Self-calibrating temperature sensors in the pharmaceutical industry

Temperature measurement instruments are widely used in pharmaceutical processes as sufficiently high temperatures must be guaranteed in all system units during the sterilization phase to ensure that all germs are killed off. The accuracy of these measurements must be verified with the help of regular sensor calibrations, since incorrect measurements can pose a hygiene risk. New technology of inline self-calibrating thermometers can contribute to minimizing the risk of incorrect measurements.

Critical aspects of manual calibration

Many companies today have established Standard Operating Procedures (SOPs) that typically stipulate an annual three-point calibration for temperature sensors. However, the greatest risk to a thermometer in a hygienic system is the manual calibration itself. Due to the nature of the procedure, the possibility of mechanical damage increases, e.g. from a fall or impact, when the process is opened, devices are removed, reinstalled or due to thermal shock when the sensor insert is introduced into the calibrator equipment.

If the calibration (e.g. one year after the previous calibration) now establishes that the thermometer is non-compliant, all batches produced within that timeframe must be examined to ascertain the extent to which the product quality may have been impaired or compromised. Tests of this type tie up substantial resources. In a worst-case scenario, a product recall may be unavoidable.

Conversely, such risks are reduced if the temperature sensor remain installed in place and in the same position for longer periods of time without being moved.

Benefits at a glance

- Accurate and reliable temperature readings are essential to ensure process sterility
- Temperature sensors with inline self-calibration minimize risk of contamination and deviation
- Technology meets the requirements for continuous process verification (FDA compliance)
- Automated documentation helps build a repeatable, traceable record database for audits, regulatory authorities

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Technology

- A miniaturized ceramic element acts as built-in fixed-point reference
- The sensor unit uses the Curie temperature effect
- The reference undergoes a phase change at a predetermined temperature
- The primary sensor (Pt100) and the reference are located side-by-side in the probe

Self-calibration technology Recent developments in the field of electrical thermometry yielded a technology that self-calibrates during operation in the process. It meets the industry demand by reducing risk while increasing plant availability. The self-calibration method uses the Curie temperature (Tc) properties of a reference material as a built-in, physical fixed-point temperature reference with proven long-term stability. The Curie temperature is a material constant associated with the material used. At a particular temperature, the reference material undergoes a phase change, which is associated with a change in its electrical properties.

The reference element is located back-to-back with a Pt100 temperature sensor according to IEC 60751 at the tip of the probe. A self-calibration is performed automatically every time the process temperature (Tp) drops below the nominal Curie temperature (Tc) of the device.

The integrated electronics unit detects the phase change automatically and simultaneously calculates the deviation of the measured Pt100 temperature from the Curie temperature as determined. The device safely stores the result of this calibration and the associated raw data in the built-in memory. This data can be retrieved at any time in the form of a calibration certificate. This process can also be automated.

Such an in-situ self-calibration makes it possible to continuously and repeatedly monitor changes to the properties of the Pt100 sensor and the electronics unit. Given that this type of calibration is performed under real ambient or process conditions, the results are more in line with reality than a laboratory test or manual field calibration [cf. Bibl. 5] where the procedures are carried out using other process media and under dissimilar installation conditions.

Bioreactor application Cells with special properties are cultivated in a bioreactor at approximately 37 °C and under optimum nutrient supply conditions until the required concentration of cells and target product is reached. To ensure safe operation, it is extremely important that only the desired cells grow, and that unwanted micro-organisms or germs from the environment do not multiply under the ideal conditions provided in the bioreactor.

Therefore, the fermentation boiler and all the connected piping must be sterilized thoroughly before each batch. To this end, saturated steam is introduced at a temperature of over 122 °C (at approx. 1.1 bar / 16 psi overpressure) for at least 15 minutes. The quality of the sterilization process must be precisely monitored by calibrated thermometers and documented.

Self-calibration (cf. Fig. 2, green point) is reliably performed during every cooling phase when the temperature drops from above 122 °C and before filling begins. This ensures that a potentially defective temperature device is automatically detected before a new batch is produced.

Fig. 1: Structure of the self-calibrating temperature sensor element

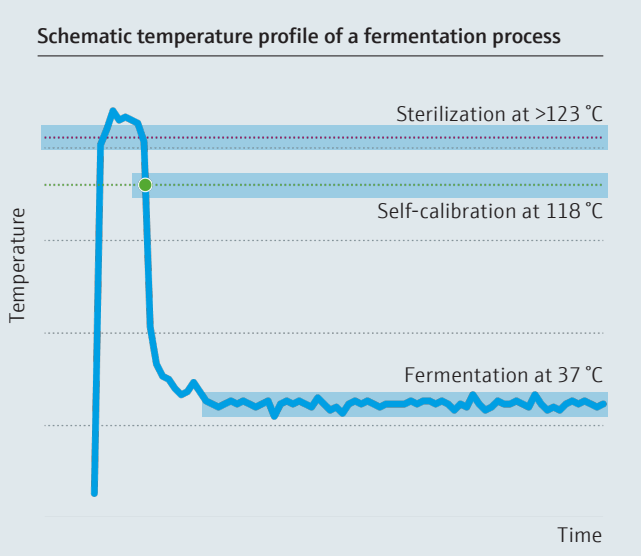
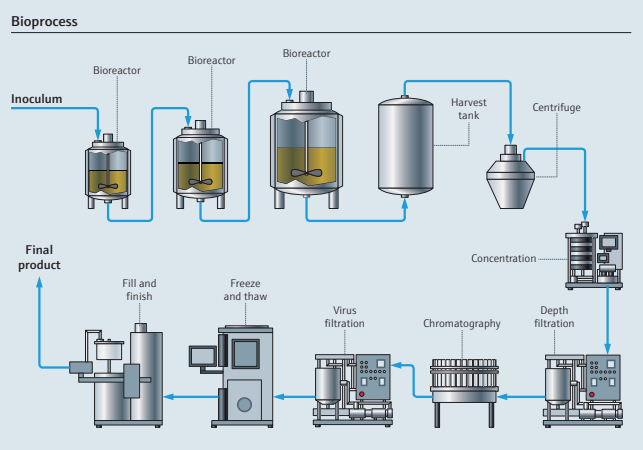


Fig. 2: Typical temperature graph based on the example of a fermentation process



Sterilization must be ensured throughout the entire bioprocess

Calibration of temperature sensors

The Callendar-Van Dusen equation and potential sources of errors

Common setup for an on-site manual calibration procedure using a block calibrator

Calibration of temperature sensors Calibration at three or more points is necessary if the behavior of the sensor (e.g. its linearity) is considered to be unknown across the measuring range and the natural laws governing the measured values are not taken into account. Platinum resistance temperature detectors (Pt100 RTDs) used at temperatures above 0 °C generally follow the Callendar-Van Dusen correlation:

$$R(T) = R_0 [1 + A\,T + B\,T^2] \text{ (T in °C)}$$

The equation describes the relationship between the electrical resistance of the sensor (the actual measured variable) and its temperature. The difference between 'good' and 'bad' sensors is based on a change in the sensor characteristic values R_0, A or B. In this case however, the entire characteristic curve changes instead of just one measured value. Due to its very low numerical value (standard value -5.775×10^{-07}) coefficient B does not play a significant role in the temperature range relevant for the pharmaceutical industry. The influence of B can only be measured at high temperatures, as it is multiplied by the square of the temperature.
Two characteristic values dominate in the temperature range under observation:

- R_0: the basic value (100 Ohm at 0 °C)
- A: the slope of the characteristic curve (standard value = 0.3908 Ohm/Kelvin)

Source of errors There are two possible sources of deviation: The offset error and the slope error. Both occurrences can be reliably addressed by a single-point calibration.

- **Offset error: Change in the basic resistance R_0**
  A shift in the basic resistance R_0 (e.g. from 100 to 99.8 Ohm) is a typical error presented by RTD assemblies. This may be caused by mechanical impact (a fall, steam hammering etc.), leading to the conductor track on a Pt100 thin film resistor to be extended or compressed as the result of an external force. If the basic value changes, the entire curve shifts, which is why this error can be easily detected with a single-point calibration [cf. Bibl. 1].

- **Slope error: Change in temperature dependence A**
  An incorrect curve slope or curvature is a less common error. This type of non-conformity is normally caused by direct contamination of the platinum in the temperature resistor and by grain-size growth at temperatures over 400 °C [cf. Bibl. 1]. Both these risks are not relevant in applications in the pharmaceutical industry as the sensors are always installed in closed inserts and a protective thermowell. Moreover, temperatures above 160 °C hardly ever occur in these applications.

Results and conclusions If a significant deviation is established during a regular single-point calibration (in contrast to the previous calibration), it is possible to rule out that subsequent measurements at any temperature other than 0 °C are accurate. Therefore, if a self-calibrating sensor indicates such a deviation, the operator is advised to take immediate action. However, if none of the numerous, consecutive, automatic calibrations (e.g. daily, weekly, for each batch) indicate a significant change in the calibration results, it can be concluded that no relevant change in the thermometer has occurred. There is no urgent need for action requiring the intervention of the operator.

Measurement uncertainty

Automated single-point vs. manual three-point calibration

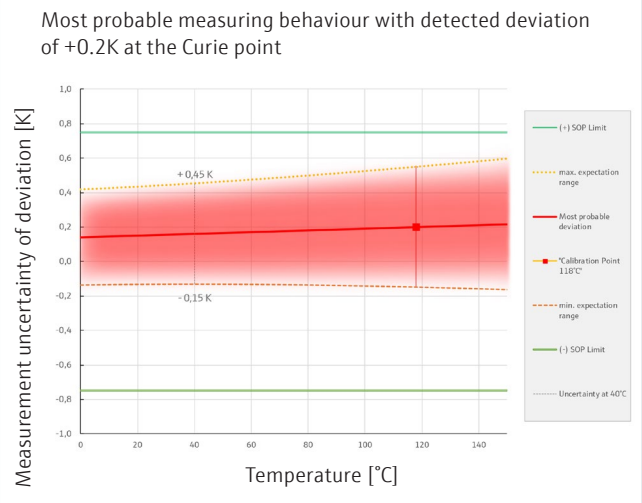


Fig. 3: Measurement uncertainty analysis of single-point calibration

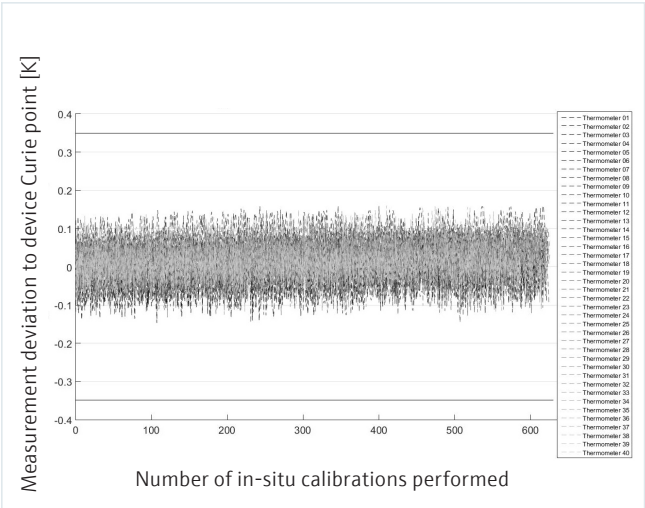


Fig. 4: Long-term analysis of detected measurement deviation at Curie point with 40 Endress+Hauser iTHERM TM371 (Source: TÜV Thüringen)

Measurement uncertainty: Single-point calibrations

An analysis conducted by the University of Ilmenau verifies how a deviation determined at 118 °C affects the entire measuring range [cf. Bibl. 2 and Bibl. 3]. As previously described, a significant deviation is most likely attributable to a change in the basic resistance R_0. A new characteristic curve can then be determined (cf Fig. 3, red). The uncertainty of this assumption increases depending on the value of the measured deviation at the Curie point and the distance from the calibration temperature. At the Curie point, the uncertainty corresponds to the measurement uncertainty of the process as certified by the German Technical Inspection Association TÜV [cf. Bibl. 14, Fig. 5]: ± 0.35 Kelvin.
If, for example, a deviation of +0.2 K has been detected at approx. 118 °C, this implies a likely deviation of less than 0.18 K at the process temperature (37 °C to 40 °C).

If the uncertainty of measurement (in the range from -0.15 K to +0.45 K at 40 °C, for instance) is also taken into account, it can be demonstrated that the thermometer is more accurate than +0.6 K and -0.2 K over the entire range.

As a general rule, a limit of ±0.75 K is defined. Temperature sensors presenting a deviation of ±0.75 K or more are removed from the system. Therefore, every sensor presenting a deviation of less than 0.2 K at the Curie point would be within the tolerance by a significant margin and thus compliant with this requirement.

TÜV was commissioned to examine the process as part of a study. To this end, TÜV analyzed more than 24 000 calibration results [cf. Bibl. 6, Fig. 4]. None of the results analyzed presented a deviation of more than **0.15 K**.

DAkkS

To determine the 'best-case' measurement uncertainty manual calibrations can achieve using dry block calibrators, it is advisable to refer to the website of the German accreditation body, DAkkS (www.dakks.de).

The calibration body D-K-15024-01-00 (2018) is suggested here as a benchmark. It is specialized in performing calibrations at its customers' premises.
According to the accreditation certificate, RTD assemblies are tested using dry block calibrators.

Measurement uncertainty of manual calibrations
To make a definitive assessment of the in-process self-calibration procedure, it is advisable to take a closer look at the method that is most commonly used today. Standard procedures in companies typically rely on dry block calibrators for manual on-site calibration to check the accuracy of RTD assemblies in hygienic applications. The procedure usually involves a yearly three-point temperature scheme. However, it is important to bear in mind that thermometers in this particular industry usually have a comparatively short immersion length, as small pipe diameters or agitators in tanks often limit the space available for installation. This means that there is often a significant physical distance between the point where a reference thermometer measures the temperature of the calibrator and the position of the sensor which is to be tested.

According to DAkkS (see info page 5), the best measurement capability is **± 0.75 Kelvin** [cf. Bibl. 4] in the measuring range from 50 °C to 400 °C.

A direct comparison reveals the following:

- Due to its far lower measurement uncertainty, automatic in-situ single-point calibrations provide a more reliable statement of conformity than a manual check performed at three points using a dry block calibrator.
- This statement is particularly true for the critical temperature range around the sterilization temperature.
- Manual calibrations are often only performed once a year as opposed to frequent automatic calibrations during every cleaning process.

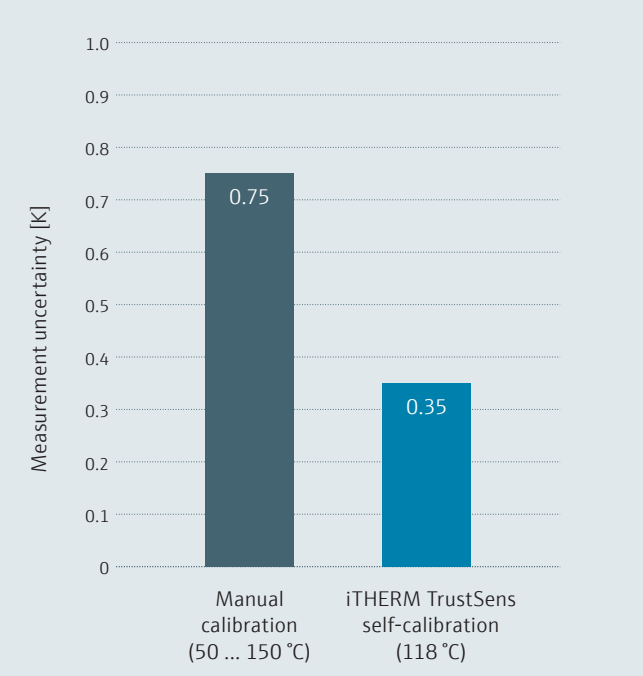


Fig. 5: Comparison of calibration measurement uncertainties

Regulatory compliance

Continuous process verification and Good Practice Guide

Self-calibrating temperature sensor technology enables users to meet the requirement for 'continuous process verification' as required by regulatory bodies and industry guidelines, such as the FDA [cf. Bibl. 7]. This is because in-situ single-point calibration minimizes the risk of a deviation going undetected until the next calibration.

In 2010 already the Good Practice Guide for calibration management predicted the availability of devices capable of self-calibration and online alerts [cf. Bibl. 12]. It specifically states that the data collected in this way can be used to extend the intervals between calibrations. The same document also mentions that it is both possible and sensible to periodically perform single-point calibrations to verify the accuracy of a device.
The self-calibration technology therefore provides a significant upgrade to the task of temperature measurement that not only increases safety but also brings additional cost benefits to the process.

The additional data recorded can help to verify that the calibration intervals can be extended without risk.

Outlook It can be assumed that regulatory authorities and auditors will demand the use of the self-monitoring technology presented here as it has already been tested and is available in the market.

Applications in the pharmaceutical industry Existing systems can be easily retrofitted since the self-calibration function has been integrated in the relevant devices in addition to the "normal" temperature measurement function. The risk minimization function is active as soon as the device enters operation: The device generates a warning or alarm upon detection of calibration deviation. Over the course of system operation, the calibration intervals of these thermometers can be extended and system downtime shortened.

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