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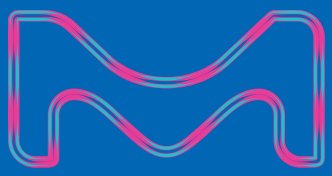
Validation Summary

PyroDetect Cryoblood Shipment



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Introduction

This summary documents the validation of the packaging configurations used for shipment of the PyroDetect Cryoblood (product reference 144.155.0001), item part of the PyroDetect System.

Three packaging solutions were addressed in the scope of this validation. A shipment simulation was performed to verify capacity of the three packaging formats to preserve the PyroDetect Cryoblood performances during its shipment

The PyroDetect Cryoblood is a temperature sensitive product. It should be stored at -80°C or lower and shipment is performed in dry-ice.

A summer cycle was applied on packaging based on the standards NF S99-700 (Oct 2007) and ISTA 7E to simulate worst shipment conditions.

Principle of the PyroDetect System

The PyroDetect System is a test for the detection and quantification of pyrogens based on Monocyte-Activation Test (MAT).

The MAT uses an innate immune defense reaction of the human blood.

Monocytes activated by pyrogens produce cytokines that are detected in an immunological assay (ELISA) involving specific antibodies and an enzyme-mediated color change.

The PyroDetect System uses cryo-preserved human whole blood as a source of monocytes (present in the PyroDetect Cryoblood 144.155.0001). The response to pyrogenic substances is determined by measurement of the Interleukin-1β (IL-1β) production.

The intention of the MAT is to prove that the amount of pyrogens in the test product does not exceed the limit of contamination (CLC, Contaminant Limit Concentration). The test is performed in accordance with the specifications described in chapter 2.6.30 on Monocyte Acitvation Test in the European Pharmacopoeia.

References

MillipreSigma Documentation Reference

The following qualification documents which support this validation summary may be consulted during a scheduled audit:

Document number or type	Title
20225646	FRPPI013-PAQP1-Qualification Protocol of Cryoblood 144155 shipment
20232902	FRPPI013-PAQR1-Qualification Report of Cryoblood 144155 shipment
User Manual	PyroDetect System Monocyte-Activation Test (MAT) User Manual
Application Note	PyroDetect System – Detection and Handling of Outliers
20131664	Validation statement of dry ice transportation packaging

Regulations

European Pharmacopoeia: 8th Edition (8.6) Chapter 2.6.30 Monocyte-Activation Test.

Standards

- NF S99-700, Oct 2007: Qualification method for thermal performances.
- ISTA 7E 10-14: Testing Standard for Thermal Transport Packaging Used in Parcel Delivery System Shipment.

Validation Purpose and Tests Summaries

Aim of the present qualification is to verify the performance of three packaging solutions (DI4 box, EMD Millipore/ Temecula box and AEROGEL box) used for shipment of the Cryoblood product.

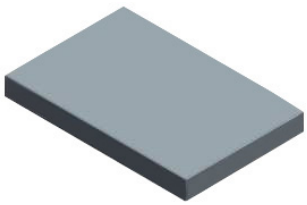
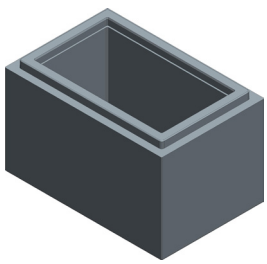
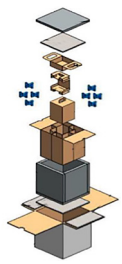
Performances of each packaging are characterized by their capacity to preserve PyroDetect Cryoblood reactivity during the shipment. Therefore, cryo-preserved blood reactivity was assessed after transport simulation using each of the three packing formats. Analysis of the endotoxin standard curve generated after the shipping simulation enabled to verify Cryoblood properties conformance.

Same performances testing was carried out after 3 months storage at -86°C in order to verify that the shipping has not reduced Cryoblood shelf life.

1. Materials

Reagents and Products	PyroDetect Kit (1.44154.0001)
	PyroDetect Cryoblood (1.44155.0001)
	PyroDetect Endotoxin Standard (1.44161.0001)
Equipment	Climatic chamber
	Wired temperature probes working at -80°C
	Calibrated -86°C freezer
	Incubator, 37°C
	Microbiological safety cabinet
	Microplate photometer for measuring absorbance at 450 nm, with the reference wavelength set between 600 and 690 nm
	Adjustable pipettes: (10 µL – 100 µL; 100 µL – 1000 µL)
	Multichannel pipettes with suitable pyrogen free containers
	Mini boxes (HIPS mini box used to pack Cryoblood vials)
	Automated microplate washer
Consumables	Suitable sterile, pyrogen-free pipette tips
	Pyrogen-free glass tubes
	15mL plastic tubes
	Pyrogen-free 1.5mL plastic microtubes
Software for data analysis	PyroDetect Data AnalysisTool (1.44299.0001)

Packaging solutions

	Box DI4	Box EMD Millipore/Temecula	Box AEROGEL
Supplier	Knauf Industries	EMD Millipore/Temecula	American Aerogel
Specifications	Polystyrene box intended for dry ice shipment.	Polystyrene box intended for dry ice shipment.	Insulated packaging for dry ice shipment.
	Internal dimensions: 460mm x 260mm x 270 mm. Wall thickness: 60mm	Internal dimensions: 525mm x 340mm x 355 mm. Wall thickness: 40mm	Not indicated.
View			
Product Packaging procedure	Cryoblood samples are packed in a plastic bag filled with dry ice in order to keep Cryoblood surrounded by dry ice.	Cryoblood samples are packed in two plastic bags filled with dry ice	Samples are packed in part 7 of the above picture.
Cryoblood packing capacity	Maximum 10 Cryoblood mini-boxes can be packed.	Maximum 22 Cryoblood mini-boxes can be packed	Maximum 22 Cryoblood mini-boxes can be packed.

NOTE: Both DI4 and EMD Millipore/TEMECULA boxes were validated by MilliporeSigma for dry ice shipment.
No validation activities were carried out by MilliporeSigma for AEROGEL box.
This packaging was nevertheless included in the study for comparison.

2. Method

Test method described in the Qualification Protocol of Cryoblood 144155 shipment (document number 20225646) supports this validation study.

Packages preparation

A unique lot of Cryoblood was used to challenge the different packaging formats in order to reduce biological variability.

3 PyroDetect Cryoblood units were placed in each packaging type, at 3 different positions, to assess the different possible placements within the box: bottom, top and middle.

Additional empty units (mini-boxes identical to those containing Cryoblood vials) were placed into each package in order to optimize package capacity and simulate typical order size (see packing capacities described above).

Each package was prepared according to the procedure used routinely at the Strasbourg warehouse:

- TEMECULA and DI4: The mini-boxes were placed in plastic bags filled with dry ice in order to keep them in contact with the freezing agent (1 bag for 10 samples in DI4 and 2x 1 bag for 11 samples in TEMECULA). These bags were lied down flat on a dry ice layer. Dry ice was added above the bags so that samples are properly wrapped and the box is completely filled with. This packaging procedure was defined and validated by Merck for both formats.
- AEROGEL: The mini-boxes were packed in compartment 7 according to supplier's instructions. Dry ice was added in parts 5 and 9 in order to keep them frozen. No validation activities have been carried out by Merck on that packing procedure.

Note: Part 8 was removed and not used for this study in order to simulate maximum order size.

Probes Installation

Right after preparation at warehouse, all packages were delivered within few hours by road to another site in order to be exposed to temperature variation.

In each packaging, 3 empty mini-boxes were equipped with wired probes in order to accurately monitor the temperature at which each Cryoblood sample location was exposed. Probes placement was performed on dry ice to minimize temperature shift of the empty mini-boxes.

Only empty boxes were equipped in order to reduce risk of product exposure to room temperature. Cryoblood products were therefore kept in dry ice during probes installation.

To compensate dry ice loss during road shipment and probes installation, the packages were re-iced before to be placed in the climatic chambers. Packages integrity was checked as well before starting the cycle.

Cycle Conditions Used for Shipment Simulation

A 5 days-cycle (120h) was applied to the three packages installed in a dedicated climatic chamber. This duration is considered as a worst case since a regular drop shipment does not typically exceed 48 hours in Europe and 3 days in North America. On top of that, dry ice transportation was validated up to 5 days for the two packaging.

Cycle parameters were defined according to standards NF S99-700 (Oct 2007) and ISTA 7E heat exposure profile.

The cycle program applied to packages included both maximum and minimum temperatures described in the two standards:

- Maximum temperature: 40°C
- Minimum temperature: 22°C

Time (h)	Temperature shift	Duration (h)
0	22°C	3
3	28°C	4
7	22°C	9
16	28°C	8
24	40°C	4
28	28°C	3
31	22°C	9
40	25°C	8
48	22°C	3
51	28°C	4
55	22°C	9
64	28°C	8
72	40°C	4
76	28°C	3
79	22°C	9
88	25°C	8
96	22°C	3
99	28°C	4
103	22°C	9
112	28°C	8

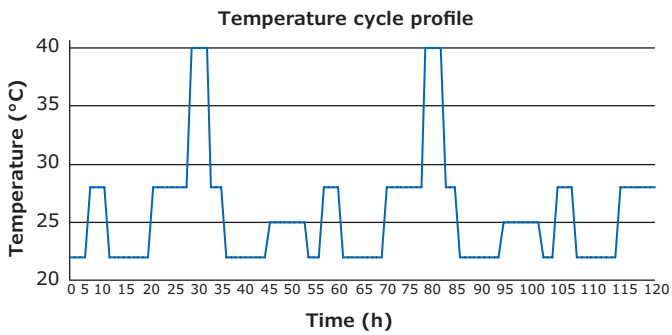


Figure 1. Temperature variations applied to the packages in climatic chamber

Note: This shipment simulation was focusing on the thermal capacity of the packages. It does not include Cryoblood product movement within packages due to handling or vibrations caused by the shipment.

At the end of the cycle, temperature probes were removed and the packages were shipped back to Millipore SAS facilities. Fresh dry-ice was added to each box in order to ensure temperature stability during the back-shipment.

Cryoblood performances evaluation

Endotoxin standard curve generation

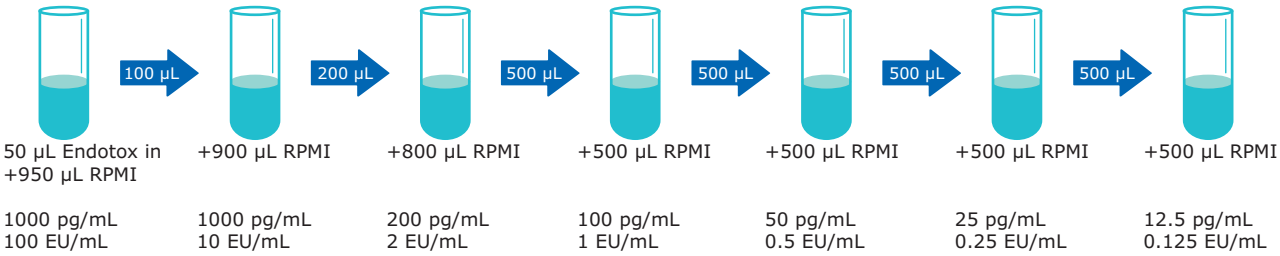
Cryoblood samples were removed the packages and stored at -86°C until to be tested, the day after.

Endotoxin standard curves were generated in presence of each Cryooblood sample in order to verify their reactivity after shipment in the different packaging formats.

All Cryoblood products from each package were tested with the same PyroDetect kit (the 3 positions were tested on the same microplate) as described below:

1

Endotoxin dilutions series were performed in pyrogen-free glass tubes and with the RPMI culture medium provided in the kit. Five endotoxin concentrations (2.0; 1.0; 0.5; 0.25; 0.125 EU/mL) were prepared according to the following scheme (**Figure 2**).



EU = Endotoxin Units

Figure 2. Endotoxin dilution series.

A negative control was prepared in parallel without endotoxin (0 EU/mL).

The five concentrations as well as the negative control were then distributed over the three cell culture microplates as described in the PyroDetect System Monocyte-Activation Test (MAT) User Manual.

One microplate was prepared for each packaging format (see below).

2

Previously diluted with RPMI, Cryoblood samples were then added to the endotoxin dilutions (4 replicates per dilution).

Non-cycled Cryoblood from same lot was also added to each plate in order to serve as a reference (CONTROL) as shown below:

	1	2	3	4	5	6	7	8	9	10	11	12
A	2	0.5	0.125	2	0.5	0.125	2	0.5	0.125	2	0.5	0.125
B	2	0.5	0.125	2	0.5	0.125	2	0.5	0.125	2	0.5	0.125
C	2	0.5	0.125	2	0.5	0.125	2	0.5	0.125	2	0.5	0.125
D	2	0.5	0.125	2	0.5	0.125	2	0.5	0.125	2	0.5	0.125
E	1	0.25	0	1	0.25	0	1	0.25	0	1	0.25	0
F	1	0.25	0	1	0.25	0	1	0.25	0	1	0.25	0
G	1	0.25	0	1	0.25	0	1	0.25	0	1	0.25	0
H	1	0.25	0	1	0.25	0	1	0.25	0	1	0.25	0

Unit = EU/mL

Figure 3. Endotoxin standard curves layout applied for each packaging format. Cryoblood locations were named as Position 1, Position 2, Position 3 and Control

3

Microplates were then incubated at 37°C for 24h.

4

Optical density measurement was performed at 450nm after samples transfer in ELISA plate, and enzyme-labeled antibody addition as described in the User Manual.

Endotoxin standard curves were finally generated by plotting the mean of the OD values of the 4 replicates measured for each dilution, against the concentration.

PyroDetect Data Analysis Tool, Art. No. 1.44299.0001 was used to do so.

All Cryoblood products were then stored at -86°C before being tested after 3 months aging.

Acceptance criteria

PyroDetect Cryoblood performances were verified by mean of endotoxin standard curve analysis.

1 Endotoxin standard curve validity

According to the Pharmacopoeia two acceptance criteria (p-values) have to be used to verify the validity of the standard curves.

Generated endotoxin standard curves are conform if:

- **Regression: p<0.01**

The regression of responses is statistically significant on a logarithmic scale.

- **Non-linearity: p>0.05**

The regression of responses on a logarithmic scale must not deviate significantly from linearity.

The required p-values were calculated using of the PyroDetect Data Analysis Tool.

2 LOD calculation

In addition to the LOD defined in the European Pharmacopoeia, MilliporeSigma guarantees by the release tests performed within the quality control, a minimum sensitivity of 0.25 EU/mL (based on LOD-calculation described in European Pharmacopoeia).

Cryoblood perfomances are therefore conform if the calculated LOD is below 0.25 EU/mL.

3 Maximal OD_{450nm} value

Maximal OD_{450nm} values were also considered to assess the performances of each PyroDetect Cryoblood sample after shipment simulation.

Indeed, OD_{450nm} measured is directly linked to Interleukin-1β (IL-1β) production by monocytes from Cryoblood, in response of pyrogen presence.

This data is therefore directly linked to Cryoblood performances as described on the picture below (see User Manual):

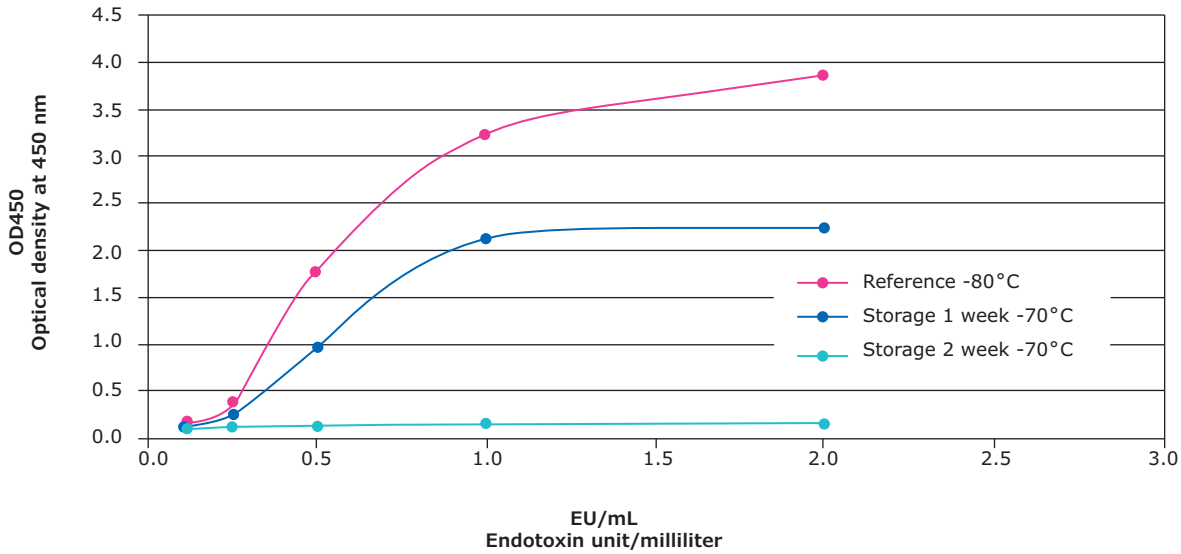
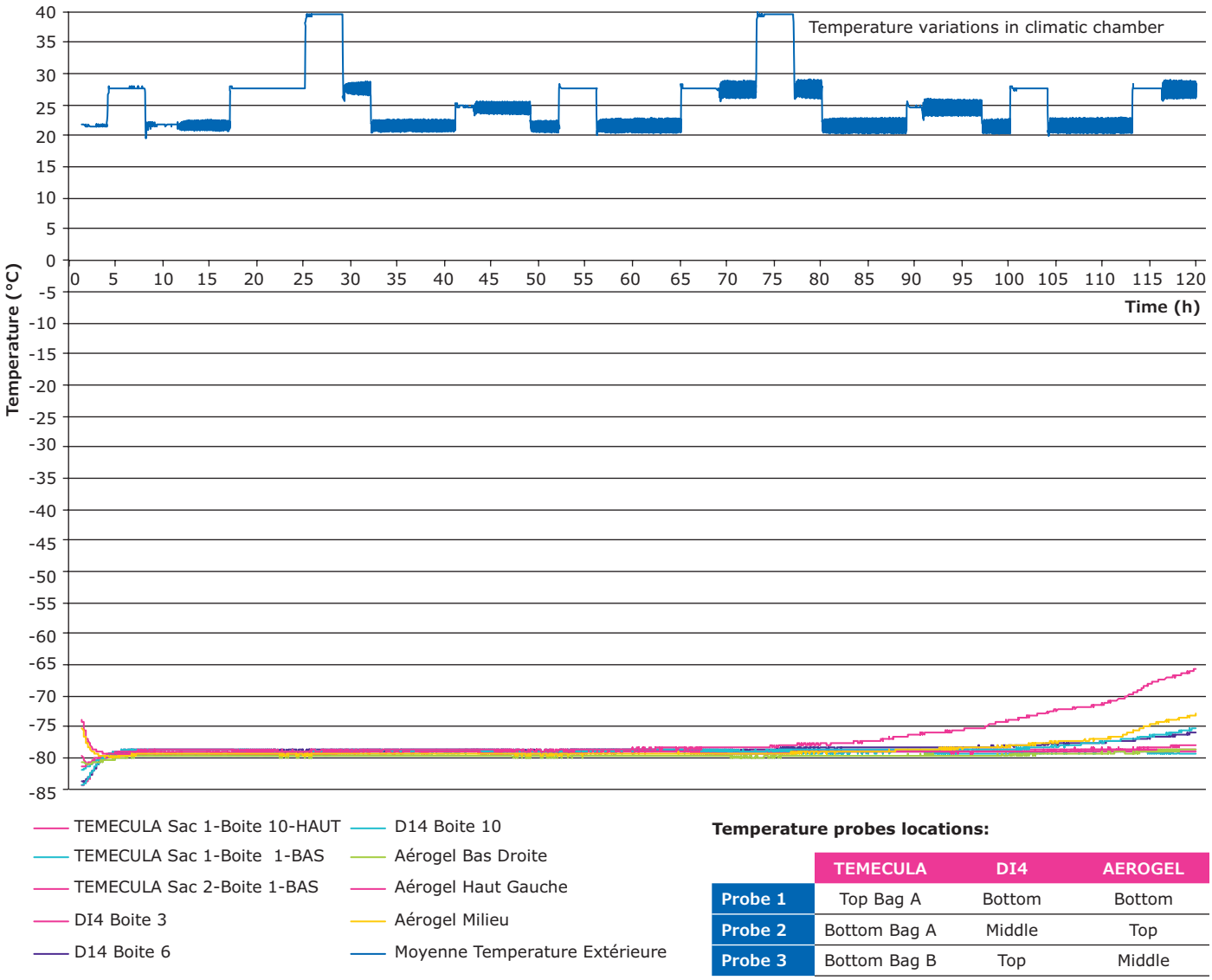


Figure 4. Examples of improper storage at -70°C after one or two weeks of storage.

Maximal OD_{450nm} close to 4.0 has been reached with a Cryoblood sample stored in recommended conditions. Based on this data, OD_{450nm} values can be used to verify performances of the shipped Cryoblood samples.

Qualification Test Results

Temperatures monitoring during cycle



Temperature probes locations:

	TEMECULA	DI4	AEROGEL
Probe 1	Top Bag A	Bottom	Bottom
Probe 2	Bottom Bag A	Middle	Top
Probe 3	Bottom Bag B	Top	Middle

Temperature variations measured in the climatic chamber (blue curve above) are corresponding to the cycle parameters described previously. Temperatures recorded during the cycle were ranging from 20 to 40°C.

As described on the above graph, temperatures recorded quickly equilibrated at -79°C into each packages after 3h.

Temperature curves obtained are similar for both TEMECULA and DI4 boxes: the temperature was maintained at -79°C until 110h.

- After 110h the temperature slightly started to increase in DI4 package to reach -75°C at the end of the cycle.
- TEMECULA format enabled to maintain temperature at -79°C during the entire cycle (120h).

The 3 temperature probes placed in AEROGEL responded in a different way:

- Probe placed at the bottom recorded a temperature stabilized at -79°C during the complete cycle, whereas,
- Probes placed at both middle and top positions recorded temperatures below -75°C after 114h (middle) and 96h (top).

Vertical configuration of AEROGEL box is aligned with this observation. Highest temperature recorded at the end of the cycle was -66°C in this package.

Cryoblood performances evaluation after shipment

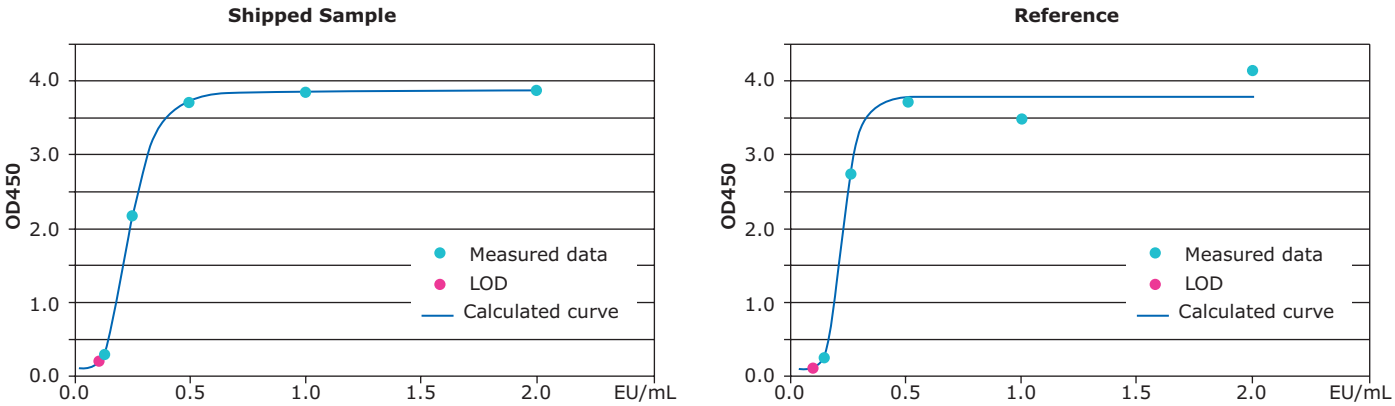
PyroDetect Data Analysis Tool was used to generate an endotoxin standard curve for each Cryoblood sample included in the study. According to EP chapter 2.6.30 requirements, this Excel®-based validated tool converts the values the photometer measures into endotoxin units (EU/mL).

By mean of a four-parameters curve analysis, this software enables to calculate both p-values: statistical regression and non-linearity. Both p-values were used in this study to verify validity of the standard curve.

The Application Note "PyroDetect System – Detection and Handling of Outliers" was used to identify outlying values, caused by handling and processing errors, contaminations or error readings that could thus lead to wrong conclusions or results (see Application Note for more information). These values were excluded from calculations.

Temecula Packaging Format

Endotoxin Standard curves



Note. As standard curves obtained were equivalent for all samples, only one position was illustrated above. This curve is corresponding to Sample 1 placed at the bottom of the bag A.

OD_{450nm} value above 4.0 was reached for the REFERENCE sample indicating that the Cryoblood lot used for this study is very reactive (see curves described in Acceptance criteria).

Maximal OD_{450nm} value obtained for the shipped sample was close to 4.0. This result proves that Cryoblood properties were efficiently preserved during the summer temperatures stress cycle applied to this packaging format.

p-values and LOD

TEMECULA	Sample 1 Bottom Bag A	Sample 2 Top Bag A	Sample 3 Bottom Bag B	Reference*
Regression p<0,01	Passed	Passed	Passed	Passed
Non linearity p>0,05	Passed	Passed	Passed	Passed
LOD<0,25 EU/mL	Passed	Passed	Passed	Passed

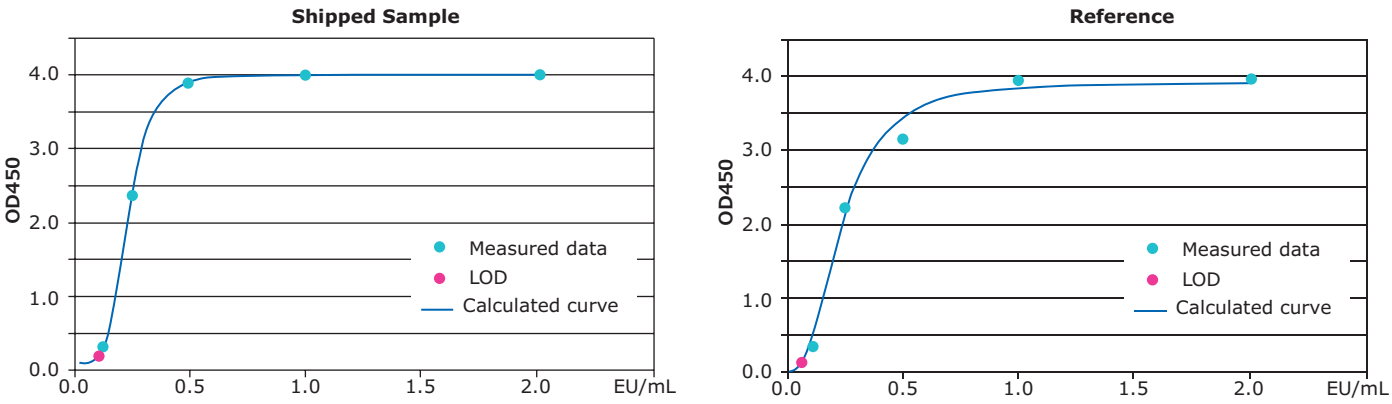
*Reference: Same Cryoblood lot, not submitted to temperature variations (standard storage at -86°C).

Both p-values and LOD calculated for the shipped samples comply with acceptance criteria. These data confirm that performances of the shipped Cryoblood were not affected by the temperature variations, whatever the sample location in TEMECULA packaging format.

As previously described, plastic bags are used to pack the samples and keep them in contact with the dry ice. Dry ice amount and packing guidelines described in the procedure allowed therefore to maintain an appropriate storage temperature up to 5 days, besides the temperature variations applied.

DI4 Packaging Format

Endotoxin Standard curves



Note. As standard curves obtained were equivalent for all samples, only one position was illustrated above. This curve is corresponding to Sample 2 placed in the middle of the box.

High reactivity of the Cryoblood lot used for this study was also emphasized by mean of this second ELISA test. Maximal OD_{450nm} values obtained for the REFERENCE and the shipped sample were both close to 4.0, showing that Cryoblood properties were efficiently preserved by the DI4 box during the temperatures stress cycle applied (see curves illustrated in Acceptance criteria).

p-values and LOD

TEMECULA	Sample 1 Bottom	Sample 2 Middle	Sample 3 Top	Reference*
Regression p<0,01	Passed	Passed	Passed	Passed
Non linearity p>0,05	Passed	Passed	Passed	Passed
LOD<0,25 EU/mL	Passed	Passed	Passed	Passed

*Reference: Same Cryoblood lot, not submitted to temperature variations (standard storage at -86°C).

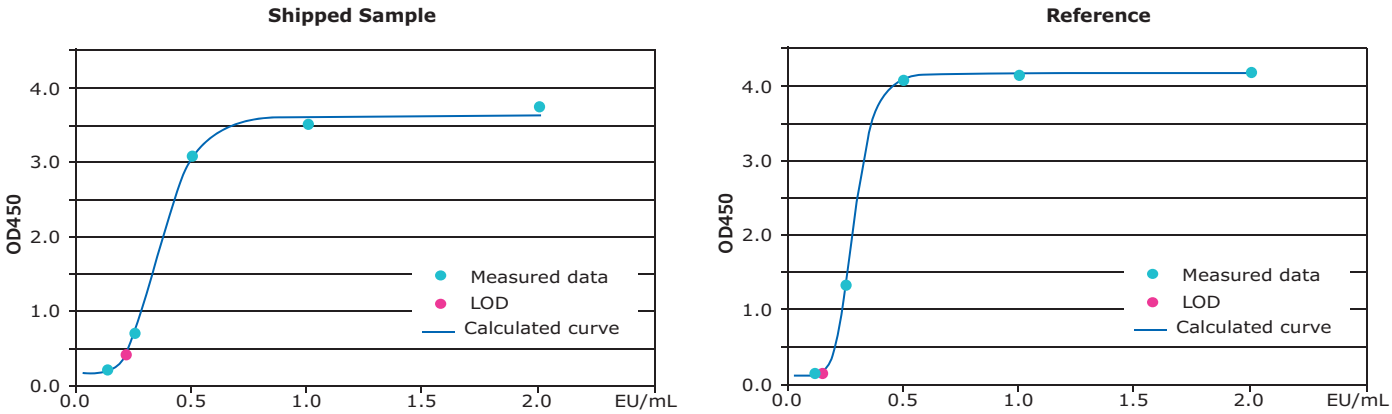
Calculated p-values and LOD confirmed that performances of the shipped Cryoblood are conform whatever the sample location in DI4 packaging format. This packaging is therefore able to preserve Cryoblood properties up to 5 days besides temperatures variations when prepared according to the current procedure.

A plastic bag is also used to keep the samples in contact with the dry ice into this packaging format.

Dry ice amount used to ship Cryoblood into this box allowed to maintain an appropriate storage temperature during the whole shipment duration.

Aerogel Packaging Format

Endotoxin Standard curves



Note. As standard curves obtained were equivalent for all samples, only one position was illustrated above. This curve is corresponding to Sample 3 placed in the top of the box.

OD_{450nm} value close to 4.0 was also reached for REFERENCE sample proving strong reactivity of the Cryoblood lot used for the study.

OD_{450nm} value above 3.5 was reached for the shipped sample placed at the top of the box. As described above, the highest temperature shift was recorded for this location. Even if the temperature has reached -66°C during the last 24h (worst case), Cryoblood properties tested were conform.

This results have demonstrated that AEROGEL pack allowed to preserve Cryoblood properties during the complete shipping simulation cycle even if dry ice vaporization occurred.

p-values and LOD

TEMECULA	Sample 1 Bottom	Sample 2 Middle	Sample 3 Top	Reference*
Regression p<0,01	Passed	Passed	Passed	Passed
Non linearity p>0,05	Passed	Passed	Passed	Passed
LOD<0,25 EU/mL	Passed	Passed	Passed	Passed

*Reference: Same Cryoblood lot, not submitted to temperature variations (standard storage at -86°C).

Conformance of the calculated p-values and LOD confirmed that performances of the shipped Cryoblood were not affected by temperature variations whatever the sample location in AEROGEL packaging format.

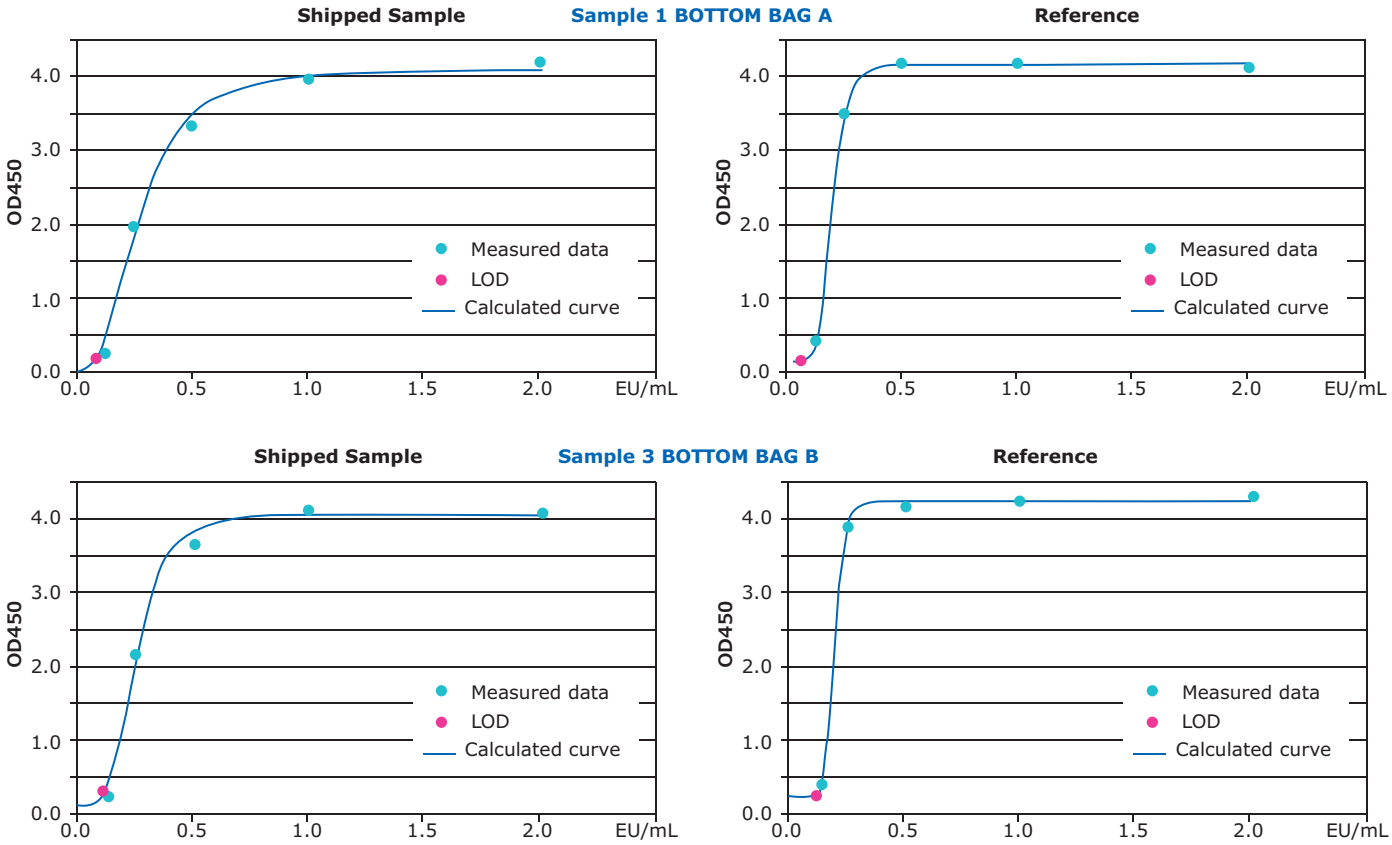
This packaging is therefore able to preserve Cryoblood properties up to 5 days besides the temperature variations applied.

Shelf life verification

Same performances testing has been performed on the shipped samples stored for 3 months at -86°C in order to verify that temperature variations applied on samples did not lead to a shelf life reduction.

Temecula Packaging Format

Endotoxin Standard curves



Maximal OD_{450nm} value obtained for the shipped samples was still close to 4.0 after 3 months storage for the two samples.

This result confirm that Cryoblood properties were efficiently preserved during the summer temperatures stress cycle applied to this packaging format whatever the sample position.

High reactivity of the shipped Cryoblood was therefore conserved until 3 months.

p-values and LOD

TEMECULA	Sample 1 Bottom Bag A	Reference* Sample 1	Sample 3 Bottom Bag B	Reference* Sample 2
Regression p<0,01	Passed	Passed	Passed	Passed
Non linearity p>0,05	Passed	Passed	Passed	Passed
LOD<0,25 EU/mL	Passed	Passed	Passed	Passed

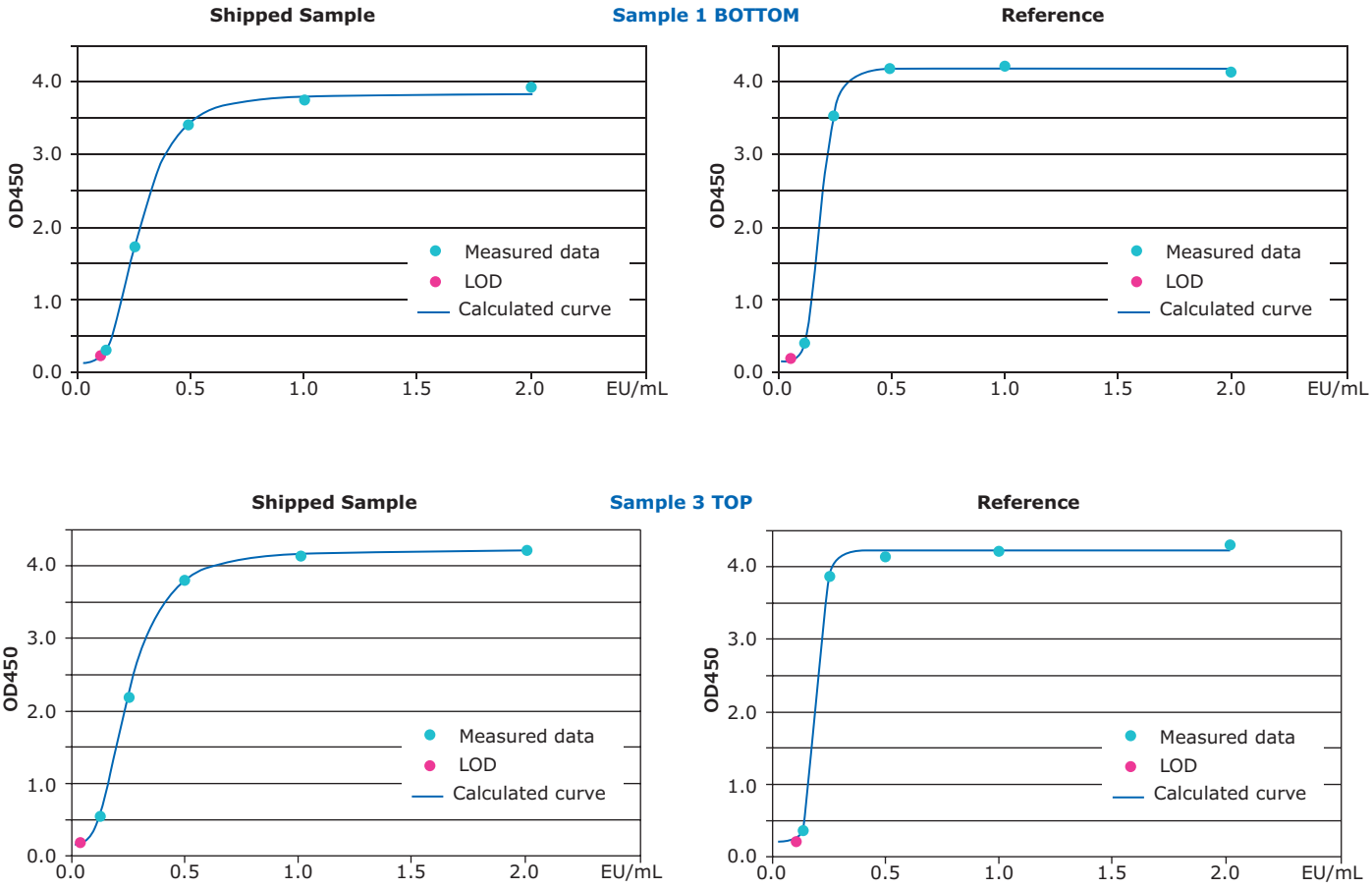
Both p-values and LOD calculated for the shipped samples comply with acceptance criteria. These data confirm that performances of the shipped Cryoblood were not affected by the temperature variations, whatever the sample location in TEMECULA packaging format.

Shelf life of the shipped Cryoblood was not reduced by temperature variations applied on the TEMECULA package.

*Reference: Same Cryoblood lot, not submitted to temperature variations (standard storage at -86°C). The samples were tested on two different ELISA plates in order to secure the testing at 3 months (duplication).

DI4 Packaging Format

Endotoxin Standard curves



Maximal OD_{450nm} values obtained for the REFERENCE and the shipped sample were both close to 4.0, showing that Cryoblood properties were efficiently preserved by the DI4 box during the temperatures stress cycle applied even after 3 months storage at -80°C.

p-values and LOD

TEMECULA	Sample 1 Bottom	Reference* Sample 1	Sample 3 Top	Reference* Sample 3
Regression p<0,01	Passed	Passed	Passed	Passed
Non linearity p>0,05	Passed	Passed	Passed	Passed
LOD<0,25 EU/mL	Passed	Passed	Passed	Passed

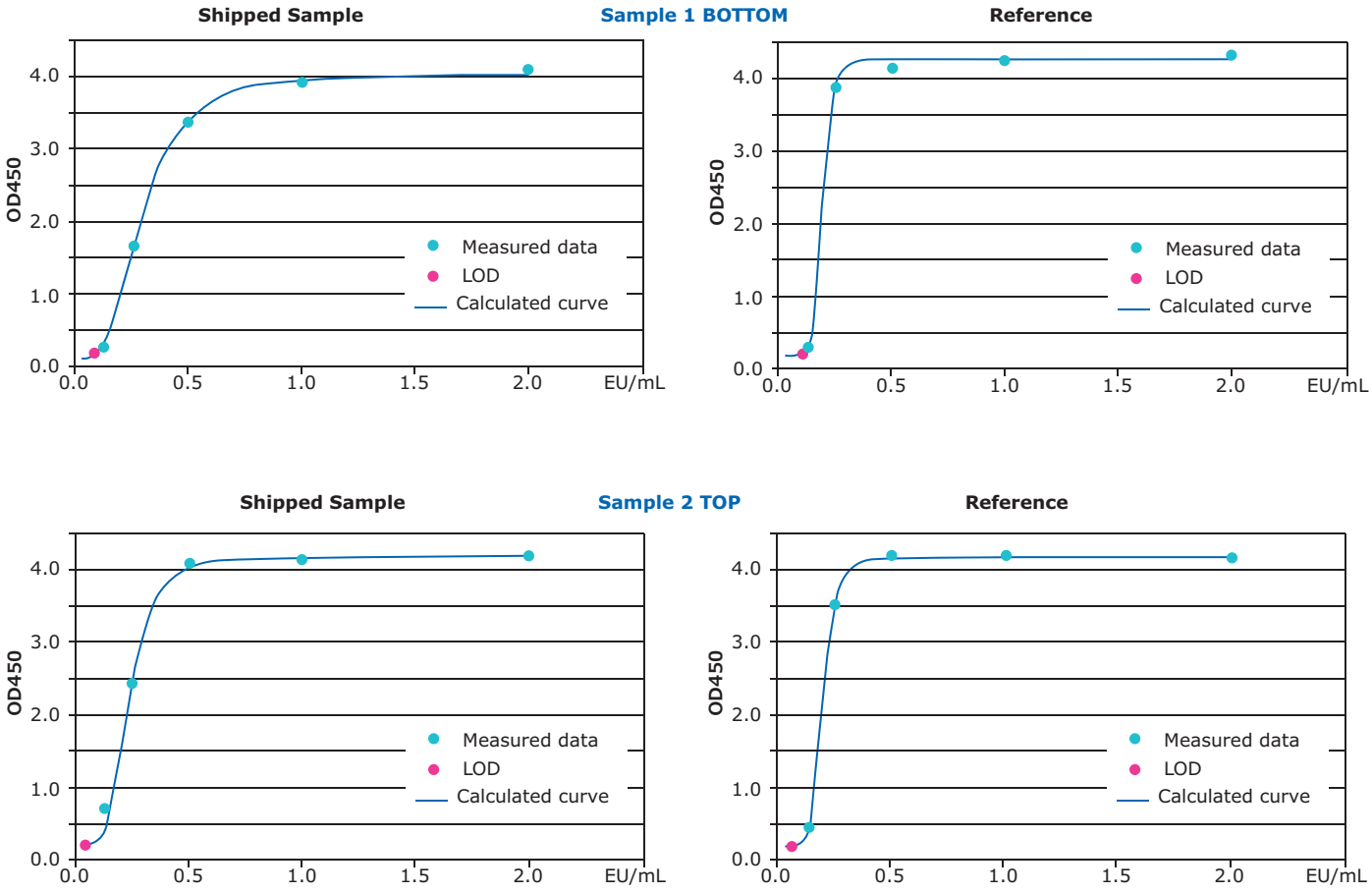
Both p-values calculated for the shipped samples and the REFERENCE comply with acceptance criteria. These data confirm that performances of the shipped Cryoblood were not affected by the temperature variations, whatever the sample location in DI4 packaging format.

Shelf life of the shipped Cryoblood was not reduced by temperature variations applied on the DI4 package.

*Reference: Same Cryoblood lot, not submitted to temperature variations (standard storage at -86°C). The samples were tested on two different ELISA plates in order to secure the testing at 3 months (duplication).

Aerogel Packaging Format

Endotoxin Standard curves



Curve's shapes and maximal OD450nm value obtained for worst sample location (TOP) were as good as the ones observed for the sample placed at the bottom of the AEROGEL box (best case).

This result showed that even if the temperature has reached -66°C during 24h for the sample placed at the top, Cryoblood properties were not impacted.

p-values and LOD

TEMECULA	Sample 1 Bottom	Reference* Sample 1	Sample 2 Top	Reference* Sample 2
Regression p<0,01	Passed	Passed	Passed	Passed
Non linearity p>0,05	Passed	Passed	Passed	Passed
LOD<0,25 EU/mL	Passed	Passed	Passed	Passed

Conformance of the calculated p-values also confirmed that shelf life of the shipped Cryoblood was not affected by temperature variations whatever the sample location in AEROGEL packaging format.

Performances of AEROGEL box were therefore confirmed by this testing at 3 months aging.

*Reference: Same Cryoblood lot, not submitted to temperature variations (standard storage at -86°C). The samples were tested on two different ELISA plates in order to secure the testing at 3 months (duplication).

Conclusion

Based on standards NF S99-700 (Oct 2007) and ISTA 7E, cycle parameters used in this study enabled to simulate worst conditions shipment of PyroDetect Cryoblood (reference 144.155.0001).

The three packaging formats addressed in this study met the quality attributes as all the results comply with the acceptance criteria.

Performances testing performed after 3 months storage confirmed that the temperature variations applied on the samples did not lead to a shelf life reduction.

Ability of each package to efficiently preserve Cryoblood performances up to 5 days shipment is henceforth considered as validated.

As both DI4 and TEMECULA boxes were validated by Merck for dry ice shipment, these two packaging solutions are the preferred standard ones.

Discussion

This shipment simulation does not include pressure drop observed during air freight express delivery.

Pressure variations were excluded from this validation based on the both consistent observations:

- In planes holds, pressure is dropping down to 0.4 bar to due to altitude. The more the pressure is decreasing the faster the dry ice is evaporating.
- In planes holds, temperature is dropping down to 10°C due to altitude. The more the difference between packaging room storage temperature and dry ice (-76°C, temperature into packages) is increasing, the faster the dry ice is evaporating. This difference is higher when performing temperature variations from 20°C to 40°C in climatic chamber than storing them in planes holds at 10°C. Here also, variations performed in the climatic chamber are considered as a worst case for dry ice sublimation.

Based on these both thermodynamics statements, we can assume that dry ice evaporation rate occurring during air freight is comparable to the one simulated in climatic chamber.

On top of that, the more the temperature is increasing the more the insulating capacity of polystyrene used is increasing. Cycle temperatures above 20°C reflect therefore a worst case as regards to packaging insulation capacities.

Considering also that dry ice sublimation rate is reduced by packaging tightness, equivalence between air freight and simulation applied in climatic chamber is verified.

The three packages included in this study are able to maintain Cryoblood at a convenient storage temperature for at least 5 days. They can be therefore used for shipping this product by plane.

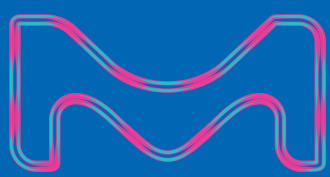
Notes:

To place an order or receive technical assistance

Find contact information for your country at:
EMDmillipore.com/offices

For Technical Service, please visit:
EMDmillipore.com/techservice

MilliporeSigma.com/BioMonitoring



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