

NISTIR 7522

Cold Chain Storage of Vaccines: A Brief Introduction to Thermometry

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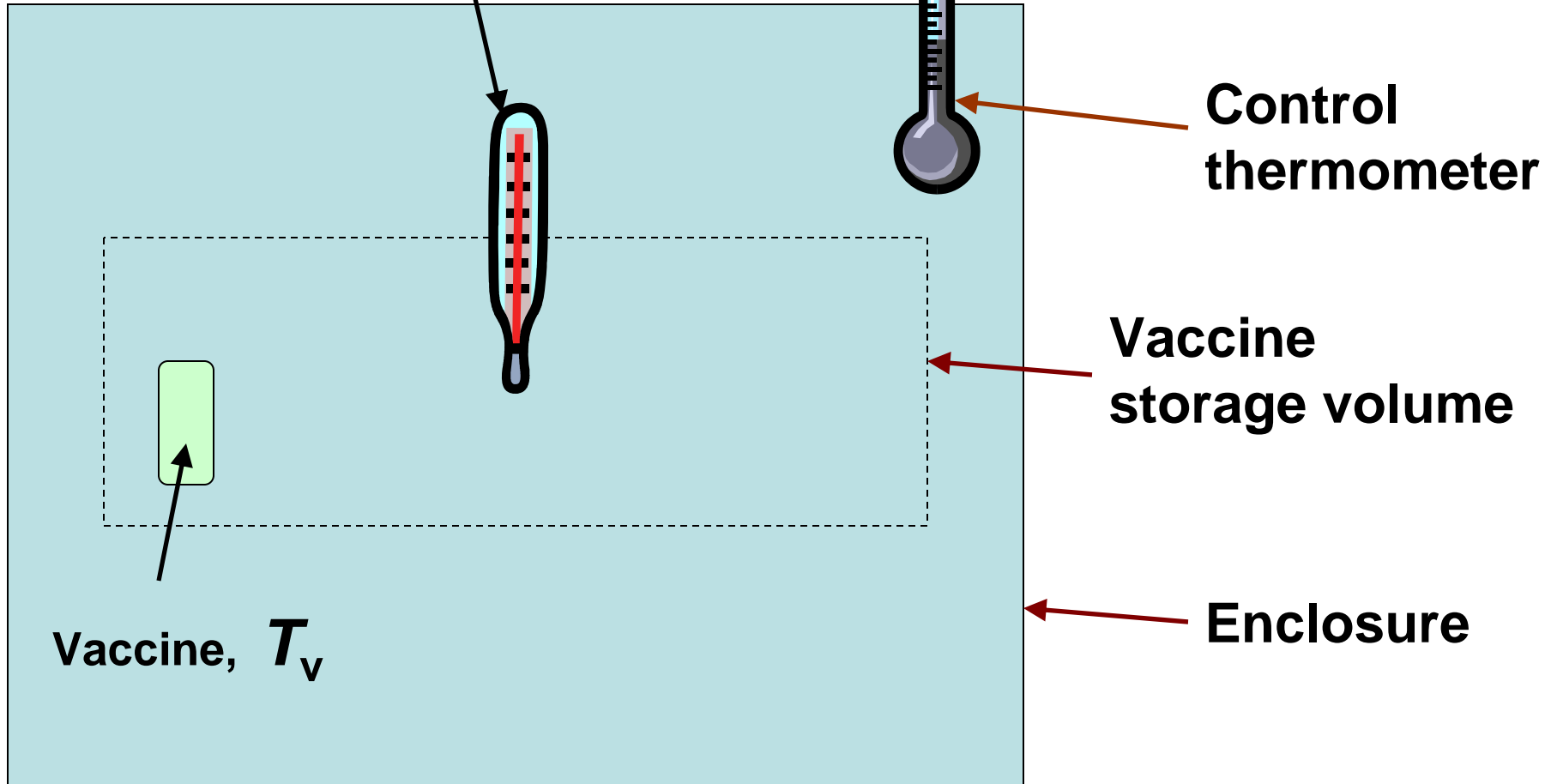
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**National Institute of
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U.S. Department of Commerce

Outline

- **Description of the problem**
- **Overview of sensor types**
- **Traceability to NIST**
- **Measurement Assurance**
- **Uncertainty & error allowances (guardbands)**
- **Certification & Calibration**
- **Proper use of thermometers**
- **FAQs**

A Cartoon of Cold Chain Storage

Certified thermometer,
reading T_{cert}



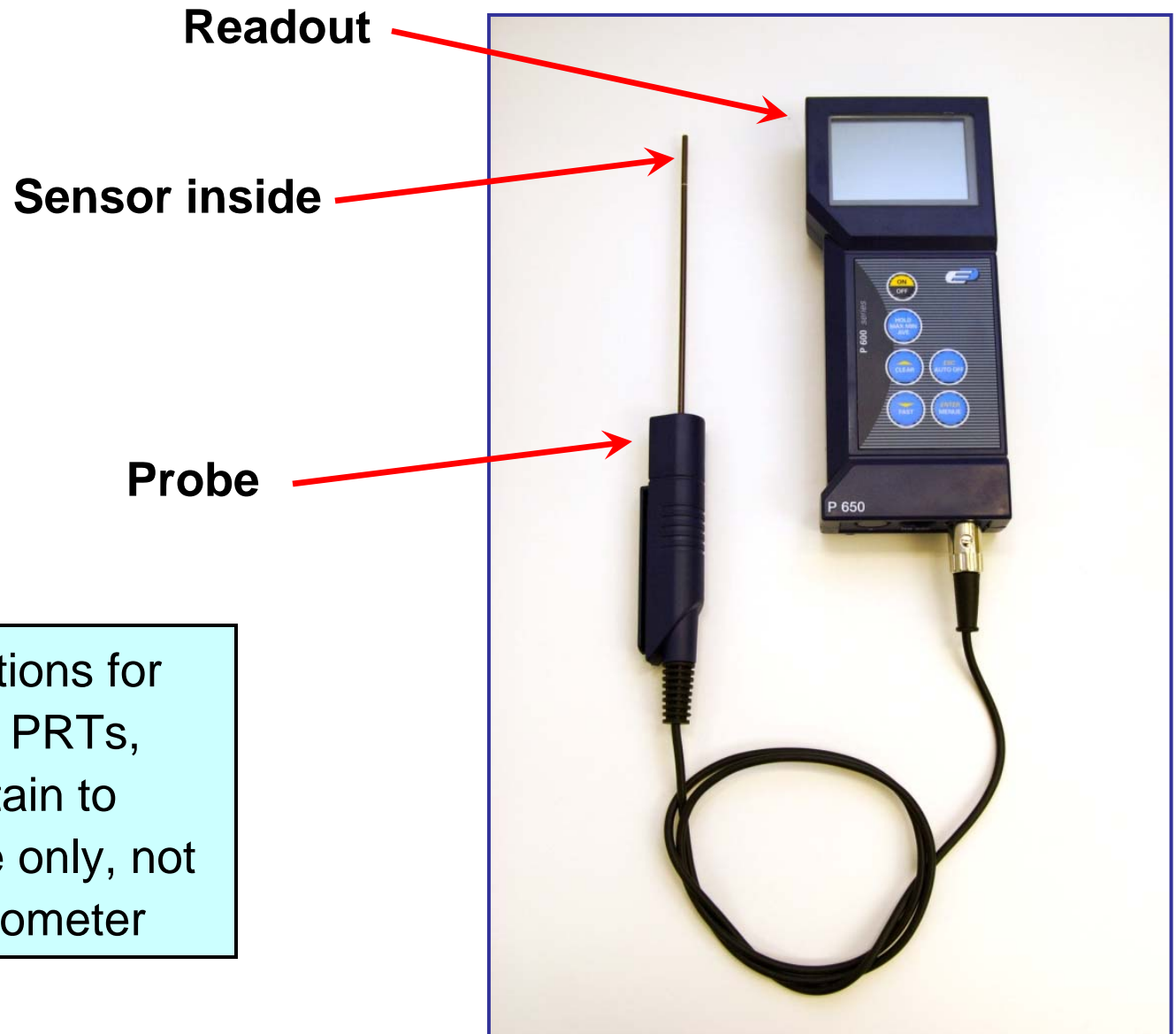
Our Goal: Maintain true vaccine temperature within specified bounds (e.g., 2 °C to 8 °C)

Complications

- **We do not measure actual vaccine temperature**
- **Reading of certified thermometer may be in error due to**
 - calibration error
 - thermometer drift
 - error in reading
- **Temperature may vary across storage region**
- **Temperature may not be stable due to**
 - doors opening and closing
 - seasonal variations of heat loads
 - separation between control thermometer and storage region

Thermometer Types

Thermometer Components



Some specifications for thermocouples, PRTs, thermistors pertain to sensor or probe only, not complete thermometer

Thermometer Types

Industrial Platinum Resistance Thermometers (RTDs, PRTs)

–196 °C to 850 °C

Thermistors

–50 °C to 100 °C

Thermocouples (TC)

–196 °C to 2100 °C

Liquid-in-Glass Thermometers (LiG)

–150 °C to 400 °C

Dial Thermometers

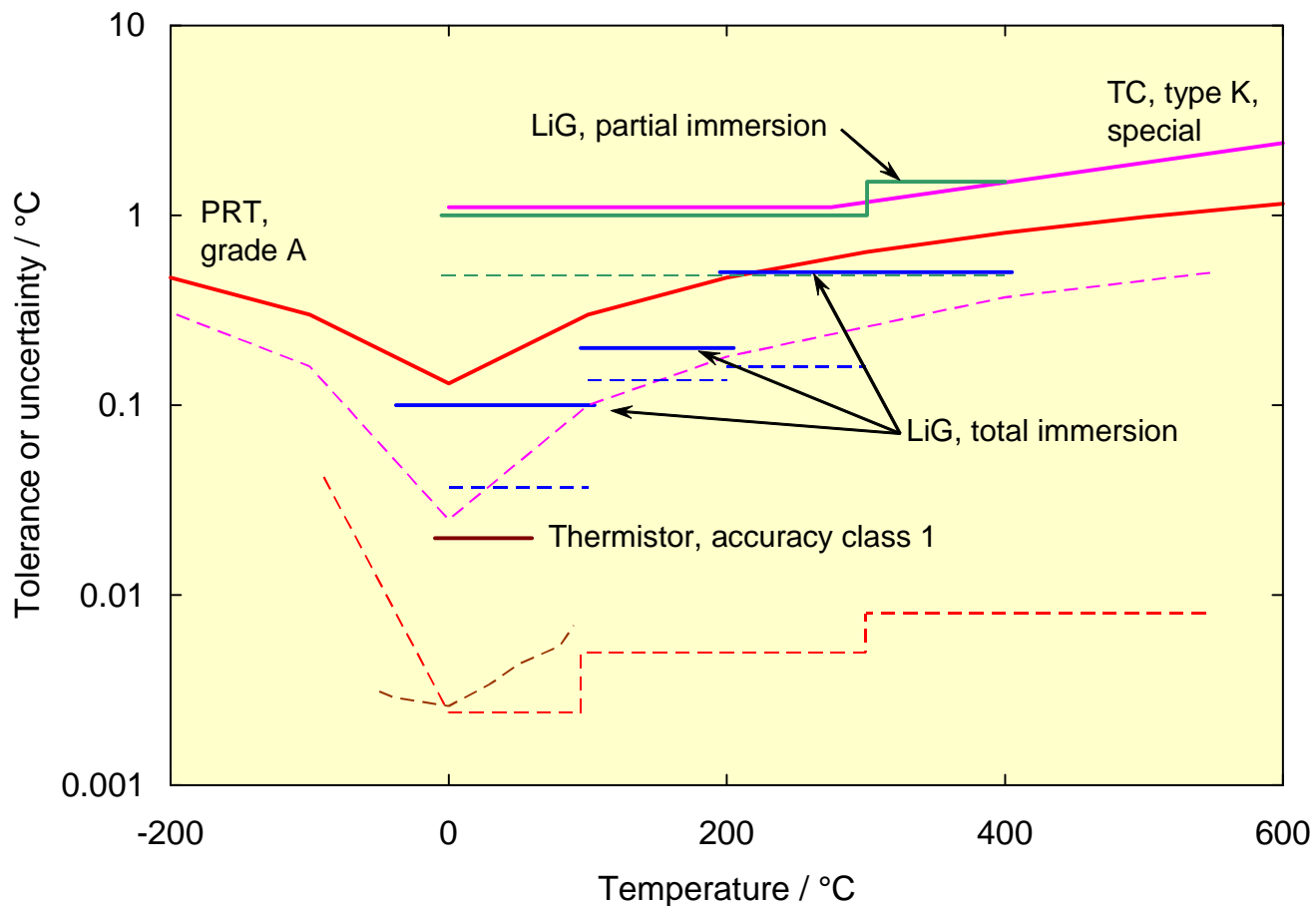
–100 °C to 400 °C

Digital Thermometers (PRT, thermistor, or thermocouple in disguise)

–196 °C to 850 °C

Data Loggers (PRT or thermistor in disguise)

Tolerances vs. Calibration Uncertainties



Colored lines: ASTM tolerances (ASTM E1, E1137, E230, and E879).

Dashed lines: NIST calibration uncertainties at 95 % confidence

Tolerances or uncertainties are \pm the indicated number

General Uncertainty & Cost Guidelines

Thermistor probe

–20 °C to 60 °C approximate range

0.2 °C uncertainty off the shelf, \$300 + \$150 certif.

(much lower uncertainties attainable with calibration & better readout)

Sheathed PRT

–200 °C to 600 °C approximate range

Uncertainty 0.2 °C near ambient, expanding to 2 °C near limits for \$300 + \$150 certif.

(much lower uncertainties attainable with calibration and better readout)

Base-metal thermocouples

–200 °C to 1200 °C

Uncertainty (0.5 % to 1% of t °C) + 1 °C, for \$200

(all uncertainties at approximately 95 % confidence limit)

General Uncertainty & Cost Guidelines (continued)

Organic-filled liquid-in-glass thermometers

–100 °C to +100 °C

4 °C uncertainty off the shelf, \$30 + certificate cost

Potential for uncertainties down to 0.5 °C near ambient at higher cost

No standardization yet

Dial thermometers

–20 °C to + 300 °C (lower limit for dial)

Uncertainty 1 % of full range or about 1 °C, whichever is greater

\$100 + certificate cost

No standardization

Maintenance & Calibration

Mercury-in-glass thermometers (for $t < 150$ °C) need a visual inspection plus a check at 0 °C.

PRTs & thermistors require checks at the upper and lower limits of use. (Single-point check OK for narrow usage range of cold-chain application).

Organic liquid-in-glass thermometers need a visual inspection plus a check at upper and lower limits of use. (Single-point check OK for narrow usage range).

Thermocouples, if used above 150 °C, require special validation techniques. For cold chain, single point check + visual inspection.

If the thermometer drifts appreciably at any of these check point, then you need to do a full recalibration, or buy another thermometer.

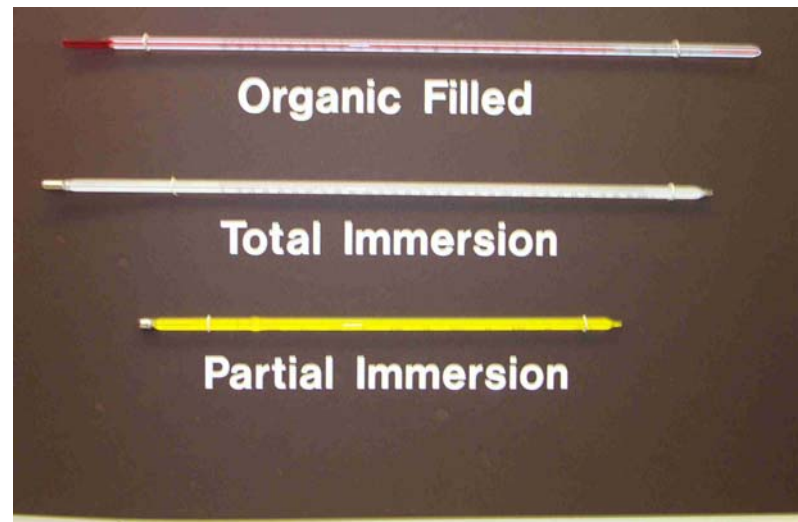
Types of Liquid-in-Glass (LiG) Thermometers

Types of ASTM LiG thermometers

- Over 120 types
- Total Immersion: bulb & full column of liquid at usage or calibration temperature
- Partial Immersion: thermometer exposed to usage or calibration temperature only below immersion line; remainder at ambient temperature

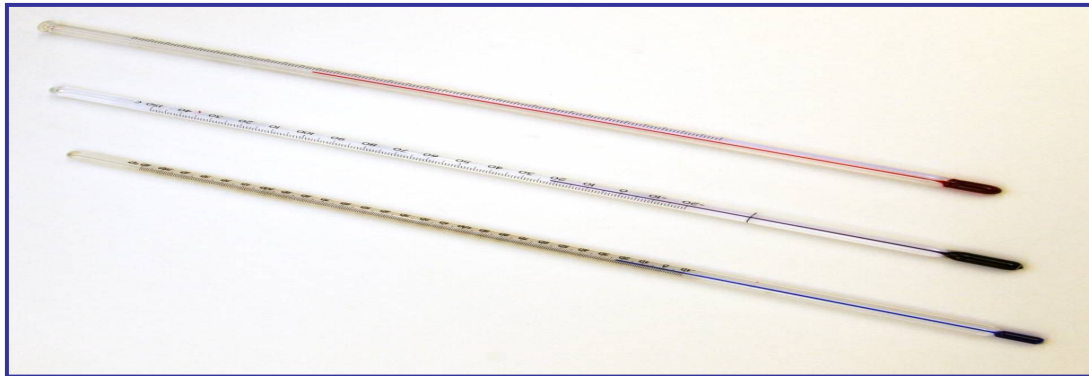
Liquids used

- **Mercury (Hg) - ASTM**
- Organic
- Mercury Thallium
- Proprietary (non-toxic)



Non-Mercury Liquid-in-Glass Thermometers

- **Organic liquids generally have inferior performance to mercury,** but are a reasonable alternative if uncertainty requirements are modest (ASTM standard just begun)
- **Beware of drainage of organic liquid down capillary wall on cooling** (not an issue for long-term monitoring of steady temper.)
- **“Next-generation” organic liquids under development** (Existing ASTM standard E2251); good accuracy, but check for separation of liquid column
- **Greater sensitivity to stem temperature:** not a limitation for cold-chain applications with thermometer totally immersed in cold region



Platinum Resistance Thermometers (PRTs or RTDs)

2, 3, or 4-wire resistance element –
nominally $100\ \Omega$ @ $0\ ^\circ\text{C}$

- Wire wound
- Thick film
- Thin film

Resistance changes as a function of
temperature

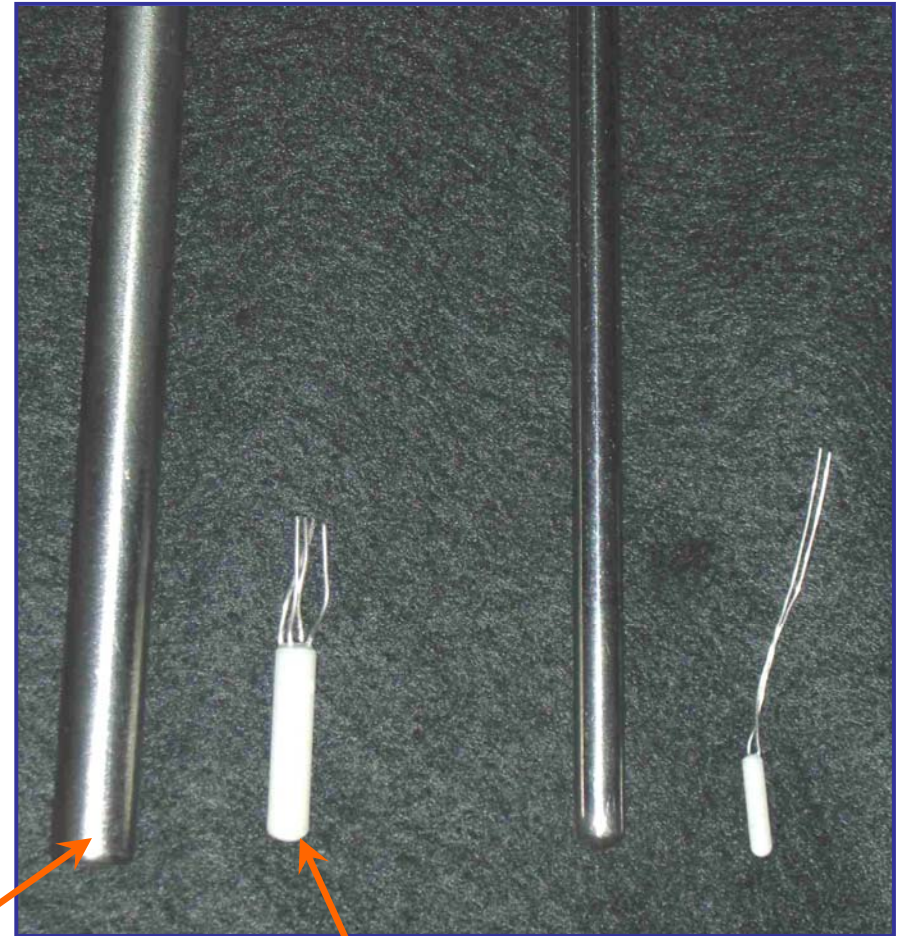
Positive temperature coefficient

Nominal temperature range of use:

- $-200\ ^\circ\text{C}$ to $850\ ^\circ\text{C}$

Nominal resistance at $0\ ^\circ\text{C}$

- $100\ \Omega$



**Steel sheath
containing sensor**

**Sensor or element
(wire-wound shown)**

Thermistors (Thermal Resistor)

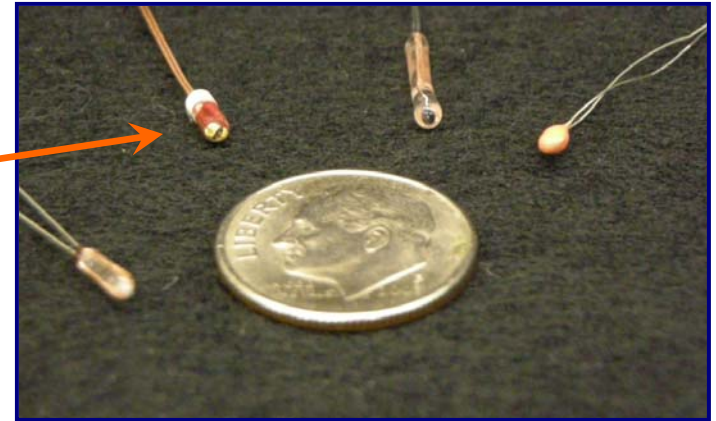
Semiconductors of ceramic material made by sintering mixtures of metallic oxides such as manganese, nickel, cobalt, copper, iron and uranium.

Temperature Range: $-50\text{ }^{\circ}\text{C}$ to $100\text{ }^{\circ}\text{C}$

Standard Sensor Forms:

bead $300\ \Omega$ to $100\ \text{M}\Omega$

probe bead in glass rod

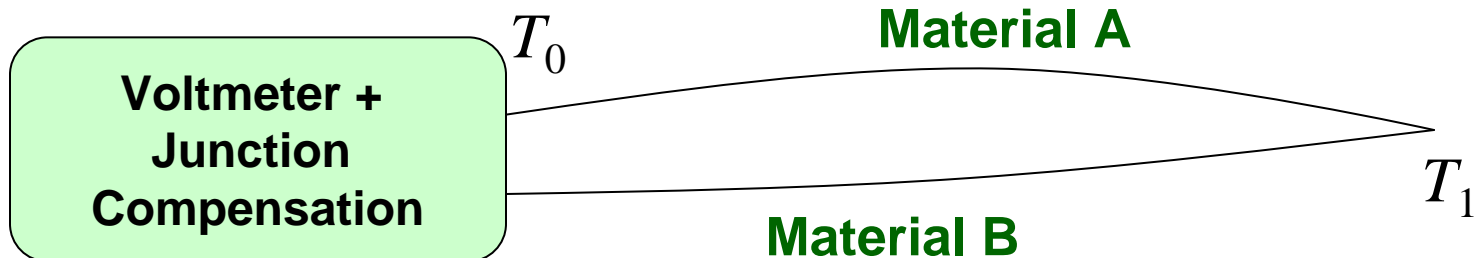


NTC: Negative Temperature Coefficient - The vast majority of commercial thermistors used as thermometers are in the NTC category.

Commonly packaged in stainless-steel sheaths

Excellent choice for cold-chain applications

Thermocouples



Standardized combinations of Material A vs. Material B (e.g, Type K).

When combined with typical readout uncertainty, total uncertainty is fairly large, unless care is taken with calibration.

Good for low-accuracy measurements over a broad temperature range



Dial Thermometers

- **Bimetallic element changes shape on change of temperature**
- **Mechanical linkage converts motion of bimetallic element to deviation of pointer on dial**
- **Friction in mechanical linkage limits accuracy**
- **Inexpensive & easy to read; not too accurate**

Traceability

Overview of Traceability to NIST

Reference: <http://www.nist.gov/traceability>, especially the Supplemental Materials link

Only a *measurement*, not an instrument or artifact, is traceable.

Evaluation of traceability is the customer's responsibility; NIST does not, in general, evaluate claims of traceability

Evaluation of traceability is one component of the laboratory accreditation process

Elements of Traceability

1. **Unbroken chain of calibrations from NIST (or other National Metrology Institute) to final instrument; each calibration with documented uncertainty.**

Traceability does imply known uncertainty to known national standards
does *not* imply that laboratories are NIST approved
does *not* imply that calibration is of high accuracy

2. **A Measurement Assurance Program must be in place to assure continued validity of a calibration (i.e., you can't keep using a thermometer calibrated in 1928 as your standard)**

Examples periodic recalibration, with examination of instrument drift
 comparison of certified thermometer with a second check thermometer
 comparison of calibrated thermometers between recalibrations
 check of thermometers at the ice point

Traceability Responsibilities

NIST

- Assures traceability of results of measurements of standards that **NIST provides** to customers
- Provides **customers** with the tools they need to:
 - Establish traceability of their measurement results
 - Assess the claims of traceability made by others

Customer

- Assesses the validity of a traceability claim from a **service provider**
- Establishes traceability of **their** measurement results

Accreditation Bodies

- Evaluates secondary laboratory's ability to achieve and maintain traceability
- Tests for competence and capability of a secondary laboratory's calibration service

Tolerances vs. Calibration Uncertainties vs. Accuracy

Tolerance band: manufacturer's guarantee that the instrument response will conform to a standard response function to within an error equal to the tolerance.

Calibrated thermometer: may or may not have a response close to the nominal response function for that thermometer type.

Response of individual unit is reported, along with uncertainties of the calibration process.

Individually calibrated thermometers cannot be considered directly interchangeable, unless the readouts or software are adjusted to incorporate the individual response function.

Accuracy: an imprecise term, approximately meaning that the manufacturer guarantees that the instrument will give the correct reading to within the stated accuracy.

Measurement Assurance

Measurement Assurance

Three examples:

1. Measurements at the ice point
2. Use of a check standard (second redundant thermometer)
3. Evaluation of historical calibration results

You don't have to do all three, but
you should do at least one.

Use of the ice point is the most precise method, but
use of a check standard gives the broadest scope of assurance

Measurement Assurance Techniques: Ice-Point Bath

Preparation:

- Ice bath consists of crushed or shaved ice, saturated with water, packed into a Thermos or Dewar
- Make a hole with a clean rod, insert thermometer into hole, and wait 10 min. for thermal equilibrium
- Ice must extend to bottom of flask, not just floating on top
- Uncertainty about 0.002 °C with distilled water, about 0.02 °C with tap water
- Try it out first on a newly calibrated probe, to be certain you are doing it correctly

What's great about the ice point:

- Can be prepared by the user
- Perfect check temperature for cold-chain applications
- Drift at the ice point can be used to determine recalibration intervals

Measuring a Liquid-in-Glass (LiG) Thermometer in an Ice Melting Point (0 °C)



Pre-chill thermometer in shaved ice, or ice + water slush.

Important if you have many thermometers, or for uncertainty better than 0.1 °C

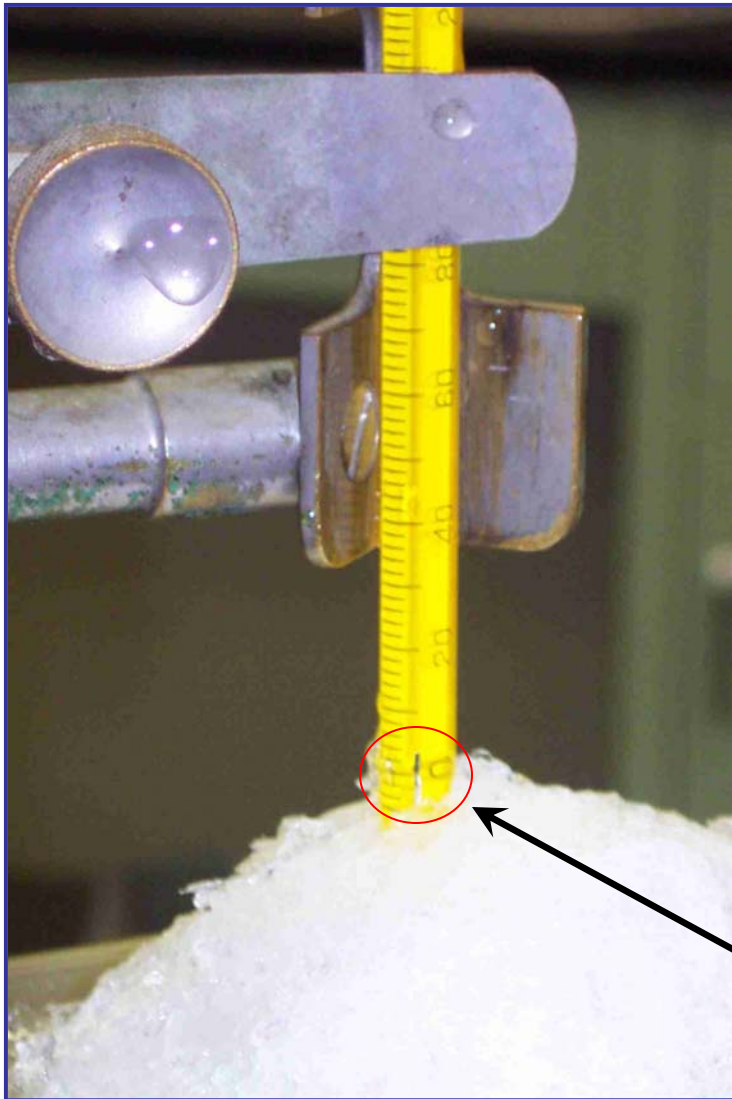
Measuring a Liquid-in-Glass in an Ice Melting Point (0 °C)



Use a clean rod (metal or glass) to make thermometer hole, prior to insertion of thermometer.

Gloves are not needed for uncertainty of 0.1 °C or higher (but they do keep your hands warm)

Measuring a Liquid-in-Glass Thermometer in an Ice Melting Point (0 °C)



Thermometer in an Ice Melting Point

10 minute equilibration time

- LiG is pre-chilled in ice
- 3 min equilibration time in the ice melting point

Siphon liquid water off as needed

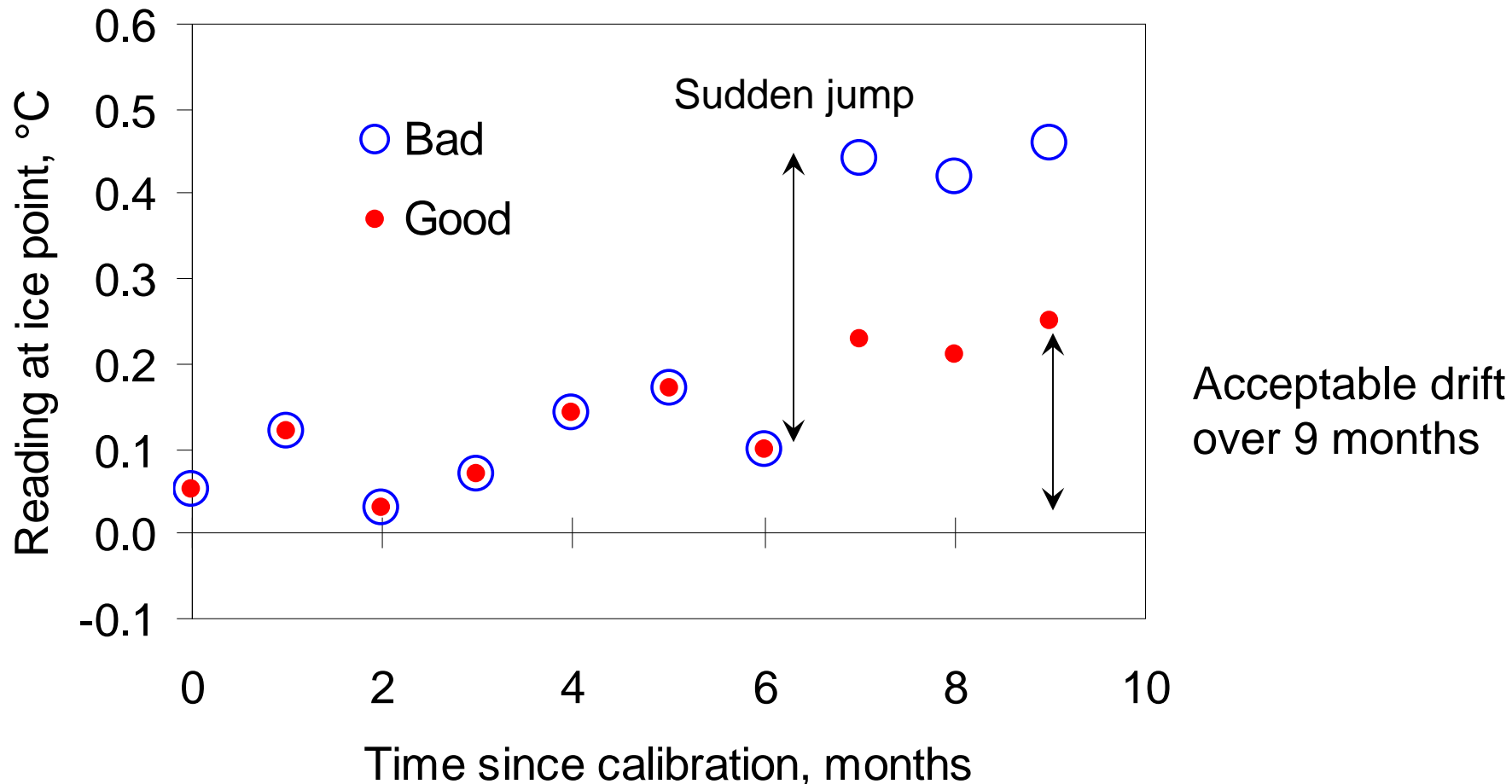
Repack ice prior to each thermometer insertion

Ice point baths for longer thermometer probes do not need the 'mound' of ice and can be more slushy.

0 °C mark just above ice; thermometer bottom rests on ice

Plotting the data from ice-point readings

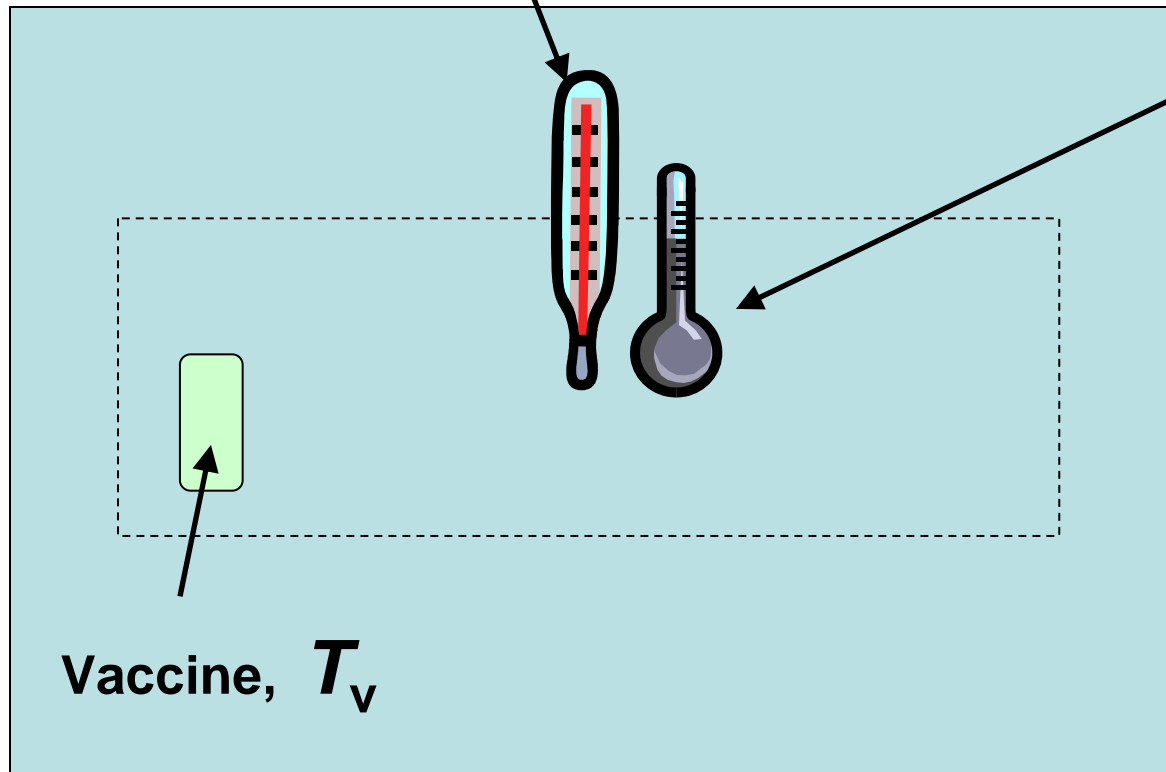
Monitor readings at the ice point for sudden changes or for values unacceptably far from 0 °C



Measurement Assurance Techniques: Redundant thermometer

This is the single most useful technique presented in this talk!!!

Certified thermometer,
reading T_{cert}

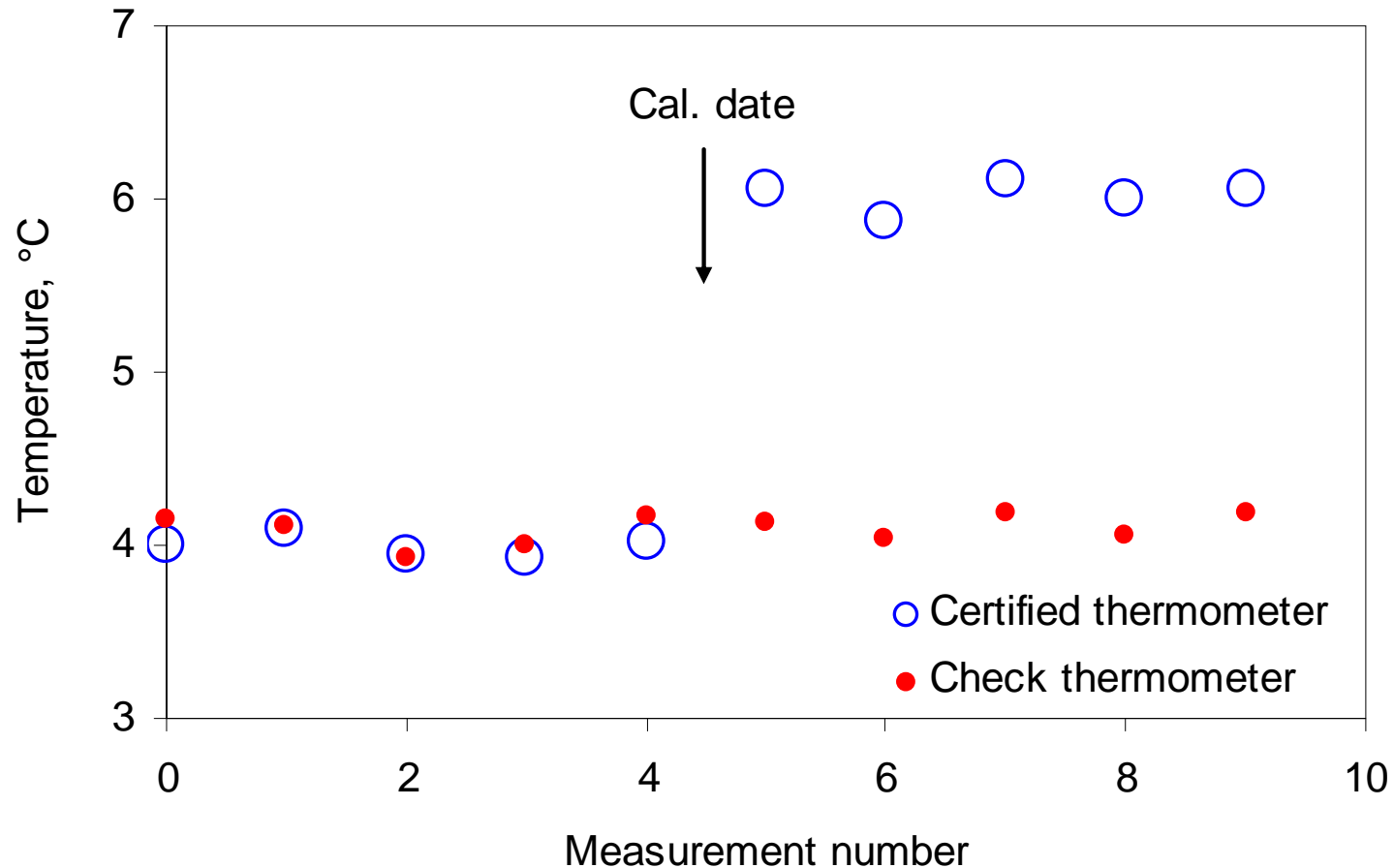


Redundant check
thermometer, reading
 T_{check}

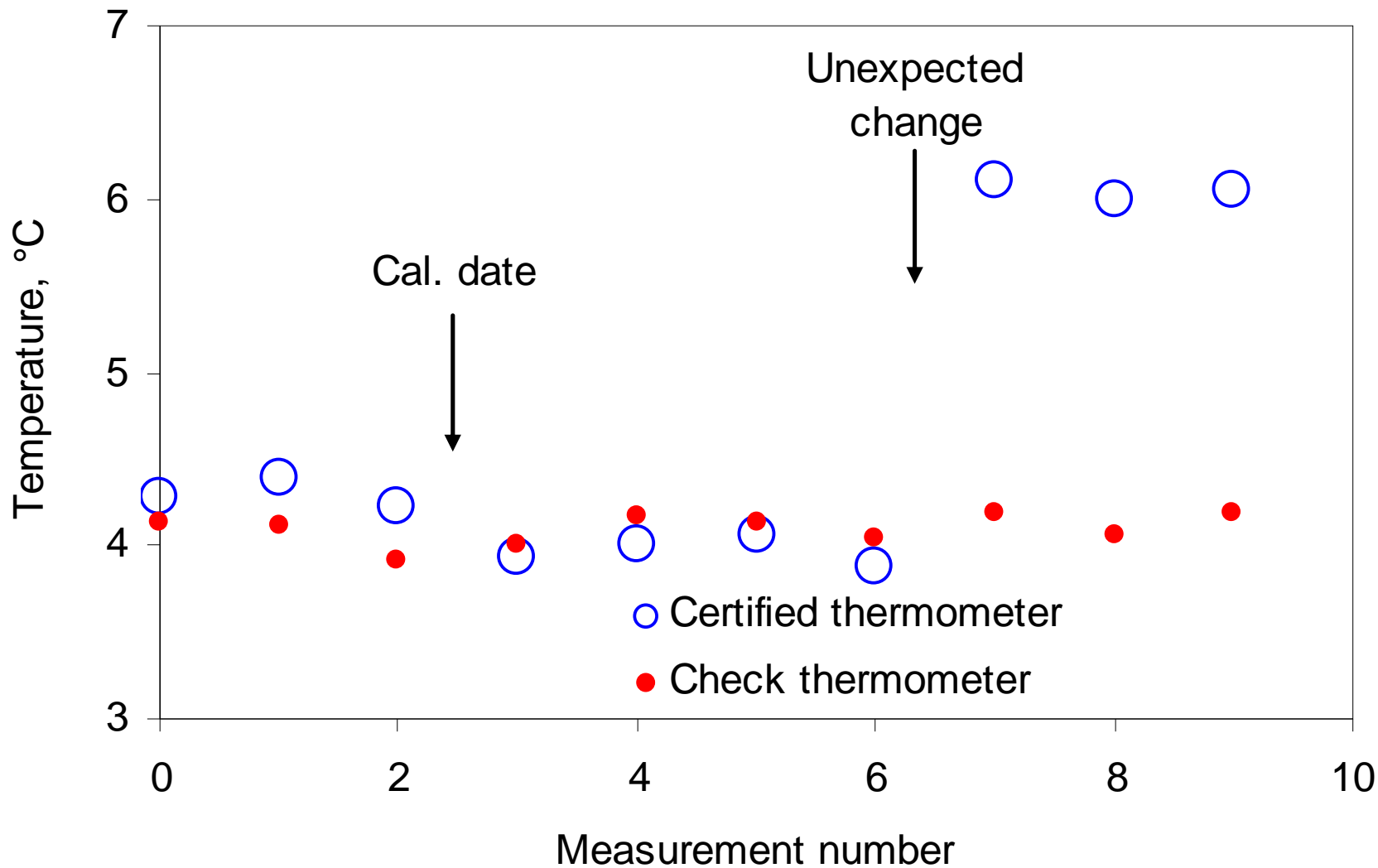
*Check thermometer
doesn't necessarily
need to be
calibrated.*

Example 1: Cal. laboratory incorrectly adjusts instrument

Large change in $(T_{\text{cert}} - T_{\text{check}})$ after instrument is returned from calibration.



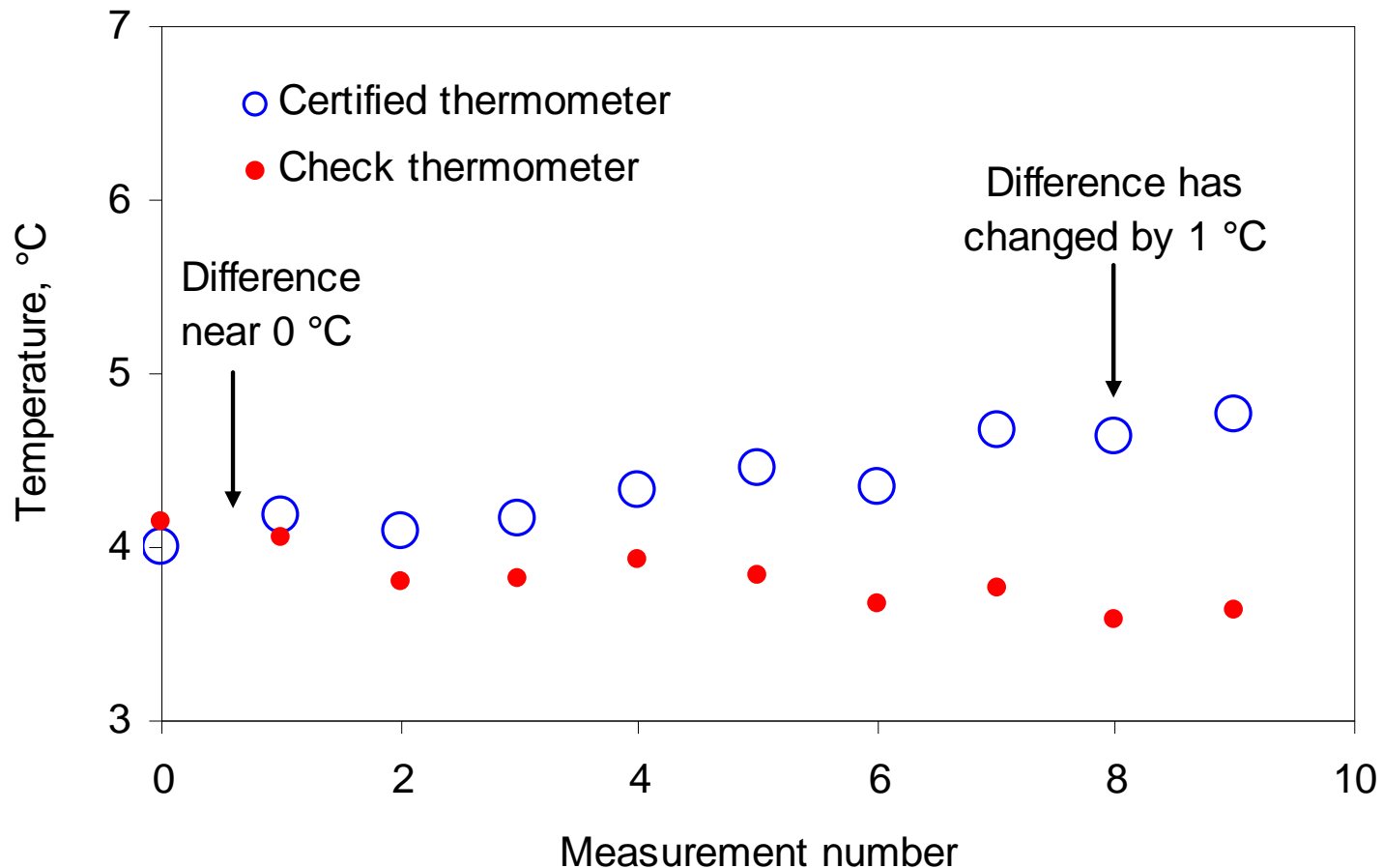
Example 2: Readout for certified thermometer dropped



Example 3: Slow divergence of certified & check thermometers

We DO NOT calibrate the certified thermometer with the check thermometer.

We DO use the change in $T_{\text{cert}} - T_{\text{check}}$ as an indicator of potential problems



Measurement Assurance: Historical Data

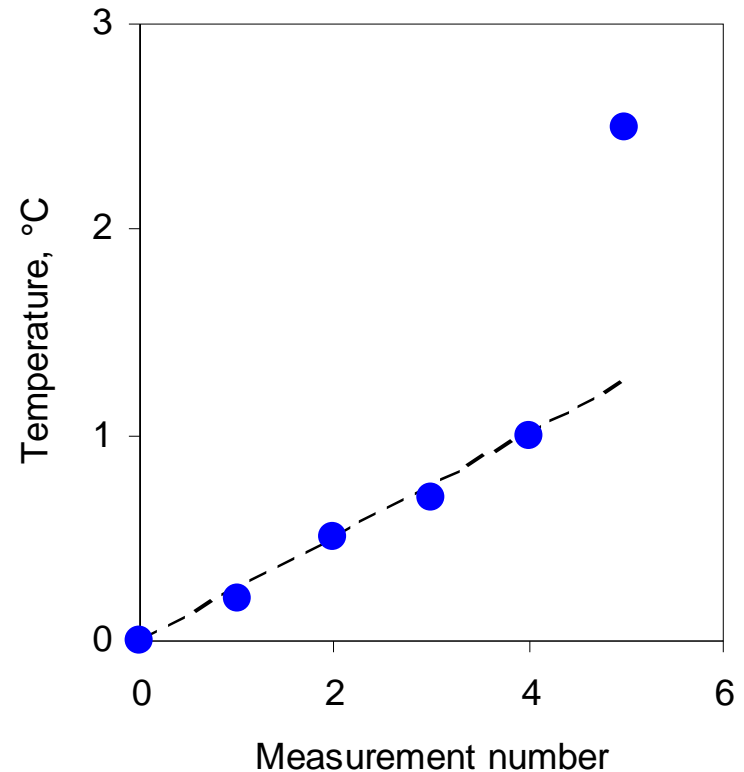
This method is only useful if the instrument is not adjusted, or if the calibration laboratory supplies both “as received” and “as adjusted” data

Case 1: unadjusted instrument

Year	Reading at 0 °C
1999	0.0
2000	0.2
2001	0.5
2002	0.7
2003	1.0

Aver. drift: 0.25 °C/year

Maximum drift of 0.3 °C/year



2004

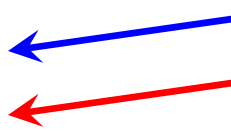
2.5

Observed drift of 1.5 °C—anomalous!

Measurement Assurance: Historical Data

Case 2: adjusted instrument

Year	As rec'vd.	As adjust.	Change from prev. year
1999	0.0	0.0	
2000	0.2	0.2	0.2
2001	0.5	0.0	0.3
2002	0.2	-0.1	0.2
2003	0.2	0.0	0.3



Aver. drift: 0.25 °C/year

Maximum drift of 0.3 °C/year

Quick Guide to Uncertainty Terminology

An uncertainty is a statistical measure of how likely the result of a measurement agrees with the true answer.

Uncertainty at 68 % confidence (“standard uncertainty”) is denoted with lower case u . The difference between the true answer and the measured value will be less than $\pm u$, 68 % of the time.

For higher confidence limits, u is multiplied by a coverage factor k to obtain the “expanded uncertainty” $U = k u$

The default for calibration certificates is $k=2$, which for normally distributed uncertainties corresponds to a 95 % confidence limit.

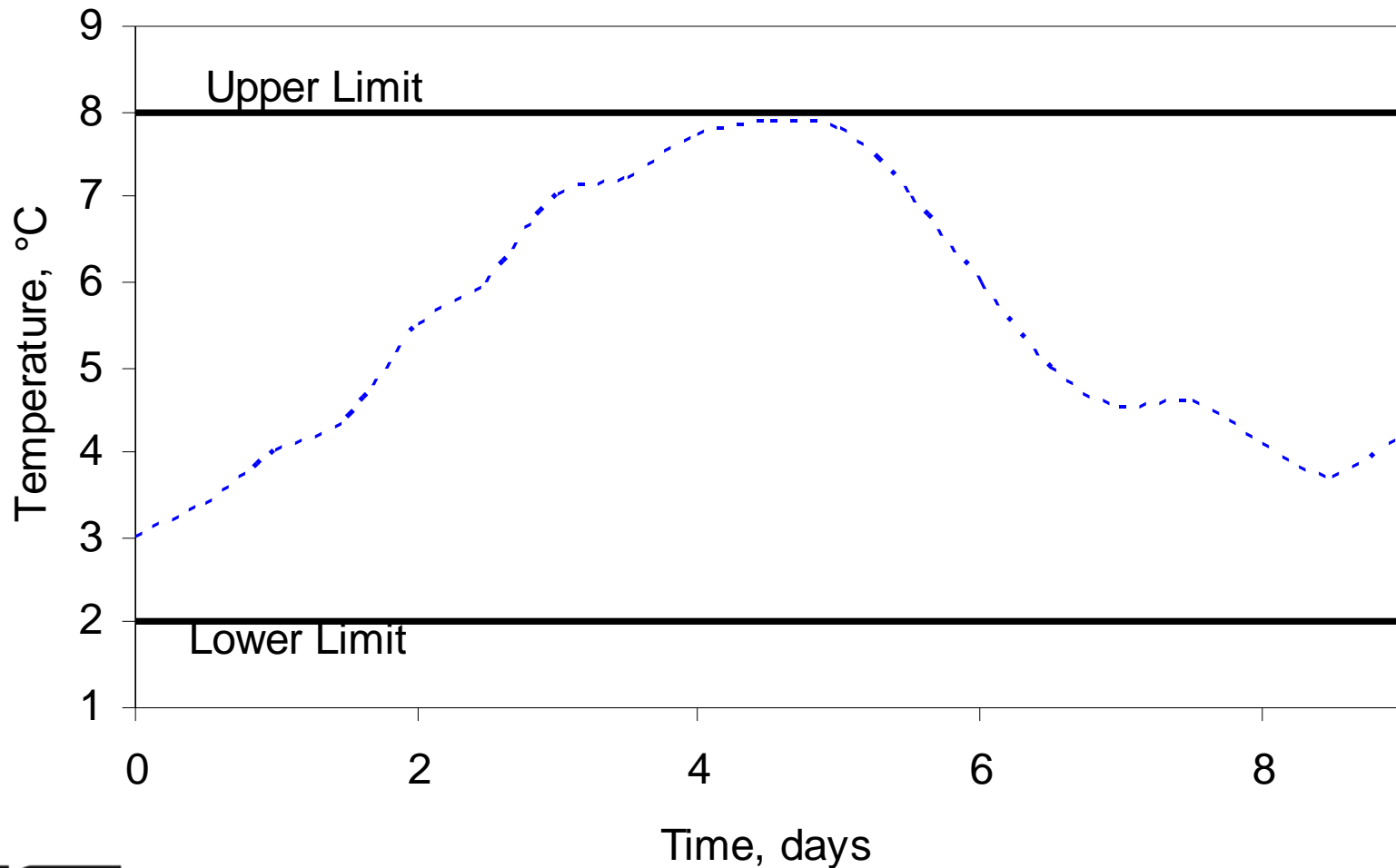
When there are multiple uncertainty components, the combined uncertainty u_c is obtained by adding the components in quadrature:

$$u_c = \sqrt{u_1^2 + u_2^2 + \cdots + u_n^2}$$

Error Allowance (Guardbanding)

Q: Is the blue line an acceptable set of readings?

A: No, probably not!



Adding up measurement uncertainties of vaccine temperature

Table of uncertainties

Instrument resolution	0.25 °C
Drift	0.25 °C
Storage volume non-uniformity	0.10 °C
Thermometer accuracy/cal. uncertainty	0.5 °C

Linear sum = $(0.25 + 0.25 + 0.10 + 0.50)$ °C = 1.1 °C = max. error

Root-sum-square (used by metrologists) =

$$[(0.25)^2 + (0.25)^2 + (0.10)^2 + (0.50)^2]^{1/2} = 0.6 \text{ °C} = \text{likely error}$$

Since the likely error in this case is approximately 0.6 °C, we should not allow readings within 0.6 °C of allowable limits

Evaluating uncertainty components

Instrument resolution:

About $\frac{1}{4}$ to $\frac{1}{2}$ of a graduation, for dial or liquid thermometers

About $\frac{1}{2}$ of smallest digit for digital instruments

Instrument drift over one year:

Obtained from historical trends of calibration results

Obtained from manufacturer's literature or specifications, or

Crudely estimated as the resolution for liquid thermometers, or the instrument accuracy for other thermometers

Non-uniformity of storage volume:

Obtained from multiple measurements of storage volume with thermometers in different positions

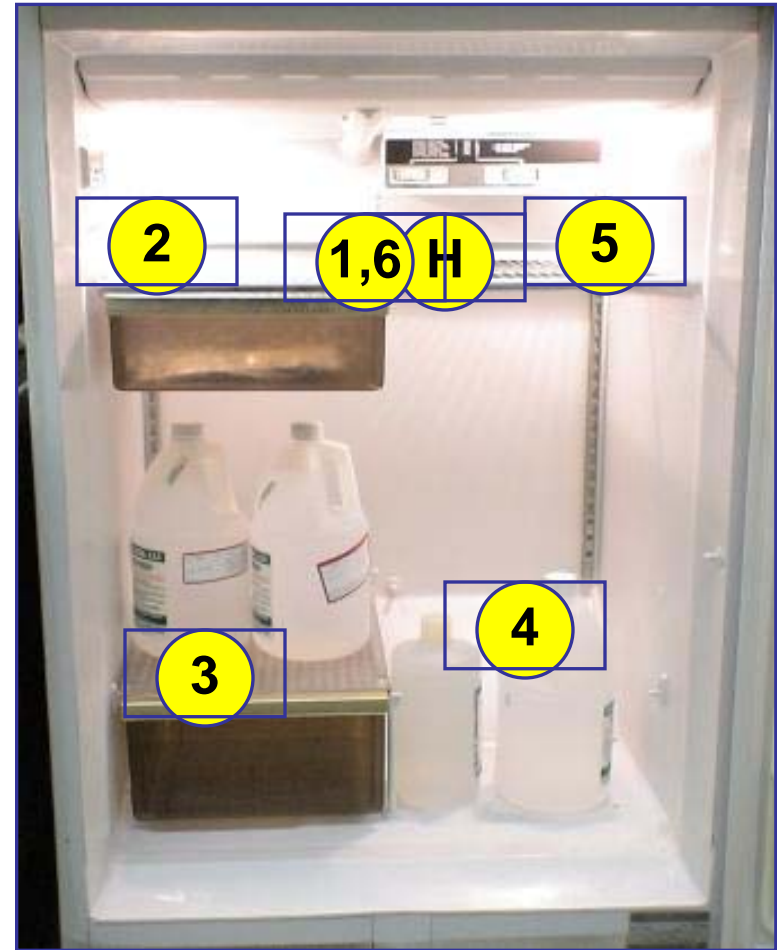
Storage Volume Temperature Non-uniformity

Non-uniformity measured by examining difference between two thermometers:

- **keep one thermometer at 'home' position;**
- **move the other one, wait for temperatures to reach equilibrium,**
- **Variation of difference between two thermometers over all positions measures non-uniformity of storage region**
- **You can make the non-uniformity as small as you need by making the storage volume smaller**
- **Only need to do this measurement once, if you do not change configuration of cold enclosure**

Numerical example of non-uniformity measurement

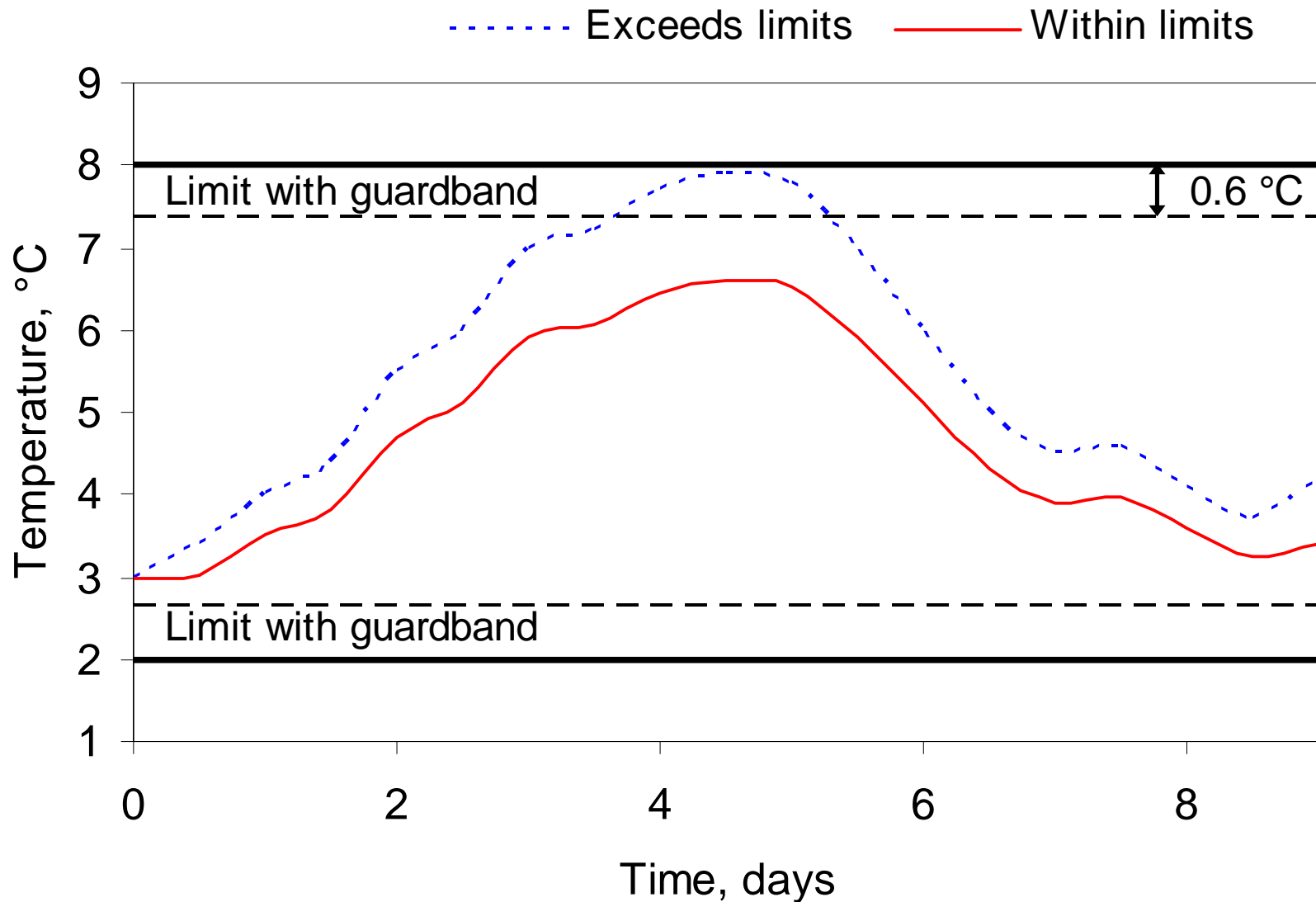
N	$T(\text{home})$	$T(N)$	$T(N) - T(\text{home})$
1	3.4	3.6	0.2
2	3.6	3.8	0.2
3	3.8	1.7	-2.1
4	3.7	1.5	-2.2
5	3.4	4	0.6
6	3.5	3.5	0.0
Average for positions 1 & 6			0.1
Maximum deviation from 1 & 6			-2.3



Top-to-bottom variation can be several degrees Celsius

Non-uniformity may depend on how refrigerator is loaded

Guardbands provide confidence that vaccine temperature is within allowed range



Guardband variation

A more accurate thermometer can give you a greater allowable variation in measured temperature

Example:

guardband of 0.6 °C gives an allowable range of 2.6 °C to 7.4 °C,
a span of 4.8 °C

guardband of 2.0 °C gives an allowable range of 4.0 °C to 6.0 °C,
a span of 2.0 °C

Calibration Reports vs. Certificates

**Internationally accepted standard for calibration laboratories is:
ISO/IEC 17025:2005 “General requirements for the competence
of testing and calibration laboratories”**

17025 Requirements for calibration reports include:

- a) title
- b) name and address of laboratory performing the calibration
- c) unique identifier of the calibration certificate
- d) name and address of the customer
- e) identification of the method used
- f) a description of the item tested
- g) results of the calibration
- h) evidence of traceability
- i) environmental conditions of the test, if appropriate
- j) uncertainty of the measurement
- k) signature authorizing the certificate

Certificates are often “Calibration Lite”

17025 elements generally included:

- a) title
- b) name and address of laboratory performing the calibration
- c) unique identifier of the calibration certificate
- f) a description of the item tested
- g) results of the calibration
- h) evidence of traceability
- k) signature authorizing the certificate

The most important elements usually not included:

- e) identification of the method used
- j) uncertainty of the measurement

Certificate statement of accuracy does not include long-term instrument drift; you must account for drift separately

Shopping for a calibration laboratory

Do you want units adjusted?

If yes, then consider:

- experience of facility with your brand of unit (esp. electronic)
- does cal. report give as-received and as-adjusted data?

Look for:

- stated traceability to NIST
- documented uncertainty
- accreditation of laboratory to ISO 17025 (not mandatory, but a sign of some level of proficiency)
- good past history

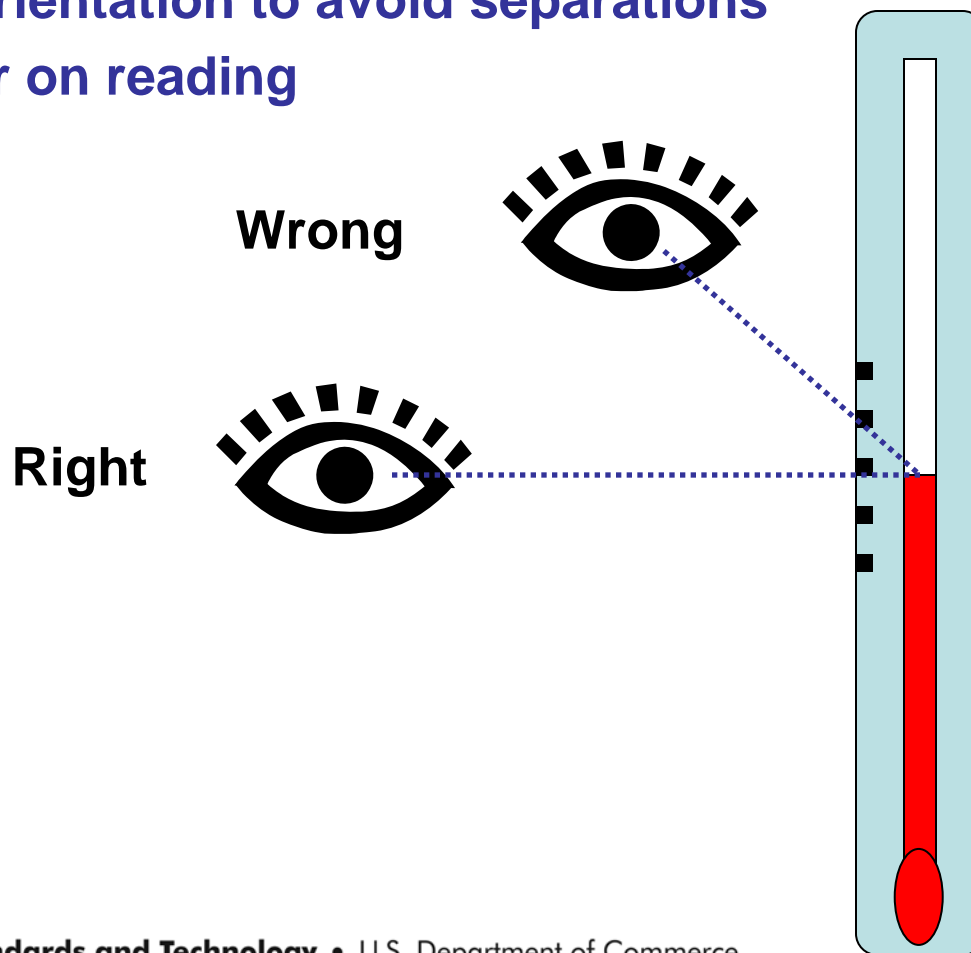
Proper Use: Thermocouples

1. Avoid kinks in the thermocouple wire passing across the door seal.
2. Thermocouples have fast time response—especially important to put measuring junction in a volume of liquid or solid.
3. Avoid use of readouts at refrigerator/freezer temperature, unless designed and/or calibrated for such use.
4. Thermocouple wire should extend from measurement point out to room temperature without junctions. Extension wire and connectors OK at room temperature.
5. Be careful that readout is set to use the correct thermocouple type to match the sensor type (types are color coded)
6. For calibrated units, be careful to use the same thermocouple with the same readout

Proper Use: Liquid in Glass Thermometers

Inspect column for separations, especially when new, especially for organic-liquid-filled

- Keep in a vertical orientation to avoid separations
- Avoid parallax error on reading



Proper Use: Dial Thermometers

- **Avoid mechanical shocks, which can damage or shift internal linkage**
- **Avoid parallax error on reading**
- **Avoid/discard dial thermometers that are susceptible to inadvertent shifting of scale**

Proper Use: PRTs and Thermistors

1. Avoid mechanical shock, which can damage sensor
2. For calibrated units, be careful to use matched sensor and readouts
3. Erratic readings are often a sign that moisture seal has been lost—measure insulation resistance or calibrate with a new sensor
4. Remember that most “digital” thermometers and dataloggers use a PRT or thermistor as the active element

FAQs for Vaccine Cold Chain Thermometry

How often should thermometers be calibrated?

- Initial calibration intervals should be based on manufacturer's recommendations or past experience with a type of instrument.
- Calibration intervals may be adjusted based on the historical calibration results of a particular instrument.
- If check measurements indicate significant drift, then recalibrate.
- If check measurements indicate large and sudden drift, remove instrument from service.
- For vaccine cold chain, a single-point recalibration at the ice point + visual inspection may suffice for liquid-in-glass thermometers.

We are getting ready to send some of our thermometers off to be calibrated. Can you help me in deciding which calibration we need to have done?

- **Vaccine cold-chain applications cover a limited range. Instruments need to be calibrated only at the upper and lower limits of use.**
- **Instruments with digital readouts should be calibrated in the same manner in which they are used. e.g., if a digital readout is used cold, then the calibration would need to be conducted with a cold readout.**
- **Uncertainty of calibration should be comparable or smaller than instrument repeatability, or significantly smaller than the allowable temperature tolerance for the vaccine cold chain.**

Is it correct for a certificate of instrument calibration to claim traceability through the American Society for Testing and Materials (ASTM)?

- **No. ASTM produces documentary (paper or electronic text) standards that describe test methods and manufacturing specifications.**
- **Manufacturers may use ASTM methods to perform calibrations that are traceable to the standards of NIST or another national metrology institute. Traceability in this case is to NIST or the equivalent in other countries.**
- **Recently, the international community has adopted the phrase “metrological traceability” to describe the traceability of measurements, to avoid any ambiguity.**

What is the difference between ASTM and NIST?

- **ASTM is a standards development organization that produces documentary standards, and related books and journals. ASTM standards are developed through a consensus process, based on the work of volunteers from manufacturers, users, and other interested parties, including NIST staff.**
- **NIST is a non-regulatory federal agency within the U.S. Department of Commerce that promotes U.S. innovation and industrial competitiveness by advancing measurement science, standards, and technology.**
- **Temperature measurements in the U.S. are traceable to NIST primary temperature standards, which are disseminated through a combination of customer calibrations and reference materials.**
- **NIST also includes an accrediting organization, the National Voluntary Laboratory Accreditation Program (NVLAP).**

Is a qualified vendor the best choice to perform thermometer preventive-maintenance activities?

- **Users can perform in-house performance checks, such as checks in an ice-point bath. As a means of validating the in-house check methods, we recommend that users try out their performance checks on newly calibrated instruments that are known to be accurate.**
- **Recalibration of thermometers should be carried out by skilled personnel using appropriate standards and facilities.**
- **Recalibration may be conducted by either a qualified vendor or a qualified laboratory within an organization.**

How important is it to establish periodic preventive maintenance and calibration schedules?

Traceability of the measurements, which is critical to maintaining the cold chain, absolutely requires periodic thermometer checks and calibration schedules.

Must periodic preventive maintenance and calibration schedules be established according to standard operating procedures?

- **Standard procedures are important, in order to maintain confidence in the measurements and to assure that important checks are not forgotten.**
- **The maintenance of traceability implies documentation of procedures and calibration results.**

**On most thermometer instrument calibration and testing certificates it is stated that: Accuracy: $\pm 0.2^{\circ}\text{F}$.
What does this really mean?**

- “Accuracy” is a common, but not well defined term, for calibration work.
- In its most common usage, “accuracy” is the manufacturer’s guarantee that the instrument will give the correct answer to within the stated accuracy.
- How long the instrument will meet this accuracy depends on the manufacturer!
- In the field of metrology, the preferred term for quantitative statements is “uncertainty”.
- In the field of thermometry, a stated accuracy is roughly comparable to uncertainty at a 95 % confidence level.

What should a provider consider before purchasing a thermometer to assist with proper vaccine storage and handling?

- **How is the thermometer to be read? Remotely or by an individual?**
- **Referring to the material on the guardband, set a target for the combined instrument uncertainty/accuracy and drift.**
- **How will the thermometer be recalibrated or revalidated? This expense is often greater than the cost of the initial thermometer.**
- **Where will the readout be located, and will this make recalibration difficult?**
- **What is the measurement assurance plan?**