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Do we need measurement uncertainty in GxP temperature mapping?

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METROTEKA

THE REAL QUESTION

In the real world of GMP, GDP and GLP, is expressing measurement uncertainty in mapping (and not just in calibration) an overkill, or there is some reason to it?

Well, the real question is would you like to know the temperature uncertainty of your product or sample in your fridge, incubator, warehouse or transport vehicle?

MEASUREMENT UNCERTAINTY IN GENERAL

Measurement uncertainty is a concept which became the most important one for measuring instrument calibration in last 10-20 years. ISO/IEC 17025 accredited calibration laboratories are not allowed to issue any calibration certificate without it.
On the other hand, in organizations' internal calibration certificates, measurement uncertainty is still rarely seen, and even more rarely stated correctly. Many people believe it is just an unnecessary overkill. Nevertheless, when speaking about calibration, the uncertainty is now a widely accepted concept - certainly. But what about temperature mapping and qualification of either fridges and incubators in GMP/GLP or warehouses and vehicles in GDP?

There are many, many guidelines (including a series of World Health Organization ones) in existence, but actually no ISO/IEC 17025 level standard for temperature mapping. The guidelines themselves rarely speak about mapping uncertainty (only about calibration uncertainty of temperature probes and data loggers used for mapping), so there is no obligation for temperature mapping providers to state mapping uncertainty.

QUANTIFIED DOUBT

Defining measurement uncertainty

But what is this measurement uncertainty - whether in calibration or in mapping? There are few generally accepted and standardized definitions, but instead of quoting them, we think it is clearer to define measurement uncertainty as quantified doubt.

We can never be 100% sure in any measurement result in GxP environments, since pharma business is also a part of the universe and the same physical laws apply. There can not be taken a single measurement in the universe in which we can be 100% sure. When we quantify our doubt in our measurement result, we call it - measurement uncertainty. Even the speed of light and the gravitational constant have their own uncertainties, just like our GxP measurements.

"There can not be taken a single measurement in the universe in which we can be 100% sure."

SIMPLE CALIBRATION UNCERTAINTY

In order to answer the question from the whitepaper title - do we need uncertainty in GxP temperature mapping, we must first understand the simpler and much more familiar concept, and that's the uncertainty of thermometers and temperature probes. After all, we will use them for mapping.

Let us use an example. Let us say we have a thermometer with a thermocouple and its ISO/IEC 17025 calibration certificate table states this:

Temperature	Thermometer reading	Thermometer error	Expanded (k=2) measurement uncertainty
+5.00	+5.3	+0.3	0.2 °C

The fourth column of the table does not simply say "measurement uncertainty", it says "expanded (k=2) measurement uncertainty". To keep things simple let us just say that the "expanded (k=2) measurement uncertainty" is the measurement uncertainty which covers approximately 95% of the probability that our result lies within that uncertainty. But what number from the table is the actual result?

The result in thermometer calibration (and by thermometer we mean thermocouples, resistance probes, NTC thermometers, data loggers of all kinds etc.) is the error of the thermometer which the table says is +0.3 °C. But we also doubt that the thermometer error is +0.3 °C, and we quantify that doubt to be 0.2 °C. Furthermore, we say that our doubt covers 95% probability of where the actual result might be. Now it starts to sound complicated again, so lets make it supersimple.

In a nutshell, if a calibration certificate states that the thermometer error is +0.3 °C, and that the expanded (k=2) measurement uncertainty is 0.2 °C, that just means that the calibration provider states that he is at least 95% sure that the error is somewhere between (+0.3 - 0.2) °C and (+0.3 + 0.2) °C. Calibration table above can then be actually read as:

"The calibration provider states that he is at least 95% sure that your thermometer error is somewhere between +0.1 °C and +0.5 °C."

The large part of the calibration uncertainty is caused not by the calibration lab, but by the thermometer which can perform differently under different conditions. People prefer to see small uncertainties for their measuring instruments in calibration certificates, but when we are speaking about doubt - as a customer you should always doubt smaller uncertainties more than large ones, because in most cases you can not check them. It is the same as trusting someone that says he can jump over 2-meter fence. It sounds impressive, but most likely - it is just not true. :)

Now you can test your own understanding of measurement uncertainty. What would you say this next table from some other calibration certificate states:

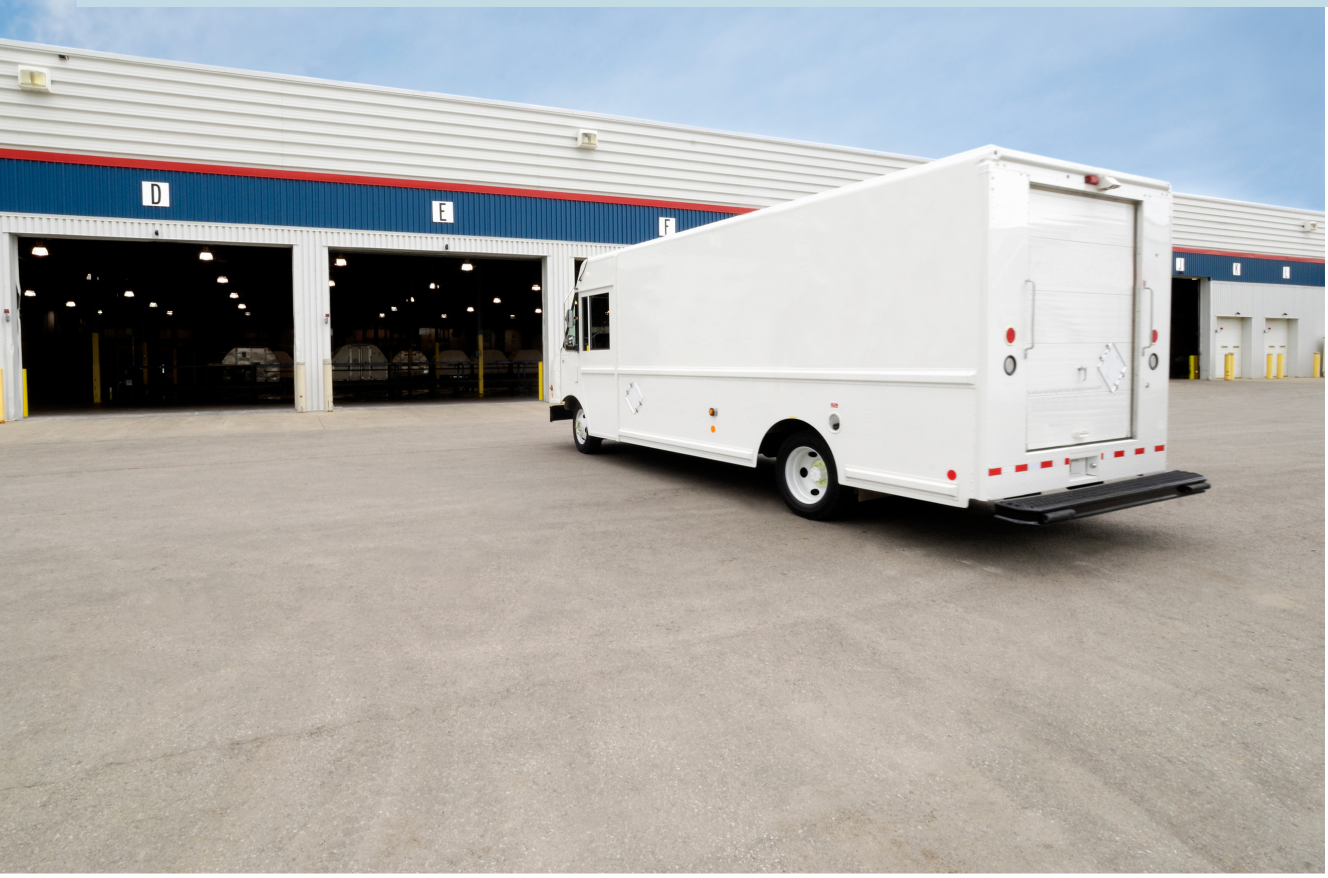
Temperature	Thermometer reading	Thermometer error	Expanded (k=2) measurement uncertainty
+20.00 °C	-19.9 °C	-0.1 °C	0.07 °C

"The calibration provider states that they are at least XX% sure that this thermometer's error at +20.00 °C is somewhere between YY °C and ZZ °C."

Note: You can find the correct answer of XX, YY and ZZ at the end of the whitepaper.

We have now demystified the meaning of the calibration uncertainty, but you still might wonder how the calibration labs come up with the quantification of it, because as a client - you just get a single number from a table as the particular uncertainty.

We will not go into real details (we would need hundreds of pages), but let us say that the things that can influence and enlarge the calibration uncertainty are the standard (in our example - standard thermometer) used for calibration, environmental conditions in which the calibration is performed, calibration method and metrologist herself, all the additional lab equipment used, and last but not the least - the instrument under calibration (in fact usually it is the biggest influence on the total uncertainty).



MOVING FROM CALIBRATION UNCERTAINTY TO MAPPING UNCERTAINTY

First of all, for temperature mapping we always use thermometers or probes which are themselves calibrated. Can we just say that the mapping uncertainty is then equal to the uncertainty of the temperature probes used for mapping? Even though some temperature mapping providers imply so, the answer is very firmly - NO. Why?

Simply said - just as the calibration object (e.g. thermometer) has a large influence on the calibration uncertainty, here the mapping object has an influence on mapping uncertainty. Calibration uncertainty of the probes or data loggers used for mapping is just a small part of the mapping uncertainty, just like the uncertainty of the calibration standard is just a small part of the calibration uncertainty.

But what exactly would be the meaning of mapping uncertainty. Unlike the calibration uncertainty of the measuring instrument which can be simply attributed to the instrument error, here things can get much more complicated.

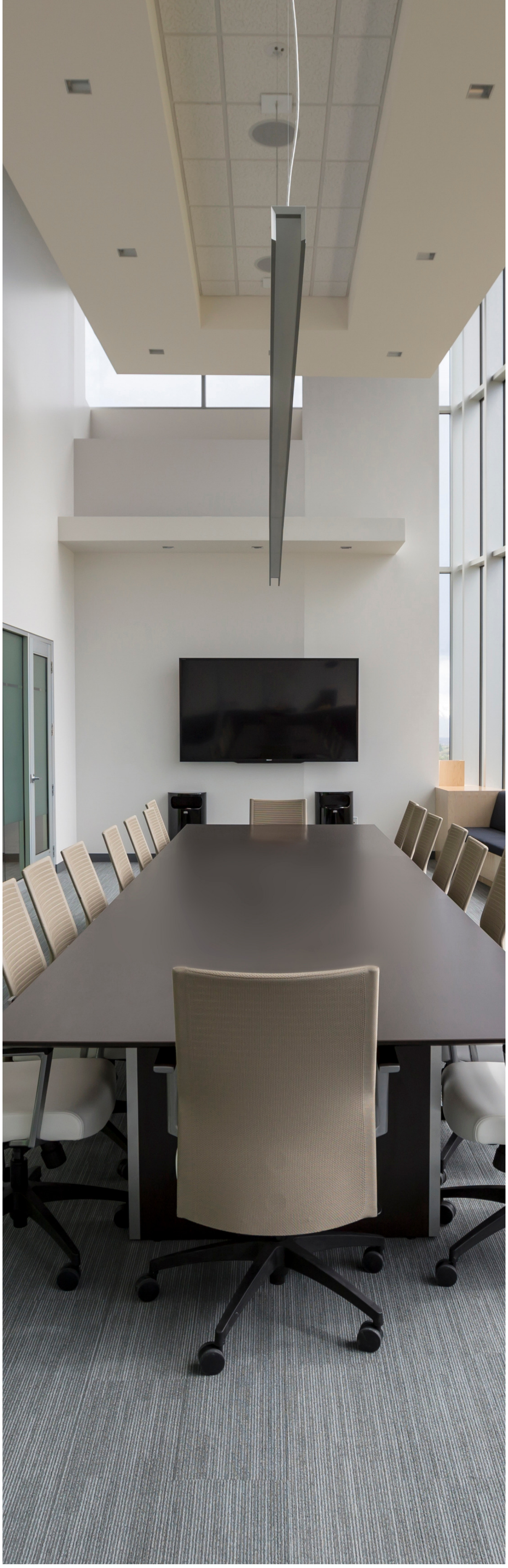
What do YOU think the mapping uncertainty should be, at this point of reading?

a) uncertainty of each single temperature measurement during mapping?
b) uncertainty of the average temperature in particular locations?
c) uncertainty of temperature in each of the locations in general?
d) uncertainty of the sample or product temperature in particular locations?
e) uncertainty of the sample or product temperature anywhere in the enclosure.

It really could be anything. All the uncertainties from a) to e) are valid uncertainties with their own meanings...

WHAT DO YOU ACTUALLY CARE ABOUT?

We can safely assume that you care about the uncertainty of temperature of your sample or product more than the other kinds of uncertainties mentioned in the paragraph before. But the problem is that this kind of uncertainty is almost never stated in mapping reports. Actually, no kind of uncertainty is usually stated in mapping reports, but in cases it is, it is never the uncertainty of temperature of your sample or product. Mainly because that uncertainty would be big, and that might look bad for the temperature mapping provider. But that also means that it is hard, almost impossible, for you as a client to get the complete information from mapping reports.



EASY WAY TO ESTIMATE THE TEMPERATURE UNCERTAINTY OF YOUR PRODUCT

Well, the best way from now on would be to choose temperature mapping providers who would help you calculate the temperature uncertainty of your product or sample.

First criterion should be that it is already an ISO/IEC 17025 calibration lab for thermometer calibration which means they should understand uncertainties associated with temperature measurement in general. And the second criterion should be that they are willing to meet and discuss with you the impact of the mapping uncertainty on your samples and products in a simple and understandable way. Metroteka is one such temperature mapping provider, but we are sure there should be others. The world is a big place after all.

But is there a way you can estimate the temperature uncertainty of your product from your past mapping reports? Fortunately, there is. It would just be a rough estimate, but probably not more that 20-30% different than the more realistic and more seriously calculated value.

To estimate the temperature uncertainty of your product or sample we must take into account these simple facts:

1.Temperature uncertainty of your product must include at least the calibration uncertainty of the probes or loggers used for mapping.

2.The temperature of your product depends on its location in the enclosure. There are warmer and colder parts of your enclosure and this influences your quantification of the doubt of product temperature in general.

3.The temperature of your product changes in time because the air temperature in your enclosure changes in time, and that also influences your doubt.

4.The temperature of your product is a little bit dependent even on the product itself because different products are heated and cooled differently by thermal radiation. (Think of black and white cars during summer.)

In the end an approximation valid between 0 °C and +50 °C for the temperature uncertainty of your product in the warehouse, vehicle, fridge, incubator or some other enclosure would be:

$$U(k=2) = 2 * \sqrt{\frac{U_{probe}^2}{4} + \frac{(T_{av,max} - T_{av,min})^2}{12} + \frac{(T_{max,unst} - T_{min,unst})^2}{12} + 0,03}$$

where the parameters from the equation are:

U_{probe} ... the expanded (k=2) measurement uncertainty of the temperature probes or data loggers used for mapping (ask your mapping provider if they included error corrections for each of their probes or loggers; if they did not, then instead of the expanded (k=2) measurement uncertainty from the certificate you should use the sum of that uncertainty and the absolute value of the error for the probe/logger for which the error is the greatest)

$T_{av,max}$ ... the hottest average temperature in your enclosure

$T_{av,min}$ ... the coldest average temperature in your enclosure

$T_{max,unst}$ ... the highest temperature of the location with the most unstable temperature in your enclosure

$T_{min,unst}$ ... the lowest temperature of the location with the most unstable temperature in your enclosure

All of those parameters you should be able to find in any temperature mapping report from the past, and now you can use them to estimate the "elusive" temperature uncertainty of your product or sample. Expect much higher uncertainties than the calibration uncertainties for temperature probes or data loggers used for the mapping.

For some particular, let us say - warehouse, it could be something like:

$$U(k=2) = 2 * \sqrt{\frac{(0,15)^2}{4} + \frac{(22,9-18,7)^2}{12} + \frac{(23,6-17,4)^2}{12} + 0,03} = 4,3$$

Note: The third factor under the square root (with 23.6-17.4 difference) is probably an overstatement because air temperature varies more than your product temperature. But if you don't have an information how much more (which you usually don't have, because it is dependant on many factors), you can just be aware that you are on the "safe side" with this approximation. On the other hand, it compensates for the simplification of the approximation and the fact that there are many more small influences on mapping uncertainty not being taken into account (like long-term drift of data loggers, for example).

Note: The fourth factor (0.03) comes from the estimate of the influence of thermal radiation between 0 °C and +50 °C.

Then calculate the average of all average temperatures (in individual locations) in your enclosure.

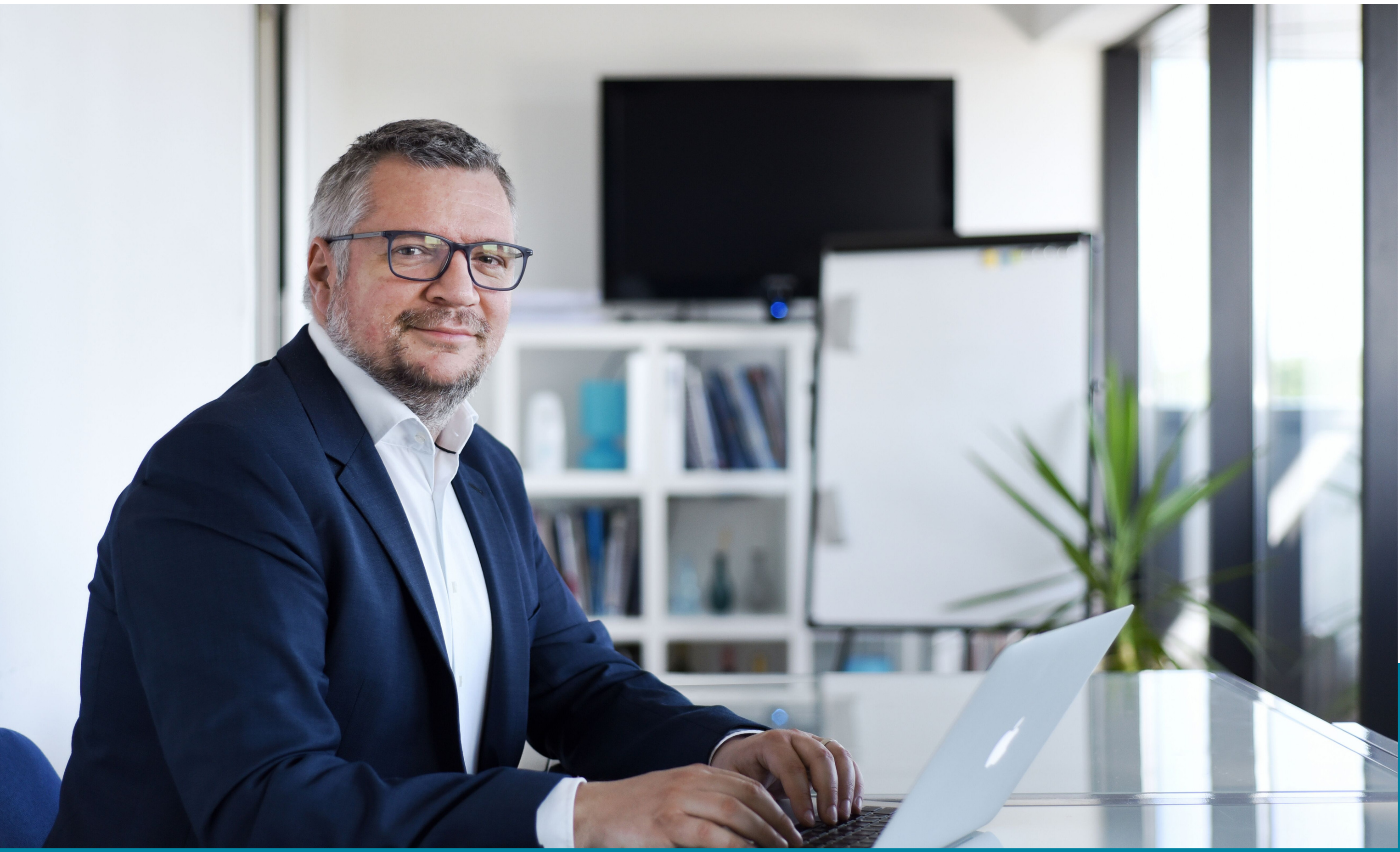
If the average of all average temperatures in your warehouse is for example +20.4 °C, that means that you can be 95% sure that the temperature of your product is between (+20.4-4.3) °C and (+20.4+4.3) °C. In other words - between +16.1 °C and +24.7 °C, no matter where, when, and no matter what kind of product it is.

Generally, of all kinds of enclosures, warehouses should have the biggest uncertainties, which is what you probably expected.

As we said before, this is only an approximation, but can be very useful when you don't have a better support of your mapping provider, and you want to know the uncertainty of your actual product or sample in your temperature-controlled enclosure.

We will be happy to hear from you and to discuss specific temperature mapping reports you get from your providers and what they actually mean. Feel free to contact us anytime at lab@metroteka.com.

About author



Siniša Prugovečki is the general manager and former head of laboratory of Metroteka. For many years he didn't know he was born on World Metrology Day, but without that knowledge he still fulfilled his destiny by moving from his graduation field of astrophysics to metrology. He founded Metroteka, which started as a ISO/IEC 17025 accredited calibration laboratory in 2009., and then in just a few years became the biggest calibration and temperature mapping provider in Croatia and one of the calibration laboratories with largest scope of accredited services in Europe. He is also the founder of LorisQ, a U.S. company which provides a digital cloud platform for managing the maintenance of measuring and monitoring equipment.

XX=95%, YY= -0.17, ZZ = -0.03