35 W/m².K
  - ColdCube™ 330L: 0.29 W/m².K
  - ColdCube™ 915L: 0.28W/m².K
- Heating module
- 12/24V DC or 110-240V AC* (consumes 9–25 amps at 12V DC) with integrated AC to DC power rectifier
- Air curtains are fitted on all Pharma ColdCube container

6.1.2. Temperature Range Table

ColdCube™ 140L

Temperature Range	Extreme Ambient Temperatures	Setpoint	Max Average Deviation from Setpoint
Temperature between 2°C and 8°C	+45 °C / -30 °C	**+4 °C**	+2 °C of setpoint
Temperature between 15°C and 25 °C	+45 °C	**+22 °C**	+1 °C of setpoint
	-30 °C	**+17 °C**	+3 °C of setpoint
Temperature below -20°C	+30 °C / -30 °C	**-21 °C**	+1 °C of setpoint

ColdCube™ 330L

Temperature Range	Extreme Ambient Temperatures	Setpoint	Max Average Deviation from Setpoint
Temperature between 2°C and 8°C	+45 °C / -30 °C	**+4 °C**	+2 °C of setpoint
Temperature between 15°C and 25 °C	+45 °C / -30 °C	**+22 °C**	+2 °C of setpoint
Temperature below -20°C	+30 °C / -30 °C	**-21 °C**	+2 °C / -1 °C of setpoint

ColdCube™ 915L

Temperature Range	Extreme Ambient Temperatures	Setpoint	Max Average Deviation from Setpoint
Temperature between 2°C and 8°C	+45 °C / -30 °C	**+4 °C**	+3 °C of setpoint
Temperature between 15°C and 25 °C	+45 °C	**+21 °C**	+3 °C of setpoint
	-30 °C	**+17 °C**	+4 °C of setpoint
Temperature below -20°C	+30 °C / -30 °C	**-24 °C**	+2 °C of setpoint

To ensure total flexibility the qualification is to be performed at all stated ranges from above.

6.2. Detailed Specifications

6.2.1. Unit Capacity

	ColdCube™ 140L	ColdCube™ 330L	ColdCube™ 915L
UNIT CAPACITY (L)	140L	330L	915L
STYLE	HEATING		
INSULATION K-FACTOR	0.349	0.286	0.280
REFRIGERATION TYPE	R134a		R404a
MAXIMUM TEMPERATURE	+30 °C	+30 °C	+30 °C
MINIMUM TEMPERATURE	-21 °C	-21 °C	-21 °C
WEIGHT (KG)	42	92	168
PEAK AMPERE (Ah) COOLING	18 A	18 A	25 A
AVERAGE AMPERE (Ah) COOLING	4 A	5 A	9 A
PEAK AMPERE (Ah) HEATING	12 A	12 A	18 A
AVERAGE AMPERE (Ah) HEATING	2.8 Ah	3.5 Ah	5.5 Ah
EXTERNAL DIMENSIONS (MM)	1000x620x710	1020x1000x910	1510x1200x1180
INTERNAL DIMENSIONS (MM)	620x425x540	810x700x615	1210x934x830

6.2.2. Picture of ColdCube™ Container

Figure 2: ColdCube with plastic curtains

7. Installation Qualification

The Installation Qualification is completed and conforms to the requirements of the Design Qualification: **GDP-TK-DQ_ColdCube**.

- The portable container has been inspected and conforms to the design qualification document **GDP-TK-DQ_ColdCube**. Photographic evidence is available on request.
- A thermal curtain has been fitted on the container as described in the **GDP-TK-DQ_ColdCube**.

8. Operational Qualification

8.1. Description of the Qualified Operation

The ColdCube™ shall be use:

- For transport of pharmaceuticals (in combination with Medical devices).
- To maintain and control air temperature at a set temperature.
- In single temperature mode (< -20°C, +2°C to +8 °C or +15°C to +25°C).
- At ambient temperature between -30°C and +45 °C (max. +30 °C ambient for temperature inside the box below -20 °C).
- According to the drivers instructions supplied by Thermo King on use of Thermo King refrigerated equipment.

The objective of this qualification is to successfully qualify the designed use of this equipment.
The Operational Qualification conforms to the requirements of the Design Qualification: **GDP-TK-DQ_ColdCube**.

8.2. Support of the Defined Aspects of Use

- For transport of pharmaceuticals (in combination with Medical devices)
  - Combination of pharmaceuticals and medical devices in one load is approved.
  - Loading open food, chemical substances etc. is not permitted, even if this is a following load, due to the possibility of cross-contamination. If necessary, a validated decontamination method has to be in place. This method has to guarantee the absence of pathogens and chemicals.
- To maintain and control air temperature at a set temperature
  - The products (pharmaceuticals) will be loaded at the correct temperature because they are leaving a temperature controlled storage location. It is stated that the refrigeration unit and box is used to maintain and not change the temperature of the products.
    The mobile container is not designed for cooling down or warming up pharmaceuticals, and therefore it should not be used for this purpose.
- This container is qualified in a single temperature mode (<-20°C, +2°C to +8 °C or +15°C to +25°C)
- At ambient temperature between -30°C and +45°C (max. +30°C ambient for temperature inside the box below -20°C).
  - This GDP qualification is performed for use in the ambient temperatures as tested. To provide qualification for the expected ambient temperatures in these regions the qualification test temperatures will be performed in the following manner, minimum to be set at -30°C (to simulate average winter temperatures in Northern Europe) and maximum +45 °C (to simulate average high summer temperatures in the South of Europe).
- The ColdCube™ container will be used for transportation between temperature controlled loading docks of storage locations.
  - Door openings can have a major effect on the temperature inside the container, depending on the difference in ambient temperature and temperature inside the container. To minimise this effect all ColdCube™ Pharma container models have been fitted with a thermal curtain, allowing the operator to open doors during the distribution operation.

  - Please note that door openings time intervals should be minimised for optimal temperature management and best practice is to loading and unloading at temperature controlled warehouse. In these warehouses the product and the environment is temperature controlled.
  - If the container is to be used with multiple door openings in a non-controlled environment, based on the results of a risk analysis a complementary Performance Qualification may have to be performed by the customer.
- The equipment has to be used according to the drivers instructions supplied by Thermo King on use of Thermo King refrigerated Equipment.
- The equipment must be run and checked to ensure that all elements are functioning correctly.

8.3. Layout of Sample-type Pharma Container Qualification

The objective of this GDP qualification is to successfully qualify the designed configuration of the equipment mentioned in the Design Qualification: **GDP-TK-DQ_ColdCube**.

For this qualification three issues are important:

- The flow of temperature controlled air in the load space has to reach all parts of the load space.
- The capacity of the unit that is used to manage the temperature within the load space has to be sufficient to maintain the products at the set temperature range recommended by the manufacturer of the product (pharmaceutical company). Therefore the base colour white plus allowable 20% decal coverage is set to the DQ. Other darker colours would decrease the cooling capacity of the mobile container.
- The temperature logging equipment used for the calibration process must in itself be calibrated to each temperature range. This will be checked and confirmed during the OQ (Operational Qualification) process.

The equipment must comply with the three requirements as laid out above and should be measured with calibrated temperature data-loggers and must be registered as such. This will be checked and confirmed during the OQ (Operational Qualification) process.

8.4. Technical and User Data

8.4.1. Risk Management for ColdCube™ Pharma containers

Assumptions that are made:

- The temperature qualification is performed in an empty body, as this is considered as the worst case scenario to higher temperature variation.
- The products (pharmaceuticals) will be loaded at the correct temperature, because they are leaving temperature controlled storage. It is stated that the box is used to maintain the temperature of the products not change the temperature, though this is possible over time.
- The spectrum of the physical state (dry, liquid), pharmaceutical forms (tablets, capsules, crèmes) of the medicines, the primary package material (plastic, glass) used to pack these are enormous. The secondary package materials will probably be boxes made from cardboard.
- The capacity of a transport refrigeration unit is regulated by ATP testing standards. Because this guideline is the current standard for temperature testing, this test protocol is used as the basis for GDP qualification, thus following the test method NFX 15-140.
- At ambient temperature between -30°C and +45 °C

- **Worst-case scenario for ColdCube™ Pharma containers:**

  The greatest difference in the set-temperatures in the load space and in extreme ambient temperatures

	Ambient temperature	Set-temperature in load space
1	+45°C	+4°C
2	+30°C	-24°C / -21°C
3	-30°C	+22°C

Figure 3: Worst-case scenario of tests for ColdCube™ Pharma containers

8.4.2. Acceptance Criteria

Regarding the acceptance criteria considered in Thermo King Protocol, the air temperature should remain within the required temperature range. For example, if the requirement is for temperature range +2.0°C to +8.0°C, the minimum air temperature recorded should not be below +2.0°C, and the maximum should not exceed +8.0°C.

8.4.3. Qualification Test for ColdCube™ Pharma containers

- Deviation of registered thermocouples for the load space; 1, 2, 3, 4, 5, 6, 7, 8, 9 should not exceed max. deviation to setpoint as mentioned in section 8.4.2 Acceptance Criteria.
- The average temperature of all thermocouples should not exceed the max. deviation to setpoint as mentioned in section 8.4.2 Acceptance Criteria.
- Ambient temperature is to be logged. The logged temperature should not exceed +/-1 °C of required temperature. Thermo couples A1 and A2.
- Return air and discharge air temperature of the unit evaporator is to be logged: Temperatures should not exceed the requirement for the specific temperature being tested.
- Test time is 2,5 hours in steady state.

Type	Single temperature configuration ColdCube™ Pharma 140L
Length	Full
Setpoints	+4°C +20°C -21°C
Ambient 1 **Ambient 2** **Ambient 3**	-30°C +45°C +30°C

Figure 4: Single temperature operation – ColdCube™ 140L

Type	Single temperature configuration ColdCube™ Pharma 330L
Length	Full
Setpoints	+4°C +20°C -21°C
Ambient 1 **Ambient 2** **Ambient 3**	-30°C +45°C +30°C

Figure 5: Single temperature operation – ColdCube™ 330L

Type	Single temperature configuration ColdCube™ Pharma 915L
Length	Full
Setpoints	+4°C +20°C -24°C
Ambient 1 **Ambient 2** **Ambient 3**	-30°C +45°C +30°C

Figure 6: Single temperature operation – ColdCube™ 915L

8.5. Thermocouple locations

There is no information in GDP guideline as to location of or how many thermo couplings for temperature measurement should be inserted into the load space during the qualification test. Therefore the locations of the thermo couplings are referred to as in the ATP guideline. ATP is using standard NFX 15-140. This means 9 thermo coupling locations are utilised in the box during the qualification test. These loggers are calibrated and the calibration documents are available under request.

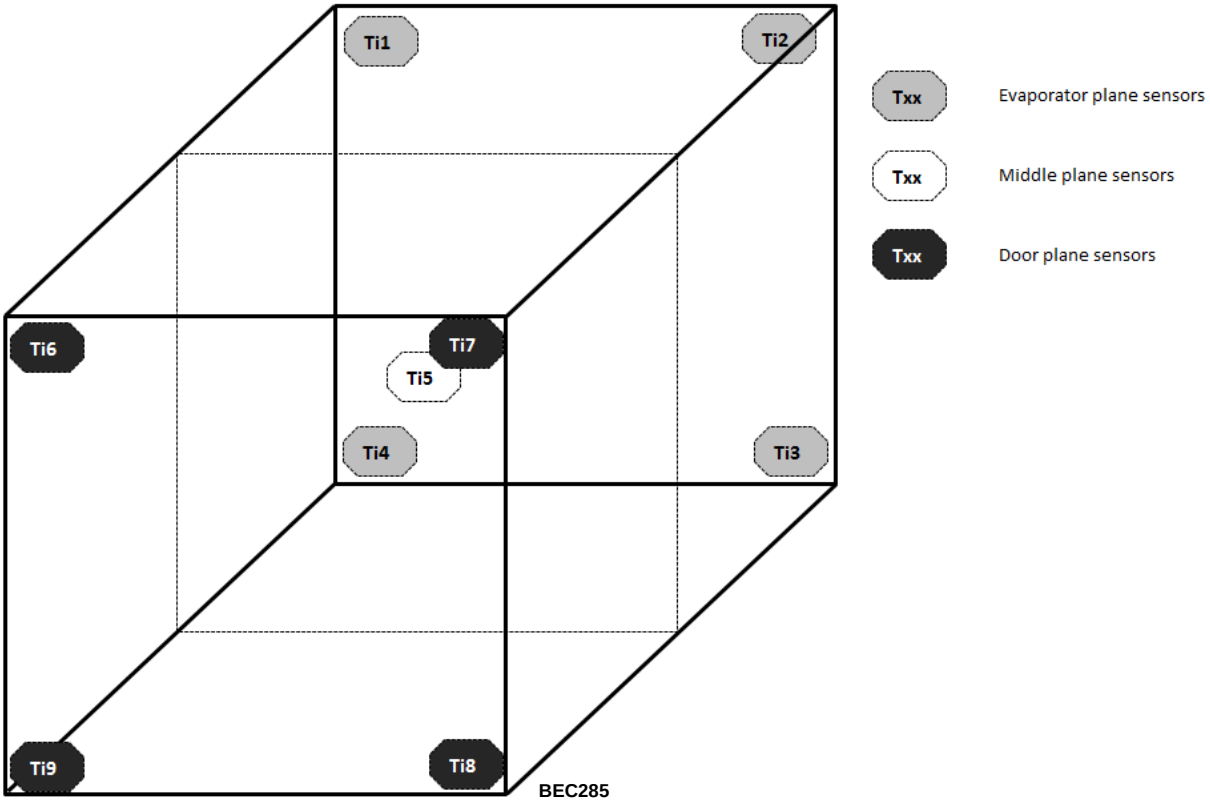

Figure 7: Thermocouple locations

BEC286

BEC287

BEC288

Figure 8: Thermocouple locations

8.6. Operational Qualification

This document confirms that,

A temperature calibration check has been performed and the results attached to this document.
The results are available on request in electronic format.

- All required risk management and due diligence protocols are in place and comply with the GDP requirements. This protocol's minimum requirements should be:
    - Scheduled maintenance
    - Breakdown repairs
    - Annual temperature calibration check
    - Access to service history
    - Asset management

9. Performance Qualification

9.1. Introduction

Thermo King designs and builds temperature controlled transport equipment.

These types of equipment can be qualified for a specific desired temperature range for the transport of pharmaceutical products.

ColdCube™ 140L

Temperature Range	Extreme Ambient Temperatures	Setpoint	Max Average Deviation from Setpoint
Temperature between 2°C and 8°C	+45 °C / -30 °C	**+4 °C**	+2 °C of setpoint
Temperature between 15°C and 25 °C	+45 °C	**+22 °C**	+1 °C of setpoint
	-30 °C	**+17 °C**	+3 °C of setpoint
Temperature below -20°C	+30 °C / -30 °C	**-21 °C**	+1 °C of setpoint

ColdCube™ 330L

Temperature Range	Extreme Ambient Temperatures	Setpoint	Max Average Deviation from Setpoint
Temperature between 2°C and 8°C	+45 °C / -30 °C	**+4 °C**	+2 °C of setpoint
Temperature between 15°C and 25 °C	+45 °C / -30 °C	**+22 °C**	+2 °C of setpoint
Temperature below -20°C	+30 °C / -30 °C	**-21 °C**	+2 °C / -1 °C of setpoint

ColdCube™ 915L

Temperature Range	Extreme Ambient Temperatures	Setpoint	Max Average Deviation from Setpoint
Temperature between 2°C and 8°C	+45 °C / -30 °C	**+4 °C**	+3 °C of setpoint
Temperature between 15°C and 25 °C	+45 °C	**+21 °C**	+3 °C of setpoint
	-30 °C	**+17 °C**	+4 °C of setpoint
Temperature below -20°C	+30 °C / -30 °C	**-24 °C**	+2 °C of setpoint

Figure 9: Capacity of equipment – temperature management

To ensure total flexibility the qualification is to be performed at all stated ranges from above.

9.2. Purpose

This protocol defines the qualification of the equipment that is designed and built by Thermo King for the transportation, under temperature restrictions, of medicines.

The qualification is based on the following documents: **GDP-TK-VMP, GDP-TK-DQ_ColdCube, GDP-TK-IQ_ColdCube,** and **GDP-TK-OQ_ColdCube**.

9.3. Scope

The scope of the qualification work (validation) will be done to the equipment of Thermo King.

A standard configuration is defined for each group.

For the ColdCube™ Pharma containers the specifications are as per the Design Qualification **GDP-TK-DQ_ColdCube**.

9.4. Evaluation of the Qualification Test

Test	Ambient	Setpoint	Min/max sensor temperature	Min/max average temperature	Average temperature deviation
ColdCube 140L					
1	+45 °C	**+ 22°C**	+21 / +23	+22 / +23	+1°C of setpoint
2	+45 °C	**+ 4 °C**	+3 / +5	+4 / +5	+1°C of setpoint
3	+30 °C	**- 21°C**	-21 / -19	-21 / -20	+1°C of setpoint
4	-30 °C	**+ 17°C**	+17 / +21	+18 / +20	+3°C of setpoint
5	-30 °C	**+ 4 °C**	+4 / +7	+4 / +6	+2°C of setpoint
6	-30 °C	**- 21°C**	-22 / -19	-22 / -20	+/- 1°C of setpoint

Test	Ambient	Setpoint	Min/max sensor temperature	Min/max average temperature	Average temperature deviation
ColdCube 330L					
1	+45 °C	**+ 22°C**	+22 / +23	+22 / +23	+1°C of setpoint
2	+45 °C	**+ 4 °C**	+4 / +6	+5 / +6	+2°C of setpoint
3	+30 °C	**- 21°C**	-21 / -19	-20 / -19	+2°C / -1°C of setpoint
4	-30 °C	**+ 22°C**	+21 / +24	+22 / +24	+2°C of setpoint
5	-30 °C	**+ 4 °C**	+3 / +6	+4 / +5	+1°C of setpoint
6	-30 °C	**- 21°C**	-22 / -20	-22 / -20	+/- 1°C of setpoint

Test	Ambient	Setpoint	Min/max sensor temperature	Min/max average temperature	Average temperature deviation
ColdCube 915L					
1	+45 °C	**+ 21°C**	+21 / +24	+22 / +24	+3°C of setpoint
2	+45 °C	**+ 4 °C**	+4 / +7	+5 / +6	+2°C of setpoint
3	+30 °C	**- 24°C**	-24 / -22	-24 / -22	+2°C of setpoint
4	-30 °C	**+ 17°C**	+18 / +22	+19 / +21	+4°C of setpoint
5	-30 °C	**+ 4 °C**	+4 / +8	+4 / +7	+3°C of setpoint
6	-30 °C	**- 24°C**	-24 / -21	-23 / -22	+2°C of setpoint

Figure 10: Result of the thermal mapping tests ColdCube™ Pharma containers

Temperature mapping results of the qualification are presented in a separate PQ report and are available on request following the signing of a NDA (Non-Disclosure Agreement).

The report number is **GDP-TK-PQ-TestReport_ColdCube**.

9.5. Recommendations

- To maintain the best temperature management within the load-space it is recommended to operate with the following set-point temperatures in the following ranges.
    - For temperature range +15 °C to +25 °C: setpoint at +22 °C. A lower setpoint should also be acceptable (+20° C)
    - For temperature range +2 °C to +8 °C: setpoint at +4 °C.
    - For temperature below -20 °C:
        - Setpoint at -24 °C for ColdCube 915L
        - Setpoint at -21 °C for the ColdCube 140L and ColdCube 330L. -21 °C is the lowest setpoint available. That setting provides a temperature management of +/-1 °C around the -20 °C limit.
- If a product needs to be kept at temperature range below -20°C, the mobile container can be stored at a maximum ambient temperature of +30°C. Above +30°C ambient temperature, the ColdCube cannot ensure to maintain the temperature with the requested range.
- Door opening tests showed a positive effect of curtains. For that purpose, in case of multiple door openings, air curtains should be fitted on the mobile container.
- Efficient loading practices and operating procedures have to be followed to ensure optimum air circulation and temperature management. Where possible, an air circulation gap of 50 mm around the cargo should be kept.
- ColdCube 915L
    - On the ColdCube 915L, at negative ambient temperature (-30 °C), no product should be located just below the airflow of the heating module, at rear left lower corner.
      An 100 mm circulation gap at the rear should be kept.
    - To maintain the best temperature management within the load-space at negative ambient temperature, Thermo King recommends changing the controller set up temperature with a -3 °C offset.

10. Appendix

Certificate of Prague Accreditation - ISO 17025

Certificate of Prague Accreditation - ISO 9001

NÁRODNÍ AKREDITAČNÍ ORGÁN

EA MLA Signatory
Český institut pro akreditaci, o.p.s.
Olšanská 54/3, 130 00 Praha 3

issues

according to section 16 of Act No. 22/1997 Coll., on technical requirements for products, as amended

CERTIFICATE OF ACCREDITATION

No. **391 / 2015**

Ingersoll-Rand Technologies s.r.o.
with registered office č.p. 292, 280 02 Ovčáry, Company Registration No. 63989069

to the Testing Laboratory No. **1680**
ETC Prague

Scope of accreditation:

Performance of functional, dynamic, seismic, climatic and thermal resistance tests of components and products to the extent as specified in the appendix to this Certificate.

This Certificate of Accreditation is a proof of Accreditation issued on the basis of assessment of fulfillment of the accreditation criteria in accordance with

ČSN EN ISO/IEC 17025:2005

In its activities performed within the scope and for the period of validity of this Certificate, the Body is entitled to refer to this Certificate, provided that the accreditation is not suspended and the Body meets the specified accreditation requirements in accordance with the relevant regulations applicable to the activity of an accredited Conformity Assessment Body.

This Certificate of Accreditation replaces, to the full extent, Certificate No.: 190/2015 of 18 March 2015, or any administrative acts building upon it.

The Certificate of Accreditation is valid until: **18 March 2018**

Prague: 3 June 2015

Český institut pro akreditaci, o.p.s.
NÁRODNÍ AKREDITAČNÍ ORGÁN
-2-

Jiří Růžička
Director
Czech Accreditation Institute
Public Service Company

ETC PRAGUE

Ingersoll Rand

Lloyd's Register LRQA

CERTIFICATE OF APPROVAL

This is to certify that the Quality Management System of:

Ingersoll-Rand Equipment Manufacturing Czech Republic s.r.o.
Ovčáry 292
280 59 Kolín
Czech Republic

has been approved by Lloyd's Register Quality Assurance to the following Quality Management System Standards:

ISO 9001:2008

The Quality Management System is applicable to:

Research, development and manufacture of refrigeration and air conditioning equipment.

This certificate is valid only in association with the certificate schedule bearing the same number on which the locations applicable to this approval are listed.

Approval
Certificate No: PRA 0004156

Original Approval: 27 September 2002

Current Certificate: 1 October 2014

Certificate Expiry: 30 September 2017

Issued by: Lloyd's Register EMEA, Prague office,
for and on behalf of Lloyd's Register Quality Assurance Limited

UKAS MANAGEMENT SYSTEMS
001

Táborská 31, 140 00 Prague 4, Czech Republic
for and on behalf of Hiramford, Middlemarch Office Village, Siskin Drive, Coventry, CV3 4FJ, United Kingdom