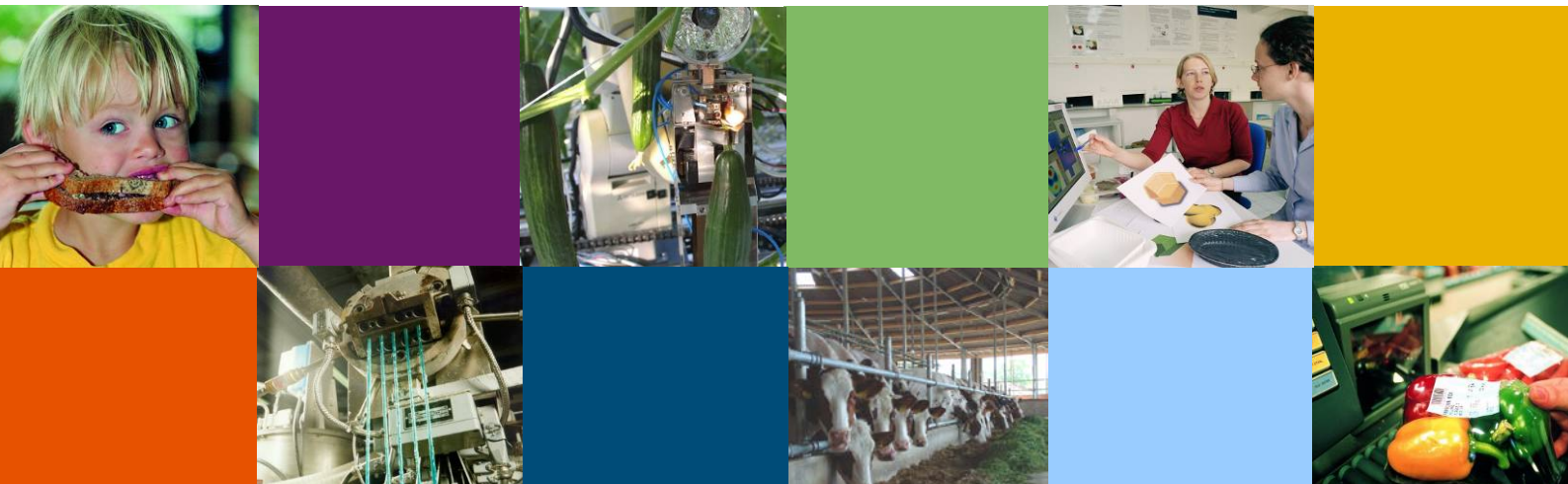
FOOD & BIOBASED RESEARCH
WAGENINGEN UR

The use of USDA sensors as calibrated temperature recorders

in view of EU guidelines on GDP for medicinal products for human use

Dr. Leo Lukasse

Report no. 1683



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Abstract

The EU guidelines on GDP of medicinal products for human use (OJ C 343/1, 23.11.2013) provide guidelines for the transport of temperature-sensitive medicines. Maersk Line wishes to demonstrate how calibrated USDA probes can be used to transport medicines in compliance with GDP compliant transport. The aim of this project is to provide an illustration of how a USDA probe could be used to monitor temperature during transport in a marine reefer container according to EU GDP. The results illustrate that USDA probes may indeed be used to monitor cargo temperatures during transport in a marine reefer container according to the EU GDP of 2013. It remains to be seen whether all shippers of pharmaceuticals accept this procedure: the main concerns anticipated are the max. number of four USDA probes and possibly the lack of traceability to national or international standards.

Content

1 Introduction

The EU guidelines on GDP of medicinal products for human use (OJ C 343/1, 23.11.2013) provide guidelines for the transport of temperature-sensitive medicines. Some quotes from chapter 9 (transportation) with respect to temperature probe calibrations:

1. 'Equipment used for temperature monitoring during transport within vehicles and/or containers should be maintained and calibrated at regular intervals at least once a year.'
2. 'If temperature-controlled vehicles are used, the temperature monitoring equipment used during transport should be maintained and calibrated at regular intervals.'

A quote from chapter 3 (storage):

1. 'Calibration of equipment should be traceable to a national or international measurement standard.'

In this latest version (OJ C 343/1, 23.11.2013) of the EU GDP the explicit requirement of calibration traceable to national or international measurement standard is not (yet) there in the chapter 9 on transportation. Consequentially a transport company may rightfully claim to maintain its temperature sensors in line with the guidelines if it calibrates the temperature monitoring probes in ice water prior to trip.

Although the permanent air temperature sensors present in reefer units are generally good and accurate ± 0.25 °C, the standard procedure is that they are never in their life calibrated. Hence they are not qualified for temperature-monitoring during transport according to this version of the EU GDP.

Every standard marine reefer container is equipped with four connections for so-called USDA temperature probes. USDA probes are in principle one-time use probes. These separate probes are routinely used in the shipment of plant material, possibly infected with undesired insects. By applying cold treatment shipments receivers can be confident that possible undesired insects have died due to the cold. For more details see http://www.aphis.usda.gov/import_export/plants/manuals/ports/downloads/treatment.pdf. In the application of cold treatment shipments according to USDA specs it is routine practice amongst intercontinental container operators to calibrate the four one-time use USDA probes prior to transport by immersing them in an ice water bath. The controller of the cooling unit records this calibration event, which is accepted by the USDA as evidence of proper probe calibration. Hence that same procedure, known to the industry, might suffice to provide customers with the service of monitoring temperatures with calibrated equipment.

The aim of this project is to provide an illustration of how a USDA probe could be used to monitor temperature during transport in a marine reefer container according to EU GDP.

2 Materials

Table 1, characteristics of container used in tests.

	manufacturer	man. date	model no.	identification no.
container	N/A	N/A	N/A	MMAU103858[2]
unit	Starcool	2010	SCI-40-W-CA	
box	MCI Qingdao	2010		

power supply during tests: 400V/50Hz.

The temperature calibration standard used as the internal temperature reference standard in the post-harvest technology dept. of Wageningen University & Research was used as a reference. See appendix 1 (p. 17) for its most recent calibration certificate. In the department's internal procedure the calibration certificate of this device is deemed valid when not older than two years. The two years interval is deemed sufficient after having observed for multiple times after each other that the probes offset is extremely stable over time. That's why the calibration certificate is currently slightly older than one year, such in deviation from the requirement of yearly recalibration stipulated in the EU GDP.

3 Methods

Tests were ran in ambient conditions at the premises of Wageningen UR, The Netherlands.
Start of tests: July 16, 2016
End of tests: July 18, 2016

The following procedure was followed:

1. One USDA probe was calibrated in ice water and mounted to the centre of the cooling unit's return air grid.
2. The calibrated reference temperature logger was mounted next to the USDA probe.
3. A multi-temperature setpoint program was ran: 12 hours @ Tset = +20 °C, followed by 12 hours @ Tset = + 5 °C and 19 hours @ Tset = -25 °C.

USDA probe temperature logging interval: 60 minutes (Maersk Line standard).
Reference temperature sensor logging interval: 5 minutes
Temperature control mode is according to standard Maersk Line procedure: i.e. Quest II at set points above -5 °C, normal frozen control at lower set points.

Fig. 1, return air grid

Fig. 2, one USDA probe and reference temperature sensors mounted in return air grid.

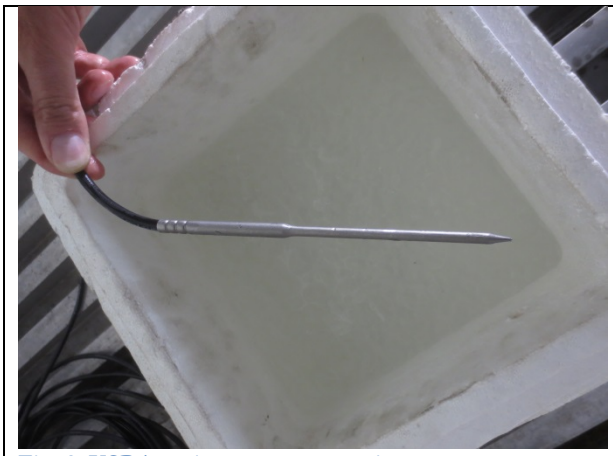

Fig. 3, USDA probe measurement tip

Fig. 4, USDA probe submerged in ice water for calibration.

Fig. 5, USDA probe being calibrated in insulated basket filled with ice water.

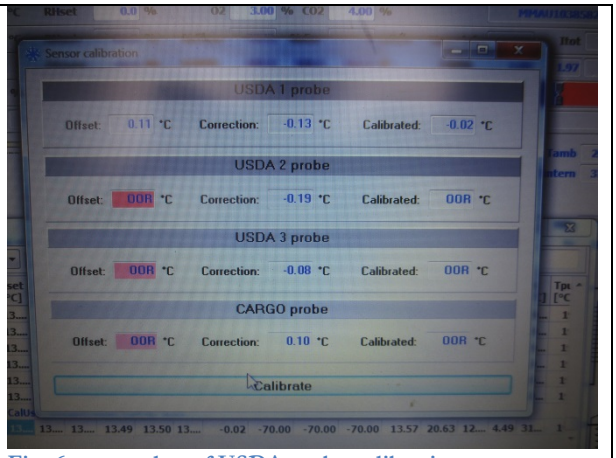

Fig. 6, screenshot of USDA probe calibration user interface.

4 Results

Fig. 7 graphically presents all collected data. Table 2 summarizes the steady state data. Note that in Fig. 7 and Table 2 Tref is the temperature recorded by the reference thermometer, not to be confused with setpoint temperature Tset. Table 3 presents the relevant selection of the raw data as downloaded from the refrigeration unit's controller after the test.

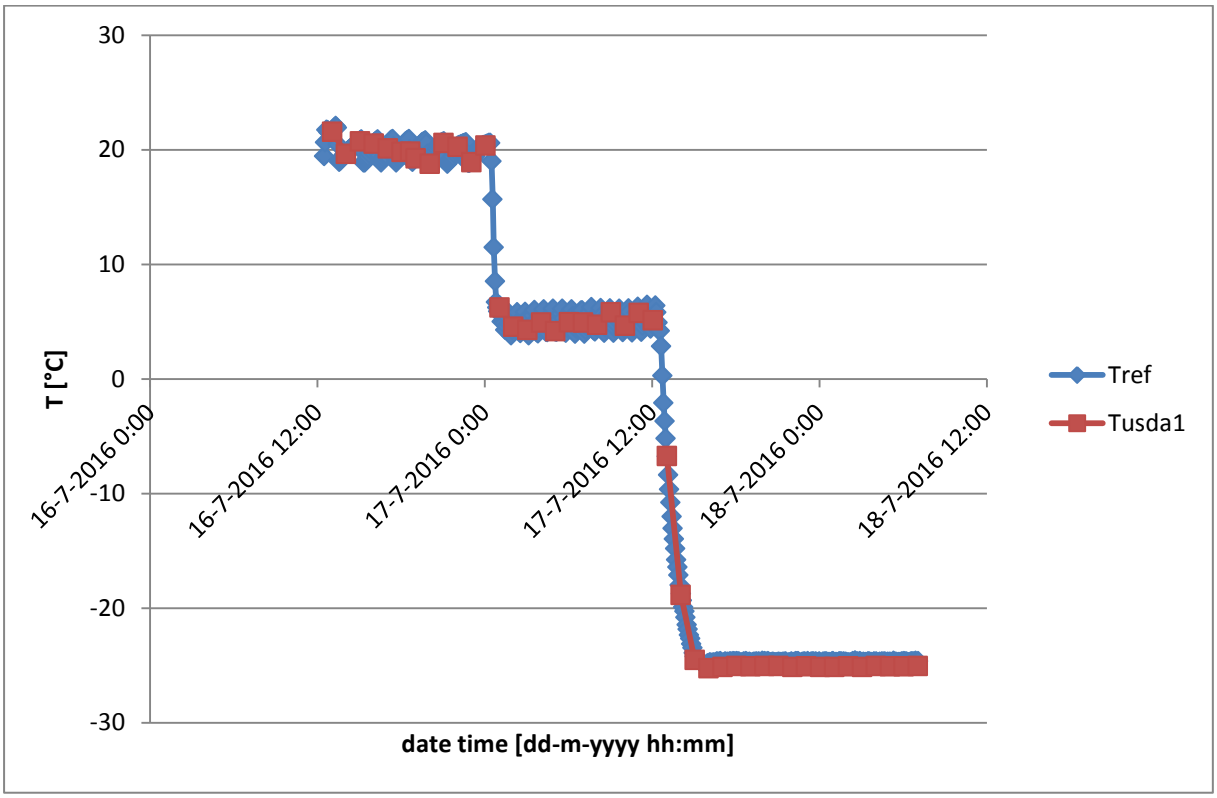

Fig. 7, graphical representation of collected temperature data.

Table 2, summary of steady state temperature data (collected over the last 10 hours of each of test condition).

Tset [°C]	avg. Tref [°C]	avg. Tusda [°C]	avg. Tref - Tusda [°C]
-25.0	-24.7	-25.1	0.4
+5.0	5.0	4.9	0.1
+20.0	19.9	19.9	0.1

Table 3, relevant information selected from datalog, i.e. the download taken from refrigeration unit's controller (note the USDA sensor calibration event in row 3).

Time	Type	Event ID	Par 1	Par 2	Par 3	Tsup [°C]	Tret [°C]	Tusda1 [°C]	Tusda2 [°C]	Tusda3 [°C]	Tcargo [°C]	Tset [°C]
16-7-2016 11:22:00	Event	20 Power up	19011	10734	17426							
16-7-2016 11:38:00	Event	17 USDA sensor calibrate	Nb 1	Old 1.64	New -0.13							
16-7-2016 11:40:00	Data					13.56	13.56	-0.04	-70.00	-70.00	-70.00	13.50
16-7-2016 12:07:00	Event	44 MTS step start	Step 0	Mins 720	Tset 20.00							
16-7-2016 13:04:00	Data					20.88	18.96	21.56	-70.00	-70.00	-70.00	20.00
16-7-2016 14:04:00	Data					20.36	19.68	19.64	-70.00	-70.00	-70.00	20.00
16-7-2016 15:04:00	Data					20.44	20.08	20.72	-70.00	-70.00	-70.00	20.00
16-7-2016 16:04:00	Data					20.08	20.04	20.52	-70.00	-70.00	-70.00	20.00
16-7-2016 17:04:00	Data					19.92	20.04	20.12	-70.00	-70.00	-70.00	20.00
16-7-2016 18:04:00	Data					19.80	20.04	19.80	-70.00	-70.00	-70.00	20.00
16-7-2016 18:40:00	Data					20.08	20.28	19.84	-70.00	-70.00	-70.00	20.00
16-7-2016 19:04:00	Data					19.76	20.04	19.24	-70.00	-70.00	-70.00	20.00
16-7-2016 20:04:00	Data					19.84	20.16	18.76	-70.00	-70.00	-70.00	20.00
16-7-2016 21:04:00	Data					20.04	20.20	20.60	-70.00	-70.00	-70.00	20.00
16-7-2016 22:04:00	Data					19.80	20.00	20.24	-70.00	-70.00	-70.00	20.00
16-7-2016 23:04:00	Data					19.80	20.00	18.92	-70.00	-70.00	-70.00	20.00
17-7-2016 0:04:00	Data					20.00	20.08	20.36	-70.00	-70.00	-70.00	20.00
17-7-2016 0:18:00	Event	45 MTS step stop	Step 0	Code 0	Tset 20.00							
17-7-2016 0:18:00	Event	44 MTS step start	Step 1	Mins 720	Tset 5.00							
17-7-2016 1:04:00	Data					4.44	11.08	6.24	-70.00	-70.00	-70.00	5.00
17-7-2016 2:04:00	Data					4.04	8.16	4.56	-70.00	-70.00	-70.00	5.00
17-7-2016 3:04:00	Data					4.20	6.68	4.28	-70.00	-70.00	-70.00	5.00
17-7-2016 4:04:00	Data					4.20	5.80	4.92	-70.00	-70.00	-70.00	5.00

Time	Type	Event ID	Par 1	Par 2	Par 3	Tsup [°C]	Tret [°C]	Tusda1 [°C]	Tusda2 [°C]	Tusda3 [°C]	Tcargo [°C]	Tset [°C]
17-7-2016 5:04:00	Data					4.36	5.56	4.16	-70.00	-70.00	-70.00	5.00
17-7-2016 6:04:00	Data					4.36	5.28	4.96	-70.00	-70.00	-70.00	5.00
17-7-2016 7:04:00	Data					4.60	5.36	4.92	-70.00	-70.00	-70.00	5.00
17-7-2016 8:04:00	Data					4.48	5.20	4.72	-70.00	-70.00	-70.00	5.00
17-7-2016 9:04:00	Data					4.72	5.36	5.80	-70.00	-70.00	-70.00	5.00
17-7-2016 10:04:00	Data					4.52	5.28	4.64	-70.00	-70.00	-70.00	5.00
17-7-2016 11:04:00	Data					4.76	5.40	5.76	-70.00	-70.00	-70.00	5.00
17-7-2016 12:04:00	Data					4.56	5.32	5.12	-70.00	-70.00	-70.00	5.00
17-7-2016 12:28:00	**Event**	**45 MTS step stop**	**Step 1**	**Code 0**	**Tset 5.00**							
17-7-2016 12:28:00	**Event**	**44 MTS step start**	**Step 2**	**Mins 1440**	**Tset -25.00**							
17-7-2016 12:28:00	**Event**	**62 QUESTII stop**	**7**									
17-7-2016 13:04:00	Data					-12.56	-6.52	-6.72	-70.00	-70.00	-70.00	-25.00
17-7-2016 14:04:00	Data					-24.96	-18.96	-18.84	-70.00	-70.00	-70.00	-25.00
17-7-2016 15:04:00	Data					-29.20	-24.52	-24.52	-70.00	-70.00	-70.00	-25.00
17-7-2016 16:04:00	Data					-27.84	-25.20	-25.24	-70.00	-70.00	-70.00	-25.00
17-7-2016 17:04:00	Data					-27.80	-25.12	-25.12	-70.00	-70.00	-70.00	-25.00
17-7-2016 18:04:00	Data					-27.72	-24.96	-25.04	-70.00	-70.00	-70.00	-25.00
17-7-2016 19:04:00	Data					-27.60	-25.00	-25.08	-70.00	-70.00	-70.00	-25.00
17-7-2016 20:04:00	Data					-27.48	-24.96	-25.04	-70.00	-70.00	-70.00	-25.00
17-7-2016 21:04:00	Data					-27.40	-25.00	-25.04	-70.00	-70.00	-70.00	-25.00
17-7-2016 22:04:00	Data					-27.32	-	-25.12	-70.00	-70.00	-70.00	-25.00

Time	Type	Event ID	Par 1	Par 2	Par 3	Tsup [°C]	Tret [°C]	Tusda1 [°C]	Tusda2 [°C]	Tusda3 [°C]	Tcargo [°C]	Tset [°C]
							25.04					
17-7-2016 23:04:00	Data					-27.20	-25.04	-25.08	-70.00	-70.00	-70.00	-25.00
18-7-2016 0:04:00	Data					-27.24	-25.04	-25.12	-70.00	-70.00	-70.00	-25.00
18-7-2016 1:04:00	Data					-27.16	-25.04	-25.12	-70.00	-70.00	-70.00	-25.00
18-7-2016 2:04:00	Data					-27.08	-25.00	-25.08	-70.00	-70.00	-70.00	-25.00
18-7-2016 3:04:00	Data					-27.08	-25.04	-25.12	-70.00	-70.00	-70.00	-25.00
18-7-2016 4:04:00	Data					-27.08	-24.96	-25.04	-70.00	-70.00	-70.00	-25.00
18-7-2016 5:04:00	Data					-27.08	-25.00	-25.08	-70.00	-70.00	-70.00	-25.00
18-7-2016 6:04:00	Data					-27.00	-24.96	-25.08	-70.00	-70.00	-70.00	-25.00
18-7-2016 7:04:00	Data					-27.04	-24.96	-25.04	-70.00	-70.00	-70.00	-25.00

5 Discussion

The USDA probe calibration procedure in ice water is physically sound. If port personnel is equipped with the right insulated jars and a sufficient amount of sufficiently small ice lumps, it is hard to imagine what can go wrong. The experience in cold treatment export locations helps to build this confidence. Whether this procedure qualifies as 'traceable to national or international standards' remains to be seen. As outlined in section 1 this non-traceability is strictly speaking not a violation of the GDP. Yet it is to be expected that not all pharmaceuticals shippers will accept this calibration procedure. Maybe a procedure with photo evidence (with date time stamp imprinted in the photos) of the followed calibration procedure may put them at ease.
The data presented in Table 3 is only the relevant part of the data available in refrigeration unit controller downloads. To the best of my knowledge the same information should be available through RCM.
In the pharmaceutical industry temperature measurement with an accuracy of ± 0.5 °C is generally accepted as sufficiently accurate. Even at the extreme temperature of -25.0 °C the 0.4 °C difference (Table 2) is still within this spec. It is not 100% clear what causes this difference. The reference temperature sensor is known to have a nice constant offset in the range -10 ~ + 32.5 °C (see appendix 1, p. 17), but has in fact not been calibrated for temperatures colder than -10 °C. USDA probes are typically meant to be used around 0 °C. It could also be that the USDA probe has a minor non-linearity which causes the offset to be a bit larger when 25 °C below set point.
The difference between the reference measurement and the USDA probe measurement is 0.1 °C at both +5 °C and +20 °C (Table 2), which is well within the ± 0.5 °C accuracy range.
Another topic that is subject to discussion is the placement of the USDA probe. It is known in the industry that return air temperature is a good representation of average cargo temperature. However it does not record the temperature extremities in potential cold and hot spots. It is good to mention that every refrigeration unit is equipped with 4 connectors for USDA probes, and shipping lines have a pretty good knowledge of where to expect the warmest and coldest locations in the load. Hence the four available USDA probes can characterise the complete range of cargo temperatures reasonably well. It is to be anticipated that some customers deem the number of probes as insufficient.

6 Conclusions

The results illustrate how one or more calibrated USDA probes may be used to monitor cargo temperatures during transport in a marine reefer container according to the EU guidelines on GDP of medicinal products for human use (OJ C 343/1, 23.11.2013).

References

OJ C 343/1, 23.11.2013. EU Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use.

Acknowledgements

I am grateful to Maersk Line, represented by Paul Clarke, for financial support of this project and making the required test container available.

Appendix 1, calibration certificate of used reference temperature monitor

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Dutch Metrology Institute

CERTIFICATE OF CALIBRATION

Number 3244865
Page 1 of 3

Applicant	Wageningen UR Bornse Weilanden 9 6708 WG WAGENINGEN
Item	A digital temperature indicator with a temperature sensor

The indicator:

Manufacturer	:	Testo
Type	:	400
Range	:	-10 °C to 32.5 °C
Resolution	:	0.001 °C
Identification number	:	00885717/310 (0563 4001.310)

The identification of the sensor(s) is given with the results on following page(s).

Calibration Procedure	The thermometer has been calibrated by comparison with a standard thermometer in a liquid bath based on the ITS-90.
	The ambient temperature was (23.0 ± 1.0) °C.
Calibration period	8 April 2015
Result	The results of the calibrations are given on following page(s). The reported uncertainty of measurement is based on the standard uncertainty of measurement multiplied by a coverage factor of $k = 2$, which for a normal distribution corresponds to a coverage propability of approximately 95 %. The standard uncertainty has been determined in accordance with the 'Guide to the Expression of Uncertainty in Measurement' (GUM).
Traceability	The result of the calibration is traceable to primary and/or (inter)national accepted measurement standards.

Delft, 09 April 2015
VSL B.V.

R. van Breugel
Principal Metrologist

VSL
Dutch Metrology Institute

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CERTIFICATE OF CALIBRATION

The sensor connected to channel 1 :

Manufacturer	:	-
Type	:	Pt100
Identification number	:	00914908/312
The immersion depth	:	at least 25 cm

Results

The result of the calibration and the related uncertainty is given here.

By means of regression a relation is determined between the generated temperature (t_{90}) and the indicated temperature (t). The table below contains this relation and the calculated coefficients. The relation is valid over the calibrated range.

$$(t_{90} - t) = \sum_{i=0}^{i=n} a_i \cdot t_{90}^i$$

i	a_i
0	-5.4761×10^{-2}
1	-4.5635×10^{-4}

The table below is made using this relation and contains the following data:
1. the temperature t_{90} according to the ITS-90;
2. the indicator value t;
3. the difference t_{90}-t.

t_{90} /°C	t /°C	t_{90}-t /°C
-10.000	-9.950	-0.050
0.000	0.055	-0.055
7.500	7.558	-0.058
32.500	32.570	-0.070

The uncertainty in the difference t_{90}-t is 0.006 °C.

This uncertainty includes a contribution from the reproducibility of the instrument, calculated using the deviations from the regression.

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CERTIFICATE OF CALIBRATION

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This certificate is consistent with the capabilities that are included in Appendix C of the MRA (Mutual Recognition Agreement) drawn up by the CIPM. Under the MRA, all participating institutes recognize the validity of each other's calibration and measurement certificates for the quantities, ranges and measurement uncertainties specified in Appendix C (for details see www.bipm.org).

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CIPM MRA

CALIBRATION
RvA K 999

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