

Metrology in Life Science Environments

Good Practices for Calibrating and Managing Sensing Instruments Used in GxP-Compliant Applications

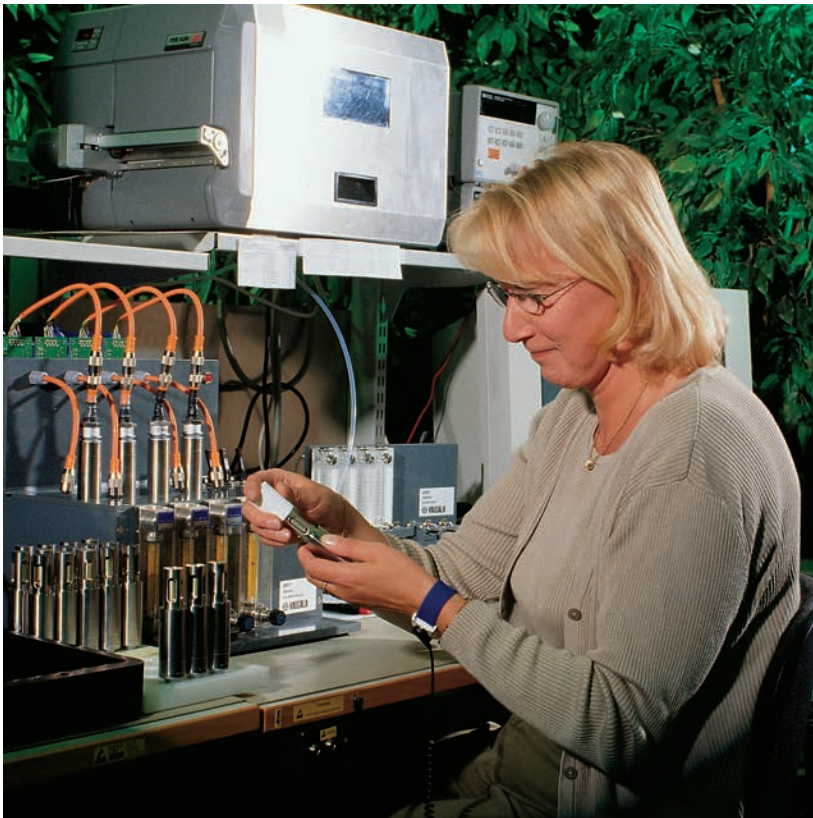


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Calibration & Metrology Terms

Accreditation

The process whereby an independent but qualified agency audits and certifies a site, its processes, and staff capabilities to a recognized standard such as ISO 17025. I.E.: A2LA American Association for Laboratory Accreditation.

Calibration

The formal definition by the International Bureau of Weights and Measures is: “Operation that, under specified conditions, in a first step, establishes a relation between the quantity values with measurement uncertainties provided by measurement standards and corresponding indications with associated measurement uncertainties (of the calibrated instrument or secondary standard) and, in a second step, uses this information to establish a relation for obtaining a measurement result from an indication.” Essentially calibration is a comparison of measurements: one measurement is a standard reference known to be correct; the other is the unit under test.

Calibration Frequency

The interval between instrument calibrations. These periods of time are determined by the conditions and the process requirements in which the instrument is used.

International Standard

A measurement that is internationally recognized as the standard of the quantity concerned.

Measurement Uncertainty

Without this parameter a measured value is incomplete. According to the NPL’s “Beginner’s Guide to Uncertainty of Measurement”:

*“Uncertainty of measurement is the doubt that exists about the result of any measurement. You might think that well-made rulers, clocks and thermometers should be trustworthy, and give the right answers. But for every measurement - even the most careful - there is always a margin of doubt. In everyday speech, this might be expressed as ‘give or take’ ... e.g. a stick might be two metres long ‘give or take a centimetre’.”**

Quality System or Quality Management System

This includes the site, infrastructure, responsibilities, procedures, processes and resources for implementing quality practices.

Resolution

The smallest reading unit provided by an instrument.

Tolerance

The limit beyond which an instrument is no longer considered accurate and reliable.

Traceability

The chain of references that can be traced to a primary measurement reference to control and document measurement uncertainty. I.E.: The National Institute of Standards and Technology (NIST) is the Measurement Standards Laboratory in the United States.

* Source: “A Beginner’s Guide to Uncertainty of Measurement” by Stephanie Bell, published by NPL, retrieved 4/28/14.
http://publications.npl.co.uk/npl_web/pdf/mgpg11.pdf

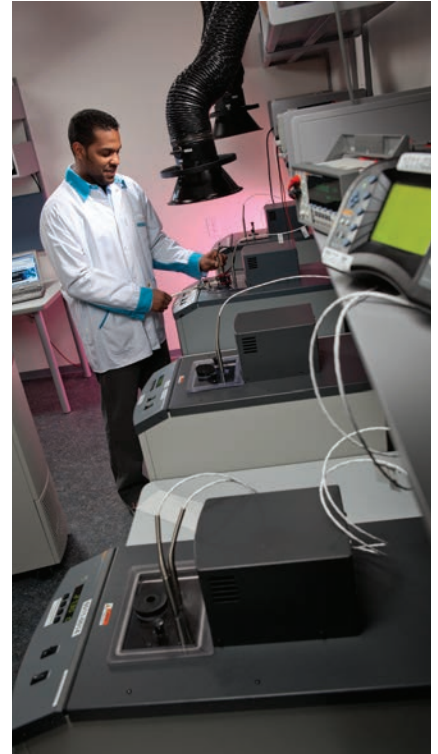
Calibration Risk Assessment

Where Do You Start?

What is Risk & How to Assess it

According to ICH-Q9, Risk Assessment involves “the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards.” Performing a Risk Assessment for product impact from out-of-specification sensing instruments is now an expectation in regulated environments. To execute a realistic and justifiable Risk Assessment, you need to understand the probability of occurrence of an adverse event, as well as the detectability and severity of the risk event.

To assess risk, we need to imagine a situation where the adverse event has occurred. Then we can study what might be affected. In the case of sensing instruments, let’s imagine a situation where the instrument in question was last calibrated six months ago. Calibration is now due and you find that the instrument is out-of-specification. Let’s be more specific and say the instrument is a thermometer that should be measuring at $\pm 0.5^{\circ}\text{C}$, but we find that it is off by $+1.5^{\circ}\text{C}$. This means that there is a $+1.0^{\circ}\text{C}$ deviation. However, we actually have no data to tell us exactly when it went out of calibration. It’s easy to think it was a slow change and it just slid gradually towards $+1.0^{\circ}\text{C}$. However, the truth is we actually don’t know; it could have been out by $+3.0^{\circ}\text{C}$ a week ago.



Quality Control & CAPA

The first thing we need to do is quarantine the instrument, and then investigate the situation. The instrument should not be adjusted or placed back into service until we know what went wrong. Likely we will want to open a Corrective Action and Preventive Action (CAPA) process so that we can determine, if possible, why the instrument has gone out of specification. This knowledge may help prevent reoccurrence. Additionally, knowledge derived from investigation can help us determine if there was any impact on product quality.

In a best-case scenario, we find out what went wrong. In this case, we can place the failure at a specific point in time, such as during a cleaning or maintenance event. However, it’s more likely that we won’t ever know with certainty. But the nature of the instrument going out of specification, combined with information from the instrument vendor, can help us understand the failure enough to make some good guesses as to whether the failure was gradual or instantaneous, constant or fluctuating, or if it was constantly one-directional or flipping in both directions.

Risks to Product Quality

Determining the effect of a risk event on product quality is more difficult. We really need to understand our manufacturing process, the properties of the product, and how a change in the variable under investigation (in this case $+1.0^{\circ}\text{C}$) will affect the product at that point in its manufacturing lifecycle. Sometimes we get lucky and see that there was no impact (such is the case if we know that the deviation was in only one direction and was not variable). For instance, if the specifications for the process are $2-8^{\circ}\text{C}$ and a review of the temperature history shows that the (failed) device gave us values of 4 to 7°C , then we can assume that although the device was reading high, the actual values would have been $3-6^{\circ}\text{C}$, and therefore within specification.

However, sometimes we require deeper investigation. In this case, background information can help so that we draw on similar investigations and other information (such as stability data) to determine the impact. We may need to pull retained samples from past lots (during a time when the device could have been out of calibration) and test them to see if there was any effect. We may actually need to do a recall if we discover a meaningful quality issue.

**See “ICH Harmonised Tripartite Guideline Quality Risk Management Q9” at ICH.org
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q9/Step4/Q9_Guideline.pdf Retrieved 4/1/2014*

Committed to Quality? Watch for Early Warnings

Sometimes we need to accept that we might not find the answer. If, however, we find enough information to determine whether or not there was a negative effect on the product, we can protect the health of consumers. The ability to perform this sort of analysis is dependent on a few important factors:

1. Good diagnostics, perhaps with vendor support, to determine the cause, nature, and timing of the failure.
2. Solid process knowledge of the product will guide an investigation to determine if there was any quality impact. This is much easier with a robust quality system with well-documented product history.

Remember that if the process parameters are being continuously monitored and alarmed correctly, there are a few things that will indicate an early warning that there is an out-of-specification instrument. There may be multiple nuisance alarms or a linear change in value trends that is noticeably different from the trends seen immediately after the last calibration. Typically we need to go back to the last calibration and determine the latest monitored values and then compare trends over time. We address this more in more depth in the next chapter: “Instrument Tolerances: Manufacturer vs. Process.”



Instrument Tolerances

Manufacturer vs. Process

The Costs of Out of Tolerance Instrumentation

When using the instrument maker's tolerance, there is often a higher risk of an "Out of Tolerance" appearing on a calibration certificate; this costs money. Consider the following scenario: You have just received back from calibration the set of temperature sensors used to monitor a warehouse. Most of the instruments have been shown to be within manufacturer published tolerances. A few of the instruments, though, are listed as out of tolerance. You now have some work to do.

The out-of-tolerance results need to be fully documented, including a full investigation into the use history of the instruments since their last calibration. All of this is required by your Quality Management system to ensure that no product has been negatively affected by the larger than expected errors in the readings. Say your investigation shows that the instrument manufacturer's tolerances for the instrument are tighter than the tolerance required to monitor the warehouse. All of the out-of-tolerance points from the calibration certificates show that the readings of the instruments are within the tolerances for the warehouse monitoring system; therefore, no products have been negatively affected.

Selecting Instruments Based on Tolerances

This is a common situation that many of us find ourselves dealing with: a difference between manufacturer tolerances and process tolerances. In many cases we have selected our process monitoring instruments based on more than just the measurement tolerances of an individual instrument.

We may have chosen an instrument with higher accuracy for a number of reasons, including:

- *Compatibility with existing monitoring systems*
- *Lower risk of an out-of-tolerance reading affecting products*
- *Better overall value*
- *The manufacturer was on the Approved Vendor List*

Whatever the reason, the manufacturer-specified tolerances are often significantly tighter than our process requires. This leaves us in a situation where we have a higher risk of an "Out of Tolerance" appearing on a calibration certificate than if the instrument had a tolerance based on the process tolerance. This in practice is costing extra money either due to an increase in calibration costs, a shortening of calibration intervals, or an increase in investigations due to out-of-tolerance conditions.

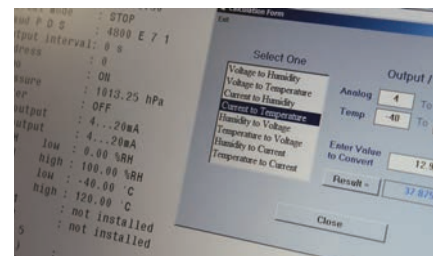
Customize Your Calibration to Your Process

There is a potential solution that will help contain costs and not increase the risk of negatively affecting product quality. When sending instruments out for calibration, define a tolerance based on the process tolerance and have the calibration laboratory use this when evaluating for in- or out-of-tolerance. The process tolerance is typically the more relevant limit than the manufacturer specification. The process tolerance was established not by looking at what the instruments are capable of performing, but by looking at the requirements of the process. It is this limit that tells us when product may be affected and is therefore a more relevant tolerance to refer to when determining whether a measurement instrument is meeting the requirements of the process.

Most calibration laboratories default to using manufacturer specifications when performing this evaluation. But, this is only because the calibration laboratory does not know what the process limits are for an instrument unless we tell them; the only information that is readily available at the calibration laboratory is the manufacturer specification. When selecting a calibration vendor, ask if they have the capability to use customer-specified acceptance limits.

Process Limits Are Critical

In most cases, this should not pose a significant problem. When sending the instruments for calibration, include instructions for the values to use for acceptance limits. Using customer defined limits instead of manufacturer specifications provides a low-risk and low-cost mechanism for reducing the extra work caused by out-of-tolerance events. It provides a more relevant analysis of the calibration results and will limit the need to reduce calibration intervals in case the equipment is not meeting manufacturer specifications.



Three Ways to Wreck an Otherwise Excellent Calibration

The top three calibration issues listed below aren't new problems, but in our experience, they are definitely issues that deserve diligence.

Adjusting Before Reviewing the Customer's Requirements

Unfortunately, this happens. Sometimes, if the device has built-in memory where the information exists, you can take a step back and adjust to the original calibration. But, with most instruments, once you've adjusted, you can't go back. This can be a bad situation, especially if you struggle with item #3, inadequate standard checks.

Transcription Errors

Any manual process comes with the risk of human error. It's easy to put the decimal in the wrong spot. There are two main safeguards: 1. Put checks in place. Analyze the results carefully to see if they are realistic, and, 2. Automate processes as much as you can to eliminate data entry.

Inadequate Reference Standard Checks

Reference standards drift too. The quality of your standards depends on your knowledge of the uncertainties of the device, its type of instrument and susceptibility to drift, and your own operating environment. Measurement and calibration are simply not meaningful without understanding the measurement uncertainties of your standard.

How to Calibrate with Saturated Salts as a Reference

Field Calibration Practices

Perhaps you have a requirement to calibrate humidity measurement instruments outside of a controlled laboratory area. For example, you may have hygrometers installed in several locations around a critical storage area or in a continuous process where removal of the instruments is not practical, or is too expensive and time consuming.

When making decisions about field calibration processes, a key decision is whether to perform a single-point or a multiple-point calibration. To make this decision based on good practice, first consider your parameters. If the operating conditions contain a wide range of humidities or temperatures, a multi-point calibration is prudent. This is especially true in a critical or regulated environment. Further, you must be able to articulate and defend calibration methods to an auditor or regulatory agency.

Humidity References

If multi-point calibration is selected as the method of practice, your next decision is how best to generate the multiple points of humidity as references. You could choose to purchase an expensive humidity generator that relies on two pressures or two temperatures, or both. These types of generators are an excellent choice with low uncertainties and high reliability. However, if you don't have the budget and are comfortable with higher uncertainties and lower reliability, saturated salts are a workable alternative.

Certain types of salt will generate specific relative humidity. In 1977 Lewis Greenspan published a list of salts and the relative humidity they generate titled, "Humidity fixed points of binary saturated aqueous solutions."* See below for a summary table:

Table 9. Equilibrium relative humidities generated over saturated solutions of a selection of salts.

| Saturated salt solution | Temperature °C | | | | | | | | | | |
|-------------------------|-----------------------|----|----|----|----|----|----|----|----|----|----|
| | 0 | 5 | 10 | 15 | 20 | 25 | 30 | 35 | 40 | 50 | 60 |
| | Relative humidity (%) | | | | | | | | | | |
| Potassium sulphate | 99 | 98 | 98 | 98 | 98 | 97 | 97 | 97 | 96 | 96 | -- |
| Potassium nitrate | 96 | 96 | 96 | 95 | 95 | 94 | 92 | 91 | 89 | 85 | -- |
| Potassium chloride | 89 | 88 | 87 | 86 | 85 | 84 | 84 | 83 | 82 | 81 | 80 |
| Ammonium sulphate | 82 | 82 | 82 | 82 | 81 | 81 | 81 | 80 | 80 | 79 | -- |
| Sodium chloride | 76 | 76 | 76 | 76 | 75 | 75 | 75 | 75 | 75 | 74 | 75 |
| Sodium nitrite | -- | -- | -- | -- | 65 | 64 | 63 | 62 | 61 | -- | -- |
| Ammonium nitrate | -- | -- | 75 | 70 | 67 | 64 | 60 | 53 | -- | -- | -- |
| Sodium dichromate | 61 | 59 | 57 | 57 | 55 | 54 | 53 | 51 | 50 | 49 | 47 |
| Magnesium nitrate | 60 | 59 | 57 | 56 | 54 | 53 | 51 | 50 | 48 | 45 | -- |
| Potassium carbonate | 43 | 43 | 43 | 43 | 43 | 43 | 43 | -- | -- | -- | -- |
| Magnesium chloride | 34 | 34 | 33 | 33 | 33 | 33 | 32 | 32 | 32 | 31 | 29 |
| Potassium acetate | -- | -- | 23 | 23 | 23 | 23 | 22 | -- | -- | -- | -- |
| Lithium chloride | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 |
| Potassium hydroxide | -- | 14 | 12 | 11 | 9 | 8 | 7 | 7 | 6 | 6 | 5 |

The values listed in the table are taken from papers by Greenspan (1976), O'Brien (1948), Wexler (1954) and Young (1967). Where gaps are shown in the table, no reliable data are available.

*See "Humidity Fixed Points of Binary Saturated Aqueous Solutions" by Lewis Greenspan, <http://www.mikrocontroller.net/attachment/158694/V81.N01.A06.pdf> Retrieved May 7, 2014



Traceability

In all regulated environments, traceability is a key concern. Is it possible to claim traceability based on the physical principle of the salt? In many ambient conditions, labs and storage areas, this practice could be defended so long as you document the process for maintaining and using the saturated salts in accordance with an accepted standard such as ASTM E104-02 (2012).

However, a more accepted method would be to use a reference hygrometer to achieve traceability to a national standard whereby the saturated salt is simply the medium to generate the calibration environment. Saturated salts require a lot of maintenance and patience to use properly, but they are an inexpensive and efficient means of creating multiple points of relative humidity.



Determining Measurement Uncertainty

If you manage controlled and regulated environments you are likely concerned with the uncertainty of measurement associated with the results obtained from the units. What factors influence the measurements obtained from a device?

With humidity instruments, which are prone to drift, it's important to understand the factors that have the greatest affect on measurement uncertainty. What factors are most heavily weighted when deciding how often to calibrate, or what uncertainty your process can sustain? Do we look at the stability of the unit itself between calibrations, the ambient temperature, errors associated with the positioning of the device, or sufficient flow across the sensor?

Overall Measurement Uncertainty

It is important when using an RH device to fully understand all the components that contribute to the overall measurement uncertainty. The performance and calibration uncertainty of a measuring device are just two factors that influence the total measurement uncertainty. Remember, each and every measurement has an associated uncertainty. A device used to make a measurement in one specific application may yield a different uncertainty when used in a different application.

In practice, measurements made outside of a calibration laboratory are subject to a huge variety of variables that are not easily quantified. Factors such as air flow, temperature gradients, temperature stability, and radiant heat sources may all contribute significant uncertainty to a measured value. These might be obvious, but also consider factors such as the proper use of the product, knowledge of the product and its applications, operator competence and alertness, unnoticed damage to the measuring device, environmental conditions outside of the chamber, and spurious electromagnetic signals (large electric motors, walkie-talkies, etc.).

Sources of Error are Highly Contingent

Coming back to the original question of “are these factors significant sources of error?” there is no single correct answer. Specific circumstances and an understanding of the purpose of the measurement will go a long way toward answering this question. For example, a standard bathroom scale is adequate for weighing yourself, but definitely inadequate for weighing 100 mg of an active pharmaceutical ingredient. This is why metrology cannot be 100% proceduralized and why we have metrologists.

Another example: if the measurement instrument is in the direct airflow of an HVAC outlet, it may see a very different temperature (and therefore relative humidity) than if the sensor is in a sheltered space. Heat generating equipment nearby or even people being located immediately next to a sensor can cause changes in readings. Actually, people tend to have a large affect, especially in low relative humidity environments because we are humidity sources (just breath on an RH sensor to see a rapid change). All of these outside influences should be considered when taking a measurement to ensure that the effects are minimized or at least understood.



Conclusion

Where do we go from here?

Now that we've highlighted key items to consider when working with sensing instruments, how do we apply this knowledge?

Important Take-aways

1. Risk Assessment & Specifications – what are the inherent risks of a process? What is the “real” tolerance of the process? Remember, it's most likely not the tolerance the manufacturer provides. It's always possible to request different tolerances (just not ones better than the manufacturer's) on the calibration certificates. Use values that are more representative of the tolerance of the process. This will, in most cases, prevent unnecessary “out of tolerance” conditions on the calibration report, thus preventing CAPA, long investigations, production holds, etc.
2. Understand the environment and how it can affect calibrations. It's critical for us to educate ourselves on our environments and processes. Further, it's even more important that we observe the calibration procedures used by others (mainly when requesting or performing on-site calibrations). It's easy to follow a manual indicating how to calibrate a product. However, it's much more difficult to understand how the *environment* can lead to incorrect calibrations.
3. Sources of error. It's important to identify the cause of the error, where it occurred, and what the effects of the error are. In many cases, the errors have simply been overlooked. Whatever the reason, identifying them is critical.

Focusing on the items highlighted in these articles can be the start to creating more reliable processes and improved performance outcomes.

Resources & Further Reading

ICH Quality Guidelines

Q9 - Quality Risk Management and Q10 – Pharmaceutical Quality Systems

- <http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html>

Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme

Annex 20 to the PIC/S GMP Guide

- <http://www.picscheme.org/publication.php?id=4>

A Recommended Model for risk-based Inspection Planning in the GMP Environment

- <http://www.picscheme.org/bo/commun/upload/document/pi-037-1-recommendation-on-risk-based-inspection-planning-copy2.pdf>

NIST

Humidity Fixed Points of Binary Saturated Aqueous Solutions

- http://nvlpubs.nist.gov/nistpubs/jres/81A/jresv81An1p89_A1b.pdf

HKITC

Evaluation of Measurement Uncertainty from Hong Kong's Innovation and Technology Commission

- <http://www.itc.gov.hk/en/quality/hkas/faq.htm>

UKAS

“The Expression of Uncertainty and Confidence in Measurement” from the United Kingdom Accreditation Service

- http://www.ukas.com/library/Technical-Information/Pubs-Technical-Articles/Pubs-List/M3003_Ed3_final.pdf

NCLSI

A Comparison of ANSI/NCSL Z540-1-1994 Part I and ANSI/ISO/IEC 17025:2000

- https://www.ncsli.org/ip/z1-17/c/a/p/Comparison_of_Z540_to_17025.aspx?hkey=ad1f8126-fc40-428a-91d8-dd6a21fa25ba

ASTM

ASTM E104 – 02 (2012) Standard Practice for Maintaining Constant Relative Humidity by Means of Aqueous Solutions

- <http://www.astm.org/Standards/E104.htm>



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