Webinar Q&A

Two industry experts bring combined experience of over four decades in validation, mapping, and monitoring to discuss best practices for controlled-temperature chambers in GxP applications.

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Presenter Bios

Paul Daniel

Vaisala Sr GxP Regulatory Compliance Expert

Paul Daniel has worked in the GMP-regulated industries for over 20 years helping manufacturers apply good manufacturing practices in a wide range of qualification projects. His specialties include mapping, monitoring, and computerized systems. At Vaisala, Paul oversees and guides the validation program for the Vaisala viewLinc environmental monitoring system. He serves as a customer advocate to ensure the viewLinc environmental monitoring system matches the demanding requirements of life science and regulated applications. Paul is a graduate of University of California, Berkeley, with a bachelor's degree in biology.

Connect with Paul on LinkedIn

Nathan Roman

Genesis AEC Director of Validation

Nathan Roman is a highly accomplished expert in equipment commissioning, qualification, and validation, with over 22 years of hands-on experience in the Health & Life Science industry. In his role at Genesis, he successfully manages a team of experts, develops business strategies, and oversees the growth of his practice, all while delivering exceptional services to a diverse portfolio of clients.

With expertise in cGMP compliant facilities, R&D labs, and temperature mapping, Nathan ensures regulatory compliance. He excels in placing temperature sensors in control chambers, streamlining processes for faster delivery. Nathan aids professionals in achieving compliance, providing training, collaborating with vendors, and offering temperature mapping guidance. An industry thought leader, he empowers clients with mapping knowledge, sensor placement strategies, and equipment qualification expertise.

Connect with Nate on Linkedin

The following questions came from our webinar: “Controlled temperature chambers: Qualification, mapping & monitoring”. The recorded webinar is available for viewing, at no cost. The presenters have answered all questions below. The questions have been edited for clarity, and in some cases, combined if they were very close to other questions.

Calibration, Validation, Qualification

What are the ideal intervals for calibration and mapping activities?

Paul: For each instrument, recalibration frequency of a fixed monitoring or control sensor should be performed based on the manufacturer's recommendation. One-year intervals are typical. However, you should modify this period based on the calibration results. You may need to do it more often (such as every 6 months), or you may be able to extend the calibration period to 18 months.

But for recalibration of the mapping sensors, that is a different story. You want to have confidence that the sensors are in calibration before and after your study. You may want to do this before and after every study, especially if you are using a sensor with high drift or high failure rates such as a thermocouple. With a high-quality data logger, you can use a longer period. But even then, I would not go more than 3 months.

For mapping, we are talking about pre-cal and post-cal. This can be a simple check to verify that the sensor is within your accuracy specs, such as 10 consecutive readings of the mapping sensor while placed directly adjacent to a temperature standard. Or it can be a full factory calibration. It really depends on the type of sensor you are using. Whatever your pre-cal or post-cal process, it needs to be a defined and approved procedure, so it is performed the same way every time. This procedure should be evaluated by a metrologist to ensure that it limits uncertainties and will give you an accurate comparison. This doesn't mean that it needs to be high-tech, expensive, or time consuming, but it does need to be effective and documented.

Nate: The ideal time duration for calibration and mapping activities depends on the specific application, risk assessment, and regulatory requirements. Calibration is typically performed every 6 months to annually.

Mapping duration can vary depending on the stability of the area being mapped or the equipment/space being mapped. A common practice for Freezers, Refrigerators and Incubators is to perform a 24-hour study to capture daily temperature fluctuations.

Typical Mapping Study Durations:

- CTU: 24 hours
- Cold-room: 72 hours (3 days)
- Warehouse: 7 days (168 hours)

Any tips on establishing calibration/process tolerances for control probes in CTU's?

Other questions: Do you rely on studies to challenge the amount of offset/error a control probe can have while maintaining distribution throughout chamber per user requirement? Do you have any experience in using monitoring probe data to characterize chamber performance and then relying on periodic review of this data to trigger chamber requalification, instead of relying on interval-based requalification (e.g., every 2 years)? If you have seen that in application, do you have any tips on establishing control limits for monitoring probes so that, when a limit is exceeded, it would trigger chamber requalification?

Paul: From a mapping perspective, all you need to do is be sure that the control probe is calibrated. As far as how best to calibrate it, I would defer to the manufacturer of the CTC/CTU. Mapping is not meant to challenge or verify the calibration of the control probe. I like to say, "Calibrate or Validate, don't do both". So, trust the calibration of the control probe, and verify it has been calibrated as part of your IQ of the CTC/CTU.

Nate: When it comes to establishing calibration or process tolerances for control probes in CTUs, it is important to consider the manufacturer's recommendations first. They would have done extensive testing during the design and development phase of the equipment to determine optimal calibration parameters.

Mapping studies are indeed not designed to challenge the calibration of the control probe, but to assess the temperature uniformity and stability within the unit under different conditions. That said, it is critical that the control probe be calibrated, and its calibration status checked as part of the Installation Qualification (IQ) of the CTU.

Regarding your second question, there is growing interest in the industry to move towards data-driven decisions for requalification events. While traditional practice has been requalifying chambers on a set interval (e.g., every 3-5 years), some companies are now leveraging data from monitoring probes to determine when requalification is needed. This can be a more efficient and effective way to ensure your chambers are always operating within their validated state.

Typically, to establish control limits for these monitoring probes, you would conduct a thorough analysis of historical data, identifying any trends, maximal, minimal, and general variation in the temperature data. This analysis would help you set control limits that are realistic and meaningful, taking into consideration the specificities of your operations and the sensitivity of your products. If these limits are exceeded, it would trigger a requalification event. It is important to note, however, that this approach should be justified through a robust risk assessment process. It is also advisable to define and document this process in your company's policies or SOPs to ensure consistency and compliance.

Is there a difference between Qualification and Validation?

Paul: Yes. Validation is for processes. Qualification is for equipment used in a process. In this case, the process is controlled-temperature storage. By performing a temperature mapping study, we are qualifying the equipment, usually as part of an Operational Qualification (OQ).

Nate: Yes. Two words, same concept, used interchangeably but there are differences between them. Validation and Qualification are essential components of the same concept. The term qualification is normally used for equipment, utilities and systems, and the term validation is used for processes.

Here is a Rule of Thumb:

- Things are qualified (equipment, instruments, software)
- Process/Procedures (the way we use things) are validated

Essentially, qualification is part of validation.

If interested in learning more about qualification and validation or temperature mapping, follow me on LinkedIn for continued Validation and Qualification tips and industry guidance.

Here is a LinkedIn post I wrote on this topic: Qualification Vs. Validation

And a related post: Verification Vs. Qualification Vs. Validation

How can we avoid unnecessary alarms due to door opening? Is a one-point calibration at the operating temperature sufficient, or should a multi-point calibration be done for the monitoring sensor?

Paul: I recommend multi-point calibration because it is more accurate and has a higher chance of satisfying auditors. I do believe it is okay to do a point-of-use check at a single point, and if the sensor passes the single-point verification, that could justify extending the calibration interval. But if the sensor fails the single point check, then I would go for multi-point calibration with adjustment. Note that this advice only holds if you have a process for a single point check that controls uncertainty. Seeing that it's almost the same amount of work, you might as well do a multi-point.

Vaisala has just developed an accredited field calibration service for our monitoring sensors. Note that, if a sensor needs adjustment, it goes to the factory and gets a multi-point calibration. The only advantage here is the time savings in not needing to remove, ship, and replace the sensor to allow for calibration.

Nate: Multi-point calibration is recommended for monitoring sensors, as it provides a more accurate representation of the sensor's performance across the entire operating temperature range.

If you verify that the data logger needs adjustment, what do you recommend your customers to do regarding impact between calibrations?

Paul: No one likes this situation. When you find any instrument out of calibration, you need to do an investigation (often called a deviation investigation or report) to determine the impact. You need to determine if the out-of-cal device caused any quality issues. For mapping, a proactive approach is to write into your protocol that a specific percentage of your mapping sensors can fail (malfunction, bad calibration, etc.) This allows you to fail a sensor due to the bad post-cal, and not have it affect your study.

Nate: As Paul said, when a sensor is found to be out of calibration, it is important to investigate its impact. Including a provision in the mapping protocol that accounts for potential sensor failures allows for the identification and removal of sensors with calibration issues without affecting the overall study. Conducting a deviation investigation helps assess the impact on data quality and integrity. Corrective actions should be taken to address any identified issues and maintain compliance with regulations and quality standards.

Can you direct me to guides that apply to freezer qualification?

Nate: Yes, there are guidelines for freezer qualification such as the WHO Technical Report Series No. 961, Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products. This report provides recommendations for the storage and transport of pharmaceutical products that are sensitive to time and temperature. Section 4.7 of this report specifically covers freezer qualifications.

You can also refer to the USP (United States Pharmacopeia), JP (Japanese Pharmacopoeia), EP (European Pharmacopoeia), and ICH (International Council for Harmonisation) guidelines. These guidelines may provide specific requirements and recommendations for validating and qualifying freezers. The ISPE Good Practice Guide on CTC Mapping and Monitoring also provides recommendations on qualification requirements, temperature monitoring, and maintenance of temperature control chambers.

What reference documents are best to use for conducting the thermal validation in cold rooms or warehouses?

Nate: Here are a few resources:

1. World Health Organization (2015). Technical Supplement 8 to WHO Technical Report Series, No. 961, 2011. Temperature Mapping of Storage Areas. Pages 15-16

2. USP (2018). USP41-NF36 <1079>. Good Storage and Distribution Practices for Drug Products Pages 5-6

3. ISPE (2021) Good Practice Guide: Controlled Temperature Chambers 2nd Edition Pages 42-44

How can we determine the periods of recalibration or requalification?

Paul: Recalibration frequency of a fixed monitoring or control sensor should be performed based on the manufacturer's recommendation. Usually this is 1-year intervals. However, you should modify this period based on the calibration results. You may need to do it more often (such as 6 months), or you may be able to extend the calibration period to 18 months.

But for recalibration of mapping sensors, you need confidence that the sensors are in calibration before and after your study. So, you may want to do this before and after every study, especially if you are using a sensor with high drift or high failure rates such as a thermocouple. With a high-quality data logger, you can use a longer period. But even then, I would not go more than 3-months.

Nate: The period of recalibration and requalification depends on the manufacturer's recommendations, regulatory requirements, and historical data of the equipment's performance. Generally, recalibration is performed every 6 months or annually, while requalification frequency is based on a risk assessment.

Do you have recommendations for mapping transportation vehicles?

Paul: Mapping vehicles is a different process than mapping a chamber. While they are temperature controlled, they are uncontrolled in that the vehicles are being taken out of controlled locations and may get adjusted or experience conditions that make it hard to ensure that nothing has changed.

In this case we could do a temperature profile, which is basically the same thing as a mapping. Then you would combine this with monitoring the vehicle (and maybe the product too) while in transit.

Nate: Mapping temperature-controlled vehicles is indeed a unique challenge due to the variables associated with moving vehicles and external environments. Here are the recommended guidelines in brief:

- Perform a Temperature Profile: Similar to mapping (as Paul mentions)
- Continuous Monitoring: Continuous monitoring of both the vehicle and potentially the product is recommended (as Paul mentions).
- Pre-Use Checks: Prior to each journey, the vehicle should be checked to verify that it is operating specifications. This can minimize the risk of temperature excursions caused by equipment malfunctions.
- Staff Training: Ensure that personnel handling the products and vehicles are adequately trained in maintaining temperature control, responding to temperature excursions, and the importance of maintaining product integrity.

Remember, the aim is to ensure product quality, safety, and efficacy from the point of loading to the point of delivery, irrespective of external conditions.

How do you strike a balance between customer requirements and good practices?

Paul: If the customer wants to do more than best practice requires, that is their prerogative and their money. If a customer wants to do less than best practices require, I will inform them of best practices, and present arguments for adherence.

Nate: Striking a balance between customer requirements and good practices can sometimes be challenging, but it is crucial for maintaining quality service and a solid business reputation. Here are a few strategies to navigate this balance:

- Clear communication
- Education (as Paul mentions)
- Where possible, be flexible in meeting customer requirements
- Prioritize Quality and Safety
- Regularly review your service delivery to ensure it meets both customer expectations and good practices.

Mapping Study Design, Duration & Intervals

Is there any merit in using hybrid mapping, i.e., air temp sensors AND buffered sensors when mapping a CTC to reflect product temp as well as environment temp?

Paul: This is the best idea I have heard of to get directly comparable data for a given buffer type. If you plan to use the same buffer in every unit, then this might be worth your time. But it wouldn't be directly comparable between units because the time lag caused by the buffer will be different based on the rate of change in temperature. So, this could be an intellectual exercise. But, if you were able to aggregate enough data for your facility that you could have a reliable calculation of the effects of a standardized buffer, such that you could map bare sensors in air and know what the buffered temps might look like, this could be effective. But you would need a very controllable buffer, like our Vaisala aluminum Temperature Damping Block.

Nate: I can see how you would think that by using both, you are covering all bases. To me this would come across an engineering study or a technical report you would perform to gather data. The air temperature sensors show us how the chamber reacts to things like changes in external conditions or when the door is opened. And the buffered sensors help us understand how the product itself is handling the temperature inside the chamber over time.

The goal, of course, is to make sure the system can keep the conditions exactly right under all circumstances. Having both types of sensors working together gives us a fuller understanding of what's going on, making sure both the environment and the product temperatures are kept in check.

Please address cold room mapping and open door/recovery studies…

Paul: Cold rooms tend to be big, which means they are more like a cold warehouse. This means we place sensors as we do for a warehouse study, but with a higher density to deal with the added factor that they are cold rooms.

Nate: Based on industry best practices, the duration for open-door tests should be decided upon using a thorough risk assessment and considering the operational requirements of the specific cold room. Typically, these tests are conducted for a period that is long enough to represent a worst-case scenario, such as the door being left open for an extended period (5-15 minutes for example). Following this, the recovery time of the chamber is observed once the door is closed.

The objective of the open-door test is to assess the stability and resilience of the temperature within the chamber, in case of such events in real operation. It's not just about the open-door period itself, but also how quickly and efficiently the chamber can recover to the acceptable temperature range once the door is closed.

While it is beneficial to gather this data for potential future incidents, preventive measures such as employee training or automatic door-closing mechanisms should also be considered as part of a comprehensive risk mitigation strategy. If the cold room is used for storing critical products or materials, the effects of a door being left open could have significant implications, hence the importance of these tests.

Finally, I agree with Paul on referencing established guidelines such as the ISPE Good Practice Guide on CTC Mapping and Monitoring. They provide valuable insights and proven methodologies for conducting these tests effectively.

What type of mappings are you performing most often, and do you see the method of mapping changing in the future? I am curious especially about continuous mapping, which seems a more economic to get away from tradition mapping, by installing many more loggers from the start.

Paul: I agree. For warehouses especially, I think continuous mapping is the way to go. However, I don't think it makes sense for free-standing refrigerators and freezers. The jury is still out on large cold rooms and freezers, but I think anywhere there are high spaces that are hard to get to, we will see that continuous mapping is better. The danger here is that is that a company will not put in a full mapping density of sensors, then claim they are doing continuous mapping. Mapping requires a lot of data loggers, at least twice that of traditional monitoring. It will be very tempting for people to use fewer data loggers to save money and fail to have enough data loggers in the warehouse to achieve continuous mapping.

Nate: I echo Paul's insights on this topic. Continuous mapping, while resource-intensive at the outset, is becoming more common especially for large-scale controlled temperature units (CTUs) like warehouses or walk-in refrigerators and freezers. It offers benefits such as real-time data, ability to quickly identify and respond to temperature deviations, and reduced need for repeated, labor-intensive, and disruptive temperature mapping studies.

However, the initial set-up, including the installation of a significant number of sensors, can be costly and require careful planning. These sensors need to be evenly distributed throughout the unit to accurately monitor temperature across the entire space. As Paul notes, the risk of this approach is the potential for an inadequate number of sensors, which could compromise the quality and reliability of the data.

On the other hand, traditional or periodic mapping is still widely used, particularly for smaller CTUs. This method typically involves a comprehensive study with a high density of sensors, followed by regular remapping at determined intervals, based on a risk assessment. This approach, while less resource-intensive initially, can incur more labor and disruption over time due to the need for repeated studies.

In terms of the future, I foresee an increasing shift towards continuous mapping for larger CTUs due to its potential benefits in real-time monitoring and quicker response to deviations. However, this will likely

depend on advancements in technology and decreasing costs of sensors. Whichever approach is chosen, the key remains the same: adequate sensor density to ensure accurate and reliable temperature monitoring across the entire CTU.

How long so we perform an open-door test?

Paul: There are a whole set of tests, such as open-door and power failure tests, that typically occur during temperature mapping. Unless you have specifications for these situations, it technically can't be considered validation or qualification because there are no acceptance criteria.

Without a specification, such as "The CTC must stay within the specified temperature range for 5 minutes when the door is left open", then you have nothing upon which to base a Pass/Fail decision. So, these tests are only required if you have a specification for these types of failures.

You may want to do the tests anyway just to get the information, as it might be useful in the future if you do have a door open event. And it is easiest to do this while you have sensors in place for temperature mapping. However, if you anticipate that leaving the door open may be a problem on a critical process, it may be better to invest in training employees to close doors, or in some sort of automatic door closing mechanism.

If I were to do a door open test, and I did not have a specification, I would leave the door open until either 1) All the sensors are out of specification, or 2) The unit reaches an equilibrium with the door open where temperatures are no longer drifting. For more information, refer to the ISPE's "Good Practice Guide on CTC Mapping and Monitoring".

Nate: The door open test duration depends on your risk assessment and operational requirements. Typically, the test is performed for a period long enough to simulate a worst-case scenario (e.g., 5-15 minutes) and then observe the recovery time once the door is closed.

What if, during a thermal mapping study in a cold room, there is a temperature excursion? Do we stop or continue the study?

Paul: It is common to see excursions during mapping, especially if you have to map the cold room while it is in use. Excursions can also occur due to the normal cycling of the cooling units, or due to defrost cycles. In your protocol, you will usually have defined acceptable excursions with their time limits and max or min temperatures. With pre-defined acceptable excursions allow you to keep mapping and collecting data. Plus, the excursion data will be helpful in determining your corrective action if any is needed.

Nate: Experiencing a temperature excursion during a thermal mapping activity is common but I agree, can be a concern, but it doesn't necessarily mean you have to stop the mapping activity immediately. The appropriate response will depend on several factors:

- Severity of excursion
- Duration of the excursion
- Source of the excursion

In any case, all temperature excursions should be thoroughly documented, including when they occurred, their duration, their magnitude, and any potential causes. They should also be analyzed and discussed in the final report.

Is it a requirement to carry out chamber mapping loaded to full capacity?

Paul: First, a bit about loaded vs empty as a challenge. I think this depends on the type of unit and how it heats and cools. If temperature is maintained by blowing air, then a loaded unit is the best challenge. If the temperature is maintained by conduction (most freezers) than the best challenge is an empty chamber. Usually, I would think of the empty chamber as the OQ, and the loaded chamber as the PQ. Your choice should be based on your validation and mapping policies and procedures. As a reality check, usually I have mapped all chambers empty, unless I was forced to map with product inside simply because there was no place to put it.

A consultant will tell you to do both, as they make more money, and an auditor will probably ask fewer questions if you do both. But to directly address your question, the requirement is to prove the chamber is capable of maintaining the specified temperatures in the *intended operating conditions*. If your company plans on allowing the unit to be packed as full as possible, then you would want to map this condition.

Nate: Do both

In all seriousness, industry standards such as the USP <1079> Good Storage and Shipping Practices and EU Guidelines on Good Distribution Practice of Medicinal Products for Human Use recommend performing temperature mapping studies under worst-case conditions. Worst-case may included fully loaded chambers.

I include loaded chamber studies in my typical Performance Qualification studies for a refrigerator, freezer, incubator, walk-in, etc. The load is usually a representative load of what is seen during normal operation. The specifics of what load conditions to test under should be determined based on a thorough risk assessment that considers the specific needs and uses of the chamber, as well as any applicable regulatory requirements or industry standards.

Should location and load information be validated when performing temperature mapping on equipment such as incubators and stability?

Further question: There are changes in temperature and humidity values according to the product placement in the equipment. Therefore, how should product placement and load content be validated?

Paul: I think of the empty chamber as the OQ, and the loaded chamber as the PQ. Your choice should be based on your validation and mapping policies and procedures. As a reality check, usually I have mapped all chambers empty, unless I was forced to map with product inside simply because there was no place to put it. If you do map a loaded chamber, you should document the load. Ideally, load data exists in your validation protocol. In a perfect world, your protocol would already tell you what load to use based on known uses of the CTC or unit in question.

Nate: Paul brings up valid points about the decision being dependent on the type of unit, its operating mechanism, and practical considerations. The decision to map an empty vs. a loaded chamber is largely driven by the worst-case scenario for the specific unit under consideration.

Industry standards such as USP <1079> Good Storage and Shipping Practices and EU Guidelines on Good Distribution Practice of Medicinal Products for Human Use recommend performing temperature mapping studies under worst-case conditions. For some units, this may be when the chamber is empty, as the lack of product could lead to more significant temperature fluctuations. For other units, such as those which control temperature through air circulation, a loaded chamber could represent a worst-case scenario, as the load might obstruct airflow and create hot or cold spots.

When conducting a Performance Qualification (PQ), we typically use a loaded chamber to best represent operational conditions, with the load usually mirroring what would be seen during normal operation. However, an Operational Qualification (OQ) could be conducted on an empty chamber to validate its performance in the absence of any product load.

The specifics of what load conditions to test under should be determined based on a thorough risk assessment that considers the specific needs and uses of the chamber, as well as any applicable regulatory requirements or industry standards. This ensures a balance between operational practicality, worst-case scenario testing, and regulatory compliance. It's not so much about validating the load itself, but rather validating the chamber's performance under the conditions it will typically operate.

Please clarify: Is it required to monitor the outside temperature during mapping? Also, Is there a standard duration for Mapping Studies?

Paul: You can get standard mapping durations from the guidance from the WHO and the ISPE. But these are a starting place, and you may want to do a longer mapping study for critical applications. There may also be situations where it is convenient to map for longer - such as over a weekend. But the shortest mapping time for a small freestanding unit would be 24 hours, though I would do 72 hours. For a warehouse, the shortest would be 7-10 days, though I would do 2 weeks.

Nate: The standard duration for mapping depends on the specific application and stability of the area being mapped. A common practice for Freezer, Refrigerators and Incubators is to perform a 24-hour study to capture daily temperature fluctuations.

The typical Mapping Study Durations

- CTU: 24 hours
- Cold-room: 72 hours (3 days)
- Warehouse: 7 days (168 hours)

Due to operational constraints, we can only do part of the validation in the morning and the other part in the afternoon or the next day. Any advice on this?

Paul: I'm sorry I do not. The entire mapping needs to be continuous. If you have a 48-hour mapping required, you cannot break this up into parts.

Nate: When it comes to temperature mapping, it's best practice to perform the test in one continuous session. This is because it allows for a more consistent and accurate capture of data across a defined period.

However, in practical terms, if your operational constraints necessitate breaking up the mapping process into separate parts, there are a few important considerations:

- Consistency: Ensure that the conditions remain as consistent as possible between the two sessions. This includes ambient conditions, loading conditions, operating conditions, etc.
- Overlapping Periods: If possible, it would be beneficial to have some overlapping time between the two sessions. This overlap can help ensure there is a continuity of data and help to validate that the conditions have not significantly changed.
- Documentation: Document the reasons for the split, as well as any measures taken to ensure consistency between the sessions. This will be important if questions arise during an inspection or audit.
- Risk Assessment: Before proceeding with this approach, perform a risk assessment. Consider potential variables that could impact the validation when it's not done in one continuous session, and how you can mitigate these risks.

Ultimately, this approach can be challenging and may require extra justification during audits or inspections, as it deviates from standard procedures. I recommend that you consult with a quality assurance specialist or regulatory advisor to ensure this method will be acceptable for the specific industry and application.

Remember, the goal of any validation process is to ensure that the system consistently performs according to its intended use and within the specified limits. As long as this can be convincingly demonstrated, and any deviations from standard procedures are well justified and documented, the validation process should stand up to scrutiny.

Is it advisable to use Mean Kinetic Temperature in validation?

Further question: For a Controlled Room Temperature Warehouse, what is your position on using MKT for evaluating temperature excursions?

Paul: Some people use MKT in temperature mapping, but I do not think it is a good idea because MKT was not designed for this. Mean Kinetic Temperature is sometimes used to evaluate temperature excursions on qualified equipment that has been mapped already. Even this practice is not consistent with the purpose of MKT. But ask yourself this, if there is a tool that is used to evaluate an excursion (deal with a failing piece of equipment) why would I want to use that to prove my equipment is working? I recommend avoiding the use of MKT, especially for mapping. It is a mathematical formula that shows that temperature excursions would not affect the product. So, the value *presumes* temperature excursions are happening. One of the goals of a temperature mapping study is to prove that temperature excursions are not happening. Therefore, MKT analysis has no use in a temperature mapping qualification.

Nate: Mean Kinetic Temperature was developed to assess the impact of temperature variations *over time* on temperature-sensitive goods, like pharmaceuticals, during storage and transport. It is indeed not designed explicitly for temperature mapping.

When we talk about temperature mapping, we're trying to make sure that everything that needs a specific temperature stays in the right conditions. Whether it's a fridge, an oven, a cold room, you name it, the goal is to show that our equipment can keep a steady, appropriate temperature everywhere, no matter what's happening around.

This is why Paul recommends against the use of MKT for temperature mapping. To me it feels a bit like putting the cart before the horse. MKT is meant for when temperatures stray from the path, and temperature mapping is all about keeping things on track.

Door open stress-testing is common. Is there a standard process for this testing. i.e., open once and for a period then shut and allowed to recover? What would be the duration for this kind of test?

Nate: There is no regulatory requirement for these tests, however there is guidance from non-regulatory agencies, such as the USP and WHO that speaks of performance testing such as scenarios including door open, door closed, and simulated equipment failure. The test duration depends on your risk assessment and operational requirements. Typically, the test is performed for a period long enough to simulate a worst-case scenario (e.g., 5-10 minutes) and then observe the recovery time once the door is closed.

An Open-Door Study is designed to assess the temperature recovery capability of the chamber (Controlled Temperature Unit, or CTU) under the worst-case scenario, specifically, when the door is left open for an extended period. If even a single sensor records a temperature outside the acceptable range, it suggests that at least part of your product could be exposed to out-of-spec conditions. Therefore, you typically don't need all sensors to exceed limits to consider it an excursion. Some parts of the chamber might be more susceptible to temperature changes than others, especially during events like door openings. Should you decide that these are tests you want to perform, I can help you develop test scripts for such testing. Please reach out to me at nroman@genesisaec.com.

Is there a preferred load configuration for Open Door/ Power Failure mapping? Empty chamber shows a worst condition, but if the unit is empty, there is no risk to products…

Paul: For a preferred load configuration, this would come from your company's (or customer's) policy or procedure on how they load their chambers. Empty is only the worst-case condition for a unit (such as a freezer) that cools by conduction. For a unit that controls temperature by air flow, fully loaded could be the worst-case condition as air flow is blocked by the load.

Nate: In some instances, testing with an empty chamber can provide useful data on how quickly the temperature can deviate under worst-case scenarios. However, this might not always reflect the real-life scenarios where the chamber is typically loaded.

In a practical context, understanding your usual load configuration and potential risks associated with open door or power failure situations can guide the setup for these tests. For example, you might consider testing under a few different configurations that reflect typical use and worst-case scenarios.

Ultimately, the goal is to understand how these events could impact the temperature conditions inside the chamber and how quickly the unit can recover to the desired temperature range.

Is the power failure study required in qualification of a 1000 Litre incubator?

Paul: You may want to do the tests anyway just to get the information, as it might be useful in the future if you do have a power failure. And it is easiest to do this while you have sensors in place for temperature mapping. However, if you anticipate that power failures may be a problem on a critical process, it may be better to invest in some sort of UPS or back-up power system to mitigate the risk of a power failure. For more information, refer to the ISPE "Good Practice Guide on CTC Mapping and Monitoring."

Nate: A power failure study may not be required for all incubators, but it is useful for understanding the incubator's performance during power outages. Assess the risk and potential impact on the stored products to determine if a power failure study is necessary for your specific case.

What guide do you follow for the distribution of sensors? And which guide is the most recommended or accepted in the industry?

Paul: You can get standard sensor placement descriptions from the guidance from the WHO and the ISPE. The WHO typically recommends more sensors. The goal is a regular geometric distribution of sensors, in three planes, in three dimensions, in all the spaces you intend to store product. You may want to add additional sensors as necessary to deal with any specific features or concerns of your space. Do not place sensors randomly. Start with the corners and the center at a minimum (for a small CTC under 2 cubic meters). For larger spaces, you may need to start placing stacks of sensors. I have outlined this in detail in Vaisala's webinar on Sensor Placement .

Nate: When it comes to determining the number of sensors and positions for temperature mapping and qualification of controlled temperature chambers (CTC), I recommend you refer to the ISPE Good Practice Guide on Controlled Temperature Chambers.

It will tell you to use 9 sensors for CTCs less than two cubic meters, and 15 sensors for CTCs between 2 and 20 cubic meters. For larger areas, you need to develop a scientific rationale for your sensor placement. Actually, WHO recommends a risk-based approach can be applied to define these locations.

Find more detailed information on my LinkedIn post: ***Temperature Data Loggers Locations for Temperature Mapping***

What would the criteria be to repeat a temperature mapping post validation?

Paul: The old practice was to simply repeat temperature mapping at regular intervals from 6 months to 5 years, depending on how critical the equipment was for the GMP process. The shorter period would be for something critical, such a stability chamber. The 5-year period might be for something non-critical

that stores inexpensive items, such as a lab refrigerator for reagents. In my experience, three years is the standard interval for warehouse in the USA.

I know that some companies simply repeat mapping every year to be safe. The new practice is to use risk assessment. This demands that we do some critical thinking, examine the history of the unit, and of similar units at your facility, to determine the value of repeating the temperature mapping. This approach is described in the ISPE Good Practice Guide on CTC Mapping and Monitoring.

However, sometimes it is just easier and safer to repeat a mapping. I think it comes down to your comfort level; Which would you rather show to your auditor or customer? A risk assessment supported by relevant monitoring data and maintenance history, or a re-validation report?

Nate: Paul handled the re-qualification aspect in his comment, but other criteria that comes to mind for repeating temperature mapping post-validation may include significant changes in equipment or the environment, relocation of the chamber, changes in operating procedures, or any other factors that could affect the temperature profile.

How can we determine the period of recalibration or requalification?

Nate: For temperature mapping requalification - I've seen the same as Paul has presented. However, there are no hard fast regulations applicable for this. New guidance suggests that controlled temperature chambers should be periodically assessed to determine the need for revalidation or remapping. The control systems, equipment, monitoring, and procedures for the units should be a part of the periodic review to ensure the unit still operates in a qualified manner.

Also, the frequency of the requalification or remapping is suggested now to be determined on the results of a risk assessment or when significant modifications are made to the unit. As for the item to consider during risk assessment: what is your level of risk of failure to maintain uniform temperature or the storage of high value/critical products or temp sensitive products may warrant more frequent requalification. Industry practice varies but should always be performed in alignment with your risk assessment and rationale for your determined frequency documented.

Annual temperature mapping is a common practice in some companies to ensure continued compliance and stability in freezers. However, the frequency may vary based on the risk assessment and historical performance data.

What is the lifespan for a temperature mapping?

Nate: The lifespan of a temperature mapping study is determined by various factors such as equipment performance, environmental changes, and regulatory requirements. A risk-based approach is recommended for determining when to conduct re-mapping studies.

When performing a revalidation, would it be best to put the loggers in the exact same locations as before, or should we add more locations following USP <1079>, thoughts?

Nate: In most cases, when conducting a revalidation, it's advisable to use the same logger locations as the original validation. This allows for a direct comparison of data to assess if the performance is consistent over time.

However, if during your review of the previous validation data, you notice areas of risk or variability that were not sufficiently covered in the previous study, then it is appropriate to adjust the locations. This might also be the case if you are updating your protocol to better align with guidelines such as USP <1079>.

If you decide to add more loggers or change their locations, just make sure to include a justification in your protocol for these changes. This ensures the changes are transparent and understood by everyone involved.

Remember, the ultimate goal of revalidation is to confirm that the system or process is still working as expected and maintaining the required conditions, so it is important to make any necessary adjustments to achieve that goal.

Any tips on establishing calibration/process tolerances for control probes in CTU's?

Continued question: Do you rely on studies to challenge the amount of offset/error a control probe can have while maintaining distribution throughout chamber per user requirement? Also…do you have any experience on using monitoring probe data to characterized chamber performance, and relying of periodic review of this data to trigger chamber requalification events instead of relying on interval-based requalification (e.g., every 2 years)? If so, what do you recommend for establishing control limits for monitoring probes such that when exceeded would trigger chamber requalification?

Nate: The original practice of regularly scheduled requalification, regardless of performance history, is gradually giving way to a risk-based approach, as suggested in newer guidelines like those from the ISPE. This approach considers the historical performance, criticality of the stored products, and other factors.

In terms of establishing calibration/process tolerances, it is indeed beneficial to rely on studies that challenge the control probe's offset/error while maintaining the chamber's distribution per user requirements. The specifics of this may depend on the type of products stored, their sensitivity to temperature deviations, and the overall operational demands of the chamber.

For your second question, using monitoring probe data to characterize chamber performance is a smart way to continuously assess the system's performance. However, it is essential to approach this with a good understanding of the chamber's operational history and behavior. Regular reviews of this data can help identify any trends or shifts in performance that may necessitate a requalification.

Establishing control limits for these monitoring probes would involve a careful analysis of your chamber's historical data, factoring out any false alarms or outliers. You'll need to consider the specific operational characteristics of your chamber, like recovery time or compressor aging, as Paul mentioned.

Just remember, the goal here is to strike a balance between maintaining compliance and efficiently utilizing resources, and the approach may vary based on the criticality of your processes and specific regulatory expectations. In cases where the risk or uncertainty is high, a more conservative approach of repeating mapping studies might be warranted.

When a CTU is relocated with in the same facility, what are the minimum qualifications needed?

Paul: If the environments are similar, it should not have a big impact. But you should repeat the IQ, with regards to things like the floor being level, enough space around the sides for airflow, and proper electrical supply. And of course, make sure it is reinstalled to the monitoring system and you are seeing good data that is similar to the data that you saw before the move. Best practice is to od these actions under change control procedures.

Nate: Paul's thoughts line up well with industry best practices. When a CTU is moved, even within the same facility, it's a good idea to repeat the Installation Qualification (IQ) to ensure the basics like a level floor, adequate space for airflow, and correct electrical supply are still met in the new location. Absolutely, reconnecting and confirming good data from the monitoring system is essential.

Building on that, I would also suggest conducting a calibration check on the CTU's sensors before and after the move to ensure the move did not impact their accuracy. And even if the new environment is similar, it could be beneficial to perform a temperature mapping as well. This will help confirm that the CTU is still able to maintain the required conditions in its new location.

As Paul said, any changes like this should be managed under change control to ensure they're properly documented and approved. That way, you're covering all your bases and maintaining compliance.

How do you map out a chamber in an efficient manner that includes RH validation?

Paul: When adding relative humidity to validation, the safest path is to have one RH sensor for every temperature sensor. There are many dual-purpose loggers that measure both parameters in one logger. But you can get by using fewer RH sensors, say 25% as many RH sensors. Most variation in RH measurement is actually due to temperature variation because RH is relative to temperature.

For warehouses, is it necessary to perform mapping during the Summer and Winter? Or can we map once during any time of year?

Paul: The expectation with a warehouse is that it will be mapped in the Summer and in the Winter, ideally during the coldest and hottest periods. In Florida, if your product is affected d by humidity, this might be slightly different periods. Please see the Vaisala webinar on the "Continuous Mapping" concept for warehouses. It can save money and increase compliance for warehouse mapping.

Nate: A common misconception in temperature mapping is that mapping of Storage Areas is only required once - however this is not the case. The regulatory bodies require proof that a facility can maintain temperature all year round.

For example, the United States Pharmacopeia, Article 36, Chapter 1079 requires two mapping studies, one in the winter and one in the summer, to capture warehouse environmental data for the most extreme outdoor low and high temperatures.

Here is a link to collection of posts on GMP Warehouse Temperature Mapping tips, guidelines and best practices I've posted on LinkedIn.

How is the distribution of data loggers with temperature mapping determined?

Paul: The goal is a regular geometric distribution of sensors, in three planes, in three dimensions, in all the spaces you intend to store product. You may want to add additional sensors as necessary to deal with any specific features or concerns of your space. Do not place sensors randomly. Start with the corners and the center at a minimum (for a small CTC under 2 cubic meters). For larger spaces, you may need to start placing stacks of sensors. Refer to the Vaisala webinar on Sensor Placement for more detail.

Nate: When it comes to determining the number of sensors and positions for temperature mapping and qualification of controlled temperature chambers (CTC), I recommend you refer to the ISPE Good Practice Guide on Controlled Temperature Chambers. This guide will tell you to use 9 sensors for CTCs less than two cubic meters, and to use 15 sensors for CTCs between 2 and 20 cubic meters. For larger areas, you need to develop a scientific rationale for your sensor placement. Actually, WHO recommends a risk-based approach can be applied to define these locations.

More information here see this LinkedIn post on temperature data logger locations.

Can Computational Fluid Dynamics studies be used to determine where sensors should be placed during mapping and provide information on how many will be sufficient?

Paul: I love the idea, but I'm not sure it is worth the time. The amount of investment to get enough data to answer this question seems like it would be much harder than just following the existing best practice.

Nate: Yes, CFD studies can help identify potential hot/cold spots and inform sensor placement during mapping. I agree with Paul's comment on this one. However, the actual number of sensors required still depends on the size, complexity, and risk assessment of the area being mapped.

When performing typical mapping, what is a customary chamber size that is being mapped? What about large chambers, for example: 8m x 8m 8m. How does this affect sensor selection and strategy?

Paul: ISPE guidance identifies three sizes of chambers. 1) Less than 2 cubic meters, 2) Between 2 and 20 cubic meters, and 3) Bigger than 20 cubic meters. You can get standard sensor placement descriptions from the guidance from the WHO and the ISPE. The WHO typically recommends more sensors. The goal is a regular geometric distribution of sensors, in three planes, in three dimensions, in all the spaces you intend to store product. You may want to add additional sensors as necessary to deal with any specific features or concerns of your space. Do not place sensors randomly. Start with the corners and the center at a minimum (for a small CTC under 2 cubic meters). For larger spaces, you may need to start placing stacks of sensors. I recommend our webinar on Sensor Placement for more information.

Monitoring & Alarms

What is the guidance on setting appropriate alarm delays for controlled temperature chambers? How do you assess risk to the chamber and the product? Is there a standard alarm delay time before action is required?

Paul: There is no standard for this. You could even consider alarms to not even be GMP, if you aren't relying on the alarm generation to make decisions. Remember, most of the time we are deciding based on the data, and the alarms also come from the data. But our question is not "Was there an alarm?", our question is "Was the data in specification?" So, if alarms aren't GMP, you can do anything you want with them.

Despite this, alarms are a useful tool, and they can help protect your product. This will be dependent on your monitoring frequency. If you take a data point every 10 minutes, then you can't really have a delay less than 10 minutes.

I would start with a default alarm delay of 2 minutes, just to allow for alarms caused by door opening. Then work from there and adjust, as necessary. You don't want to get a bunch of false alarms, as that will only make people start to ignore alarms. Setting appropriate alarm delays for controlled temperature chambers involves a risk-based approach that considers factors such as the criticality of the product, allowable temperature range, chamber performance history, and regulatory requirements.

Nate: There is no standard alarm delay time universally applicable across all scenarios. Setting appropriate alarm delays for controlled temperature chambers involves a risk-based approach that considers factors such as the criticality of the product, allowable temperature range, chamber performance history, and regulatory requirements. The goal is to strike a balance between detecting excursions promptly and avoiding false alarms.

It is recommended to conduct a comprehensive risk assessment to assess the risk to the chamber and the product. Factors such as temperature stability, response time for corrective actions, and acceptable temperature ranges should be considered.

The selected alarm delay time should be documented with a rationale and periodically reviewed to ensure ongoing effectiveness. Ultimately, the appropriate alarm delay for controlled temperature chambers should be determined through a tailored risk assessment process that ensures product integrity and regulatory compliance.

Regarding alarm limits for monitoring sensors, should they be set at the acceptance criteria for the overall mapping during qualification, or should they be set based on characterized data from mapping to detect atypical performance?

Paul: I think alarm limits should be standardized as much as possible. Worst-case scenario is that all freezers (for example) have different alarm thresholds and delays. This seems like a logistical nightmare. So, I would stay away from customized alarms. Generally speaking, the atypical performance you want to detect will be from power failures, door openings, and compressor failures. The atypical performance that might indicate a problem or need for maintenance can be obtained from doing statistical analysis of the monitoring data. So, use the monitoring report for this goal, not the alarms.

Nate: Paul brings up a valid point regarding the standardization of alarm limits for monitoring sensors. It is generally recommended to establish standardized alarm limits as much as possible, rather than customizing them for individual units or chambers. This ensures consistency and ease of management across multiple units or facilities.

The primary purpose of alarm limits for monitoring sensors is to detect emergencies or critical events such as power failures, door openings, or equipment malfunctions that could jeopardize the integrity of the controlled environment. These alarm limits should be set at a level that aligns with the overall acceptance criteria established during the qualification process.

While standardized alarm limits ensure consistency and immediate detection of critical events, utilizing the monitoring data and statistical analysis provides a valuable tool for ongoing performance evaluation and identification of potential issues that may require attention.

How long do sensors work if battery-operated?

Paul: Battery operated data-loggers can have a long lifetime. Vaisala's DL-Series data loggers are known to function for over 8 years. But battery life will vary according to several factors, including the operating temperatures, the frequency of data collection, and the quality of the device. If your device has a battery that can be changed or charged, I will change/charge before every mapping to reduce risk.

Nate: As said, battery life varies based on usage, the frequency of readings, strength of the Wi-Fi signal, and other factors. Many can operate for several months to a year on a single battery, but you should check the specifications of each device for more accurate information.

How can we avoid unnecessary alarms due to door opening? Is a one-point calibration at the operating temperature sufficient or should a multi-point calibration be done for the monitoring sensor?

Paul: Alarm delays are a good way to avoid false alarms. If your monitoring system doesn't allow alarm delays, you can consider buffering the sensor by placing it in a larger object that will heat up or cool more slowly than air.

Nate: To avoid unnecessary alarms, consider implementing alarm delays or adjustable alarm setpoints that account for short-term fluctuations caused by door openings. Proper staff training on minimizing door opening duration and frequency can also help reduce unnecessary alarms.

Multi-point calibration is recommended for monitoring sensors, as it provides a more accurate representation of the sensor's performance across the entire operating temperature range.

In regard to hot spot monitoring, do you change sensor locations when you are re-mapping the unit if the hot spot changes?

Paul: I don't believe in hot spot monitoring unless we are talking about a warehouse. In cold units, which are generally 2 cubic meters or smaller, if you monitor the hot spot, then you are having the monitoring sensor in a different location in every unit. I have never seen this in reality, though I have

heard of it. Every freezer I have ever seen has the monitoring sensor on the wall, near the door, on the door handle side, to keep it out of the way in a standard location, and placed to monitor the most common risk event, which is a door open scenario. I think the idea to monitor the hot spot is the result of a misunderstanding. You don't actually see it in regulation, and it shows up in guidance only rarely.

Historically, we did look for the hot spot and cold spot, but this was just an easy way to analyze the data - if the hot spot and cold spot are within specifications, then the data is good. The hot spot and cold spot didn't actually matter unless there was a temperature excursion. When people started writing guidance for Good Distribution Practice, which is often for non-GMP folks, somewhere they added this idea that you should monitor the hot spot.

My experience leads me to believe that this is a waste of time. You mapped the unit proving it can maintain temperatures. You can trust your validation. The monitoring probe is not there to be a single point long-term mapping of a hot spot. The monitoring probe is there to identify emergency situations, like a door open or a compressor failure. However, many people disagree with me, and they have written this hot-spot monitoring into their SOPs and Policies. If that includes you, then yes, you will need to move your monitoring probe.

Nate: Yes, in a walk-in cold room or warehouse, if hot spots change during a re-mapping exercise, adjust the locations of data loggers to accurately monitor and capture the new hot spots. However, for the typical commercial-off-the-shelf freezers, refrigerators, incubators, and environmental chambers that we perform mapping studies on I will agree with Paul's comment.

Is the location with the greatest variance during validation a good place for a permanent sensor?

Paul: It's a great start having a monitoring probe in the chamber. Most people put them in the same place in every chamber to keep things logistically simple. Imagine having the probe in a different location in EVERY chamber! Usually it's on the wall, middle height, same side as the door handle, 8 to 10 inches in. This placement protects against the number 1 threat - the door being left open. I think if you passed your mapping qualification, you PASSED. There isn't one spot that almost passed and needs to be monitored more than the others. The permanent sensor is there to catch emergencies, not to second guess your temperature mapping. If you have a policy or procedure that dictates the location of the monitoring probe, then that's where it goes.

Nate: I agree with Paul that most importantly, monitoring probes are there to catch emergencies rather than questioning your temperature mapping. However, it's also important to consider that the location with the greatest variance during validation can provide additional valuable data for ongoing performance monitoring.

The spot with the highest variance can help you observe how the CTU behaves under extreme conditions, and therefore it's not a bad idea to have a sensor there. That said, this should not replace the standard monitoring position that Paul mentions, nor should it substitute for the manufacturer's recommended placement of the control probe.

The control probe is strategically placed by the manufacturer to provide a representative measurement of the temperature within the CTU. It should be noted, however, that the control probe location might not always coincide with the area of greatest temperature fluctuation.

In essence, it's crucial to have a well-rounded monitoring system in place that observes both typical and extreme conditions. This strategy includes following the manufacturer's recommendations for the placement of control probes, considering areas with the highest variance from the validation study, and maintaining a standard position for emergency detection. Remember that a comprehensive understanding of your CTU's behavior under various conditions will help ensure product safety and quality.

Can you discuss best practice for monitoring sensor placement?

Paul: In 95% of the chambers I have ever seen, the sensor ends up on the wall, same side as the door handle, about 8 to 10 inches in.

Nate: Paul's common highlights a common practice in sensor placement for monitoring systems. However, for a more holistic understanding of the temperature dynamics within the chamber, some considerations could enhance the effectiveness of monitoring.

In line with best practice, sensor placement should be dictated by a risk-based approach. This involves identifying critical locations within the chamber that are likely to experience temperature variations. These can include areas near the door, corners, close to cooling vents, and areas that are typically heavily loaded or lightly loaded.

The position of the manufacturer's control probe is also significant, as it governs the system's temperature control response. This location is typically selected by the manufacturer to best represent the average temperature within the chamber. Monitoring at this location can provide a reference for the overall temperature control performance.

It is also essential to consider the typical loading patterns in the chamber when placing these sensors. Thus, while the monitoring sensor is indeed crucial for detecting emergencies, a well-distributed sensor placement strategy can provide more comprehensive insights into the temperature profile of the chamber under normal and worst-case conditions.

Would you recommend moving control and/or monitoring probes in small to medium CTCs based on mapping data?

Paul: I would never move a control probe - leave that only to the manufacturer of the unit. I might move a monitoring probe, which would not change the thermal profile. But in a small medium CTC, there aren’t many places to move it to that make sense.

Would you please clarify whether it is required to monitor the outside temperature during mapping? Also, what should be the standard duration for Mapping?

Paul: I think this is a good practice for only for environments that have a wall that is shared with an uncontrolled space, or with the outside. Usually this would be a warehouse or a cold-room. For a free-standing CTC, such as a refrigerator, if it is in a temperature-controlled space, I see little value in knowing the outside temperature.

But for a warehouse that gets seasonal mapping, I would want to know the outside temperature because I want to be able to prove that I mapped at the hottest time in the summer, or the coldest time in the winter.

Nate: Monitoring the outside temperature during mapping is not always required but can provide valuable context when assessing environmental factors influencing the mapped area. Usually this would be a warehouse or a cold-room, not a CTC.

For your second question, the standard duration for mapping depends on the specific application and stability of the area being mapped. A common practice for Freezer, Refrigerators and Incubators is to perform a 24-hour study to capture daily temperature fluctuations.

Typical Mapping Study Durations

- CTU: 24 hours
- Cold-room: 72 hours (3 days)
- Warehouse: 7 days (168 hours)

Is it preferred to use an external reference probe to the probe within the environmental chamber? - Environmental chamber vs. RH standard? Why is it that some sensors only have RH adjustment and not Temperature?

Paul: I would only use an external reference probe if the environmental chamber was being operated in an uncontrolled space. IF it is in a controlled space, with HVAC, then the temperature/RH should be similar all year round, so there is no reason to measure it as you map.

Nate: The choice between using an external reference probe and the internal probe of an environmental chamber largely depends on the requirements of the specific application, the accuracy required, and the type of environmental chamber being used.

Generally, an external reference probe may be preferred for several reasons:

- Higher accuracy
- Calibration

However, the use of the internal probe can also have its advantages:

- Simplicity
- Cost
- Protection

If you're looking to measure relative humidity (RH), an environmental chamber is a device that can provide controlled conditions, including humidity. However, these devices can sometimes have a wide range of error.

On the other hand, RH standards provide a more precise humidity level. If you need to calibrate your sensors to a high level of accuracy, or if you are doing work that requires a very precise RH, then you might prefer to use an RH standard.

Some sensors are designed to only measure and adjust for relative humidity, and do not have a temperature adjustment. The main reason for this is that adding temperature sensing and adjustment would increase the complexity and cost of the sensor. Your choice would depend on your specific requirements. If you need a high level of accuracy, an external reference probe or an RH standard might be the best choice. For simpler or less critical applications, the internal probe of an environmental chamber and sensors that only adjust for RH might be sufficient.

What are the affects environmental conditions on thermal mapping?

Paul: There are many factors that affect the temperatures in your controlled area. Volume, height, materials of construction, control probe location, doors, and windows, use patterns, materials stored inside, sizing of the cooling system, location of vents, insulation, etc. In this webinar, I go into some of these details.

Nate: Environmental conditions play a significant role in thermal mapping. Factors such as external temperature, humidity, air flow, and even sunlight can influence the thermal characteristics of a controlled area.

Additionally, the operational conditions of the space such as frequency of door openings, the quantity and thermal properties of the items stored within, and the activity level within the area can also introduce temperature variations.

For example, areas close to doors or windows may exhibit different temperature profiles due to external influences. Also, areas densely populated with products or equipment may have different temperature characteristics compared to open spaces due to the heat dissipation from the items stored.

Ultimately, understanding these environmental and operational conditions and their impact on temperature distribution is crucial in designing and conducting an effective thermal mapping study. This understanding also helps in making informed decisions about where to position temperature sensors and how to interpret the resulting data.

In your experience, have you observed an approach of leveraging monitoring sensor data to evaluate to need to requalify a CTU?

Paul: Yes. This is the current recommendation from the ISPE for determining whether or not to repeat a mapping. This is part of a larger risk assessment involving maintenance history, similar units, alarms, and the value of what is stored.

Nate: In my experience, a well-implemented monitoring system, paired with a robust review process, can provide the necessary data to make an informed decision about when to requalify. This system, if coupled with a holistic risk assessment that considers the maintenance history, alarms, value of stored items, and performance of similar units, can provide a comprehensive view of a CTU's operational status.

That said, it's crucial to remember that while this approach can be efficient and effective, it shouldn't replace the need for a well-structured and periodic validation plan. Both strategies should be used in harmony to ensure the continued operational integrity of your CTUs.

Acceptance Criteria & Reporting

What do you recommend as calibration & validation specifications for large custom build temperature & humidity walk-in chambers?

Paul: Your acceptance criteria for temperature and humidity should be defined by the specifications of the unit. What you store inside the chamber usually drives that, and often this follows the values for stability testing. My expectation, especially for a newly constructed chamber, is that there would be no excursions at all. As far as calibration tolerances, for your monitoring probes, I would expect a maximum of ± 0.5°C, but I'd go for something better, such as ± 0.25°C, and ± 2% RH.

Nate: When establishing calibration and validation specifications for large custom-built temperature/humidity walk-in chambers, it is essential to follow industry best practices. Begin by referring to applicable regulatory requirements and guidelines such as FDA, ISO, or industry-specific standards. Consider the intended use of the chamber and the criticality of the stored products. Establish calibration intervals based on manufacturer recommendations, equipment history, and risk assessments.

Validation should include temperature and humidity mapping, demonstrating uniformity, recovery time, and alarm functionality. Acceptance criteria should align with regulatory requirements and the chamber's intended use. Regular performance monitoring, maintenance, and periodic requalification should be part of an ongoing quality assurance program.

We just built custom temperature/humidity walk-in chambers (~1200 cubic feet). What validation tolerances and calibration tolerances do you recommend for the chamber?

Paul: See answer above.

Nate: For validation tolerances and calibration tolerances of your custom walk-in chambers, it is recommended to follow industry standards and guidelines such as ISO 17025 and the manufacturer's specifications. These standards provide a framework for establishing appropriate tolerances based on the intended use of the chambers and the criticality of the processes being performed inside.

It is crucial to consider factors such as the required temperature and humidity ranges, the sensitivity of the products being stored or tested, and any applicable regulatory requirements. Consulting with qualified calibration and validation experts can help ensure that your tolerances align with industry best practices and meet the specific needs of your application.

Are acceptance criteria typically based on the operational range? Or should you have the same acceptance requirement for a 2-8°C Fridge vs -80 Freezer with operating range of -90°C to -70°C?

Paul: Acceptance criteria is based on what you plan to store in it and what policies your company has on qualifying a CTC. I don't think I have ever mapped to operational range.

Nate: In general, acceptance criteria for temperature mapping studies should be based on the specific operational requirements of the equipment being validated. It's important to consider the intended use and the criticality of the products stored or processes carried out within the equipment.

While it may be tempting to apply the same acceptance criteria across different temperature-controlled units, it is more appropriate to tailor the criteria to the specific equipment and its operational range. The acceptance criteria should reflect the allowable temperature variations that ensure product integrity, compliance with regulatory requirements, and adherence to industry best practices.

Ultimately, a risk-based approach should be followed, considering the characteristics of the equipment, the requirements of the stored products, and any applicable regulatory guidelines or industry standards to establish appropriate acceptance criteria for each individual temperature-controlled unit.

How can you establish the number of sensors to remove from a thermal mapping due to technical failures, without affecting the study?

Paul: There will always be an affect to the study when you remove a sensor due to failure. The question is, how many can we remove and not have too big of an impact on the study. Historically, I have used a 10% allowable failure rate. Note that that was applied to thermocouples which fail more often than data loggers. But the idea holds true for more reliable data loggers and it's a good idea to allow for at least one sensor fail, otherwise you will be repeating studies too often.

Nate: I agree with Paul, the typical acceptance criteria for all the validation protocols I've written and executed, when related to execution or sensor post-calibration or post verification in the life sciences industry, had a 90% confidence level most often used. If this was not pre-populated or specified in your protocol, then you will need to treat it as a deviation.

The minimum number of sensors required for a study should be established during the document development phase and based on the size and complexity of the area being mapped. If sensors fail during the study, the remaining sensors should still provide sufficient coverage. If not, the study should be repeated with properly functioning and calibrated sensors.

In the performance report, what statistical calculations should be made? Should you take the uncertainty of the instruments used in the qualification? If yes, where should they be considered in the result?

Paul: I wouldn't do any statistics other than the Maximum and Minimum for each location. If the Max and the Min are all within spec, then the unit passes. Averages and MKT I just don't see the value in these. Others will disagree.

Nate: Different contexts and requirements will necessitate different approaches.

When conducting temperature mapping, the most fundamental considerations are to ensure that your equipment maintains a consistent, suitable temperature across all its areas under all expected conditions, and to demonstrate this fact clearly in your reporting.

Provide the Minimum (Min), Maximum (Max), and Average temperatures from your measurements, this is a standard and widely accepted approach. These figures give a clear, straightforward representation of the temperature range and average within your equipment, which can be directly compared to your operating range and acceptance criteria.

This approach can be more than sufficient for many applications, especially where temperature variations are relatively minor, and the main concern is ensuring the temperature remains within a specific range.

In terms of the thermal mapping report, what are data should be included? Data such as minimum and maximum temperature and mean kinetic temperature?

Paul: All I like to see in a mapping report in minimum and maximum temperatures. Some companies like to use averages as well to help determine location of the monitoring sensor. I would NOT use MKT for anything related to mapping - that is not the intent or purpose of MKT, especially for a cold room. MKT is really only applicable to ambient room temperatures.

Nate: The Final Report should provide a clear overview of the entire qualification execution, summarize the results obtained and document any discrepancies.

- Identify the equipment/system being undergoing qualification
- List all test case performed including whether those test cases passed
- A summary of the key results obtained during the testing along with a discussion of any non-conformances (deviations) encountered, their impact, and how they were resolved
- A conclusion statement whether the equipment/system met the defined requirements of the acceptance allowing for the release of the equipment/system.

As for what data to summarize: Provide the Minimum (Min), Maximum (Max), and Average temperatures from your measurements, this is a standard and widely accepted approach. These figures give a clear, straightforward representation of the temperature range and average within your equipment, which can be directly compared to your operating range and acceptance criteria.

What is the importance of average values obtained in a mapping to assess relocation of monitoring sensors/devices vs the maximum deviation value?

Paul: Unless we are dealing with a warehouse, I don't think statistics or maximum deviations are the factor that dictates placement of a monitoring sensor. Monitoring sensors 99% of the time end up in the same place. They are on the wall of the unit, on the same side as the door handle, maybe 20 cm back from the door. This keeps them out of the storage space, and near the single biggest temperature threat - a door left open. Imagine what would happen if the hot spot were in the middle of the chamber, and you tried to monitor at that location? You would have to protect the sensor, and you would use up 25% of the valuable storage space in your chamber. It just doesn't make sense.

Now warehouses are a different story, as they will have several monitoring sensors, and you can place a sensor at the hot or cold spot and not affect operations too much or place the sensor in danger. In this case, I would use both statistics and max/min to determine the worst-case locations and then place sensors accordingly. It is worth noting that this idea to place monitoring sensors at the hot/cold spot is a new idea in the last 10 years and is part of the Good Distribution Practices movement to quickly educate distributors on how to map and monitor correctly. I think it represents a wrong idea and confuses a useful data analysis technique (looking at max/min to ensure we are within specification) with a desire to identify the hot/cold spot for some actual purpose (such as monitoring sensor placement).

We have some Vaisala data loggers. Do you ever experience breakage on the thermistor cables?

Paul: I have only seen the cables break a few times and it was not during mapping. Usually, it happens when a freezer or refrigerator is moved, and the data logger is attached to something else. The cable then stretches and breaks due to the heavy freezer or fridge pulling it too tight. When conducting a Performance Qualification (PQ), we typically use a loaded chamber to best represent operational conditions, with the load usually mirroring what would be seen during normal operation. However, an Operational Qualification (OQ) could be conducted on an empty chamber to validate its performance in the absence of any product load.

Is the square footage of an area you are mapping required for the report?

Paul: Yes, I would expect the dimensions of the space to be in the protocol in the system description section, as a support for your validation approach. You can duplicate this info in the report, but it needs to be in the protocol more than the report.

Nate: In the pharmaceutical industry, documentation is vital in all stages of validation, including temperature mapping.

“If it is documented it didn't happen.”

This includes the physical dimensions of the area being mapped.

The size of the area or the volume being mapped should be clearly stated in the validation protocol, as Paul mentions.

This information assists in justifying the number of sensors used and the placement of these sensors. It provides context for understanding the complexity of the space and the potential challenges that might be associated with ensuring consistent temperature control.

While it's not strictly necessary to restate these dimensions in the final report, it can be beneficial for clarity and completeness. Including such information in the report provides an immediate reference for anyone reviewing the document without needing to cross-reference the initial protocol. It ensures a standalone comprehensiveness of the report, which is useful for auditors or other stakeholders who might review the report independently of other documentation.

What is a temperature buffer?

Paul: Usually you map temperature with a sensor that is measuring air temperature. Sometimes, the chamber will have temperature swings high and low, and the air temperature cannot stay in specification. But products we store in the chamber have some mass, and they don't change temperature as fast as air. A buffer, like putting the sensor in a bottle of glycol, will make the sensor response slow down and more closely represent the product temperature. Always best to use as small a buffer as possible, so the sensor is more sensitive to temperature changes than your product.

Nate: A buffer is used in temperature mapping to more accurately represent the thermal properties and behaviour of stored products. In environments where air temperature can fluctuate rapidly, products with mass don't change temperature as quickly.

A common way to buffer temperature sensors is to place them in a material with similar thermal properties to the products, often a bottle of glycol or a similar substance. This slows down the sensor's response time, helping it to mimic how the product itself would react to temperature changes.

Remember, the goal of using a buffer is not to 'smooth out' the temperature data or to mask temperature excursions, but to provide a more accurate representation of what the product experiences during storage or transport.

Which temperature buffer do you recommend if one is to be used?

Paul: I don't recommend temperature buffers for mapping. Your first attempt should always be sensors in air.

Nate: I agree with Paul. First attempt for mapping should always be in air. However, temperature buffers such as glycol, glass beads, or aluminum damping block can be used to mimic the thermal properties of stored products. The choice of buffer depends on the specific application, regulatory requirements, and thermal properties of the stored products. In my point of view, what we store is the most important, so buffering it will probably be more accurate in evaluating the temperature impact.

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Paul: In validation, there is a general rule to test the worst-case scenario. That is why it is recommended to map air temperature. It is also simpler, as you don't need to deal with buffers, procedural controls on what can be stored in the unit and explaining your choice of buffer. Save the effort and complexity of buffering until you already know that your CTC fails the mapping qualification with bare sensors in air.

I do agree with you, sensors buffered to match the product give more applicable information. However, this process is harder to perform, harder to maintain, and harder to defend under audit.

Nate: I agree with Paul. First attempt for mapping should always be in air. However, temperature buffers such as glycol, glass beads, or aluminum damping block can be used to mimic the thermal properties of stored products. The choice of buffer depends on the specific application, regulatory requirements, and thermal properties of the stored products.

Can family approach of CTUs based on same model be used for OQ?

For instance: If you had a fleet of identical equipment, would you map each one independently or leverage 1 or 2 examples as justification for use of the rest of the fleet?

Paul: I call this modeling and it is done occasionally. However, just because something is the same make and model, they are not all the same. Sometimes different parts can be used inside, and it will still have the same make and model number. Plus, these items are mechanical, and they age over time, so an old unit and a new unit will behave differently. The safest way is to map them all. A safer alternative that

will save you time is to do a very detailed study (say 24 loggers) on a few units of different ages. Then based on that data, do very lightweight mappings (1 to 4 dataloggers) on all the others, and on any new equipment.

Nate: Using a "family approach" or "grouping" for Operational Qualification (OQ) of Controlled Temperature Units (CTUs) of the same make and model can be an efficient method, but it comes with caveats.

It's important to remember that even if CTUs have the same make and model, differences can occur due to variations in manufacturing, component replacements, and age-related wear and tear. So, two identical units might not behave identically over time.

An accepted practice within the industry is to perform detailed mapping studies on representative units from different ages and service life. These 'worst-case' units can provide a basis for understanding the behavior of similar units.

Following this, less intensive verification studies (with fewer data loggers) can be conducted on the remaining CTUs. Any new equipment should also undergo this verification to ensure consistency.

However, it's crucial that this approach is supported by a robust risk assessment and is justified in your validation plan. Ensure your approach aligns with regulatory expectations and good manufacturing practices. Each situation will be unique, and the approach may need to be adjusted based on specific requirements and risks.