Thermal Validation in the Pharmaceutical Industry:
An argument against the use of thermocouples

The pharmaceutical industry is a highly regulated environment based on research, evidence, record-keeping, and validation. The term "thermal validation" is the process of validating / qualifying equipment and storage facilities to prove that they will create and maintain the temperatures they are designed for.

For those responsible, choosing the right validation tool is decision #1 - and making that choice requires a thorough understanding of different sensors types. This paper will specifically focus on two common sensors: thermocouples and thermistors (see table below).

contact with each other. The thermocouple works by generating a small voltage signal proportional to the temperature difference between the junctions of two metals.

In contrast, a thermistor is a resistive device made up of metal oxides that are formed into a bead and encapsulated in epoxy or glass. As temperature changes, so does resistance, causing a large voltage drop.

Both sensors are quite small and normally encased in a protective shell, stainless probe, or wire coating, meaning that they may look very similar to the end-user.

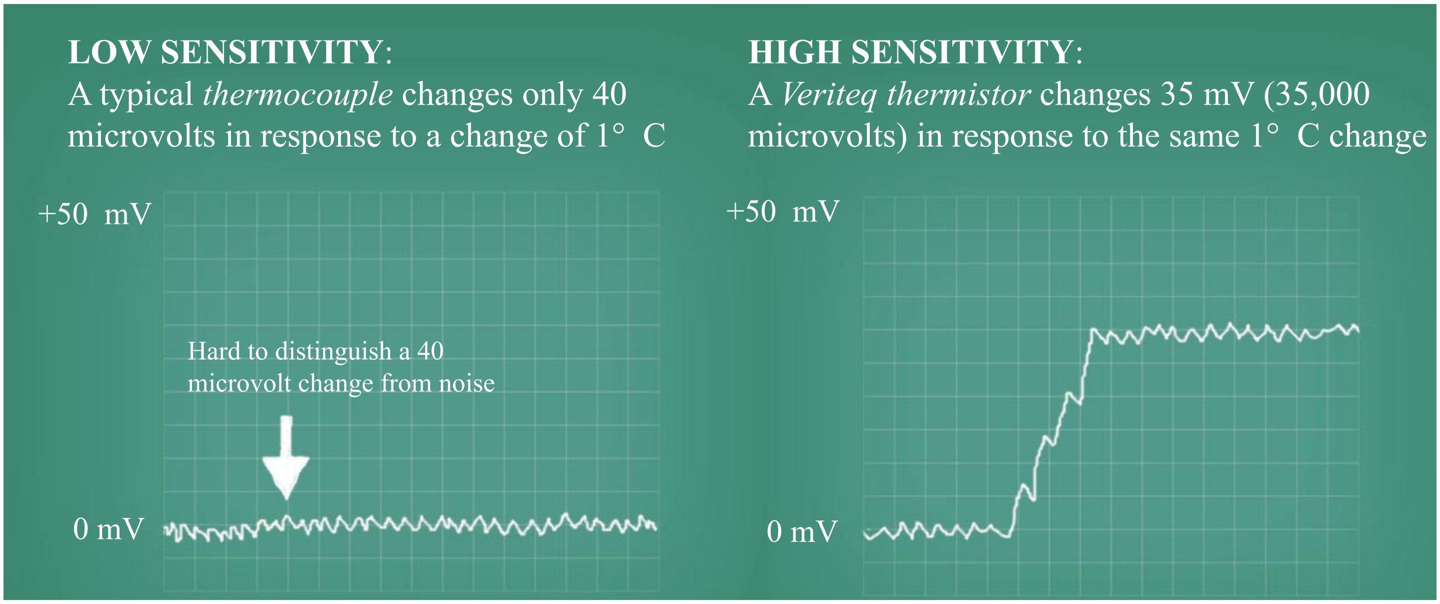
	Thermocouple	**Thermistor**
Temp. Range	-270 to 1800°C (-454°F to 3272°F)	-86 to 150°C (-123°F to 302°F)
Sensitivity	Low	High
Stability	Low	High
***Time-savings**	Lengthy set-up	Minimal set-up
***Sources of Error**	Many	Few
***Accuracy**	Low	High
Ideal Applications	High temperature oven profiling, Cryogenic freezing	Warehouse monitoring, Stability testing, Chamber qualification, Cooler and Freezer Monitoring, Lab monitoring, Cold Chain monitoring.
* This comparison looks at a total data logging system, and not just the sensor.		

With nearly a decade of experience using both thermocouples and thermistors, Veriteq Instruments knows the advantages and disadvantages of each sensor, and will discuss them as they relate to data logging in the pharmaceutical industry. This paper will also include specific references to Veriteq data loggers, which utilize internal thermistors. But first, a brief definition of thermocouples and thermistors:

A thermocouple is made of two dissimilar metals in

Temperature Range
Thermocouples offer the widest range of measuring capabilities, which admittedly makes them a suitable choice for extreme temperature applications such as oven profiling and cryogenic freezing.

However, in the range of –86 to 150°C (-123°F to 302°F), thermistors become an option, and for most applications they are the better choice. Thermistors



*Theoretical temperature change at 25° C

are primary sensors, meaning that they operate independently, without the need for a second reference sensor. In fact other systems, including thermocouple systems, often use thermistors as their reference sensor.

It should be noted that the stated temperature range of –86 to 150°C (-123°F to 302°F) is just for the thermistor itself, and not for an enclosed Veriteq data logger. Veriteq data loggers are designed to withstand the range of -86 to 85°C (-123°F to 185°F) meaning that the loggers themselves can be placed in the temperature environment and left there. This makes them an ideal solution for chamber qualifications, stability testing, warehouse, cooler and freezer monitoring.

Veriteq's solution for the higher range of 85°C to 150°C (185°F to 302°F) requires an external thermistor probe that allows the connected data logger to remains outside the high temperature environment.

Sensitivity

The term sensitivity refers to the size of signal received in response to a temperature change, and is an important component of sensor accuracy. Thermistors are highly sensitive; in fact the name thermistor evolved from the phrase "thermally sensitive resistor". Stuart Ball, an electrical engineer and author for *embedded.com* writes that "of all passive temperature measurement sensors, thermistors have the highest sensitivity."
In comparing thermistors with thermocouples, Stuart goes on to say: "The voltage produced by a thermocouple is very small, typically only a few millivolts. A type K thermocouple changes only about 40 microvolts per 1°C (1.8°F) change in temperature."

"The voltage produced is very small and amounts to only a few microvolts per degree Celsius. Thermocouples are therefore not generally used within the range of -30 to 50°C."

With such a small voltage to measure, it becomes difficult to distinguish an actual temperature change from noise. Enercorp Instruments Ltd., a provider of thermocouples and thermistors, speaks directly to this issue: "The voltage produced is very small and amounts to only a few microvolts per degree Celsius. Thermocouples are therefore not generally used within the range of -30 to 50°C (-22 to 122°F)." <www.enercorp.com/temp/Thermistors_comparision.html>.

The picture above is a visual representation of the increased sensitivity that a thermistor based system (such as a Veriteq data logger) detects as compared to a thermocouple system.

Stability

Thermistors are very stable, which makes them ideal for portable applications such as warehouse and chamber qualifications. For example, Veriteq data loggers can be moved frequently and still maintain an accuracy of +/- 0.15°C (+/-.27°F).

To prove the point Veriteq recently checked the calibration of 106 data loggers after a year of use in the field. Each logger was checked at the following calibration points: -20°C, 25°C, and 70°C. The results were impressive, showing less than 1% of the points to have any excess drift. Still, Veriteq recommends that data loggers are re-calibrated on a yearly basis.

Thermocouples, on the other hand, are known for low stability, which is why a pre-cal / post-cal is required with every use.

Time-savings

A veriteq data logger is a system in itself, and one that is easy to use. Each data logger, containing a thermistor, is simply set to the desired sampling frequency and then placed in the monitoring location. Following the test period, the data is downloaded via a PC or PDA. The system is very straightforward and doesn't require any stringing of wires - the result is a significant time savings.

In contrast, a thermocouple based set-up can be quite time consuming, especially for high-accuracy applications requiring a pre and post-calibration. For example, qualifying a chamber with a thermocouple system involves first putting all sensor ends (i.e. the hot junctions) inside a calibration unit and going through the pre-calibration process. Following a successful calibration, the thermocouples are strung from the central data logging unit, to the

Sources of Error		
	Thermocouple System	**Veriteq Thermistor System**
Physical damage to sensor	'Cold working' degrades thermocouple wires as they are repeatedly bent, stepped on, or shut in chamber doors.	There is minimal risk because the sensor is protected inside the data logger.
Non homogeneity (consistency of thermocouple wire and the environment it runs through)	Always present to some extent	N/A
Cold Junction reference error • Temperature deviation between cold junction reference point and the actual cold junction • Accuracy of cold junction sensor	The single largest source of error	N/A
Pre & post calibration errors • Reference transfer calibration error • Traceable temperature standard • Environmental stability • Movement of sensors	In field calibration introduces many sources of error	Pre & post calibration is not required
Operator Error	High level of knowledge required to minimize errors	Less risk as the system is relatively simple
Analog to Digital conversion	Minor	Minor

chamber, through a door seal, and then taped into various positions. Care must be taken to keep a good seal on the door while minimizing damage to the thermocouple wire. Only then can the data collection begin. And when that is complete, all thermocouple sensors must still be moved to the calibration unit for post-calibration. Finally, it is not uncommon for thermocouples to fail the post-calibration, meaning that the whole process may need to be repeated.

Sources of Error

Being a self-contained unit means that Veriteq data loggers have less error sources to deal with - there are no wiring errors, no cold junction errors, and no errors associated with in-field calibration (see table on previous page).

In contrast, thermocouple systems have numerous sources of error, the most significant being the cold junction reference error. Goran Bringert, of Kaye Instruments, states the following: "A change in ambient temperature is the most significant source of error in thermocouple measuring systems, particularly multi-channel systems with internal cold junction references" <www.kayeinc.com/reg/files/measurement-integrity-validation.pdf>.

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Accuracy

High accuracy is critical for temperature validations because of the 4:1 rule, which recommends that instruments be at least 4 times as accurate as the parameter being measured/validated. Therefore, Veriteq data loggers, with their accuracy of +/- 0.15°C (+/-.27°F), can be used to monitor/validate parameters as tight as +/- 0.60°C (+/-1.1°F).

As for thermocouple based systems, a leading provider claims to have a total system accuracy of +/- 0.28°C (+/- 0.5°F). While this may be true from a theoretical point of view, it would require having optimal conditions available. Others in the industry believe that +/- 1-2°C (+/- 1.8-3.6°F) is a more realistic accuracy for such a system, meaning that it could be used to validate parameter specifications of +/- 4-8°C (+/- 7.2-14.4°F), applying the 4:1 rule. In any event, very few people dispute the fact that thermistors are more accurate than thermocouples.

Conclusion

When choosing a system for performing thermal validations the first question asked should be "what kind of sensor is being used?"

Thermocouple sensors should be avoided because they involve a lengthy set-up, numerous error sources, and marginal accuracy. It would be best to restrict thermocouple systems to applications involving very high or very low temperatures, simply because there are no other choices available at those extremes.

In contrast, thermistor sensors are ideally suited to high accuracy monitoring in the range of -86° to 150°C (-123°F to 302°F). The Veriteq thermistor based system is highly sensitive, stable, accurate and easy to use. In addition it eliminates the many error sources associated with thermocouple systems, and allows for a much quicker set-up time. In short, you save time, experience less hassle, and obtain high-accuracy results.

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