E-BOOKLET

Experts in Temperature Monitoring

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Content

1. Temperature and Pharmaceuticals

1.1. What are “temperature sensitive pharmaceuticals”?

Numerous products are considered to be “pharmaceuticals,” including drugs, medicinal products, biopharmaceuticals, API, research materials, human body samples, even medical devices. What they all have in common is that their properties, and therefore their quality, change with temperature. For example:

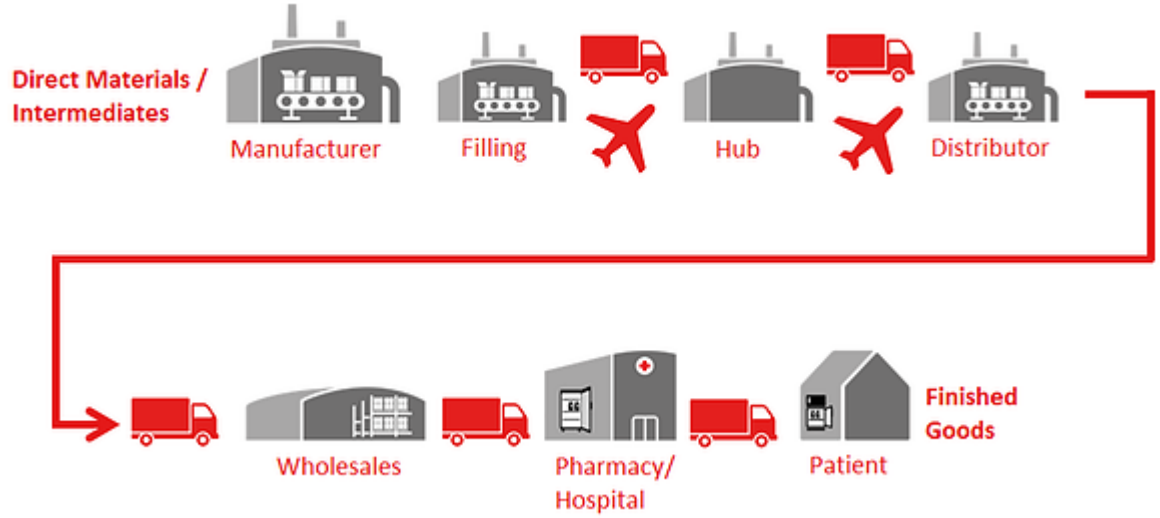
- Proteins decompose depending on time and temperature. The higher the temperature, the faster they fall apart
- Insulin can crystallize if frozen. If insulin is frozen, it might be harmful to the patient
- Gel turns to liquid at high temperatures

Compared to food products, pharmaceuticals typically do not change their smell and optical appearance when exposed to wrong temperatures. However, they do change their potency and their effectiveness. Therefore losing stability budget might be harmful to patient safety.

1.2. Which products fall under the category of “temperature-sensitive pharmaceutical products”?

Common regulations do not list all temperature-sensitive products in the pharmaceutical and healthcare environment. When the “Cold Chain” industry started in 1980, temperature-sensitive pharmaceutical products typically referred to refrigerated products like vaccines, insulin or biopharmaceuticals. In addition to that, blood and blood products, as well as research materials and human body samples, required temperature monitoring too. Since the 2015 revision of the EU GDP guidelines, API and room temperature products, such as small molecules and over-the-counter drugs, were also included into the scope of temperature-controlled logistics. Since the new regulation on medical devices came into force, medical devices which include some sort of an active pharmaceutical ingredient (e.g. coating) must also be considered inside the scope of temperature-controlled logistics.

1.3. The pharma supply chain



Like most supply chains of industrialized products, the pharma supply chain is complex and consists of multiple steps. Furthermore, the supply chain of every pharmaceutical product looks different and depends on the product complexity as well as the production region. While expensive products like genetically engineered drugs typically have a very short supply chain, low-price over-the-counter drugs like Aspirin have a much more complex supply chain with multiple steps between production and patient. What all pharma supply chains have in common is the distinction between the transportation of Active Product Ingredients (API) and finished packaged products. Lately, the scope of temperature data monitoring is increasingly including the last transportation mile to the pharmacy or even to the patient. Direct-to-Patient shipments (DtP) are becoming increasingly popular and important, especially with regard to clinical trials. This is also the case for personalized drugs.

1.4. How relevant is humidity for the pharma supply chain?

Humidity is relative to temperature and represents the amount of water present in the air. Humidity is highly relevant in pharmaceutical production as long as the product is in its open form before primary packaging (i.e. liquid or powder). After primary packaging, the relative humidity typically loses its direct relevance to patient safety. It is nevertheless common to monitor relative humidity in warehouses to avoid negative impact on the labeling and packaging (i.e. paper, cardboard). In most shipments however, the only quality relevant parameter is temperature. Data loggers therefore usually do not monitor humidity inside the transportation container.

1.5. Transportation conditions vs. storage conditions

Although every pharmaceutical product has an individual stability budget, they are “clustered” into standard temperature data range groups for storage and for transportation. As storage conditions we typically see the temperature ranges -196 °C, -80 °C, -20 °C, 2-8 °C and 15-25 °C. As transportation conditions the labels are "liquid nitrogen" (-196 °C), "dry-ice" (-78 °C), 2-8 °C and 15-25 °C. The storage condition “frozen” (-20 °C) is not very often seen in transportation for mainly two reasons. Frozen products are, in most cases, not sensitive to ultra-low temperature. It is therefore cheaper to use dry ice than to use expensive and complex compression cooling.

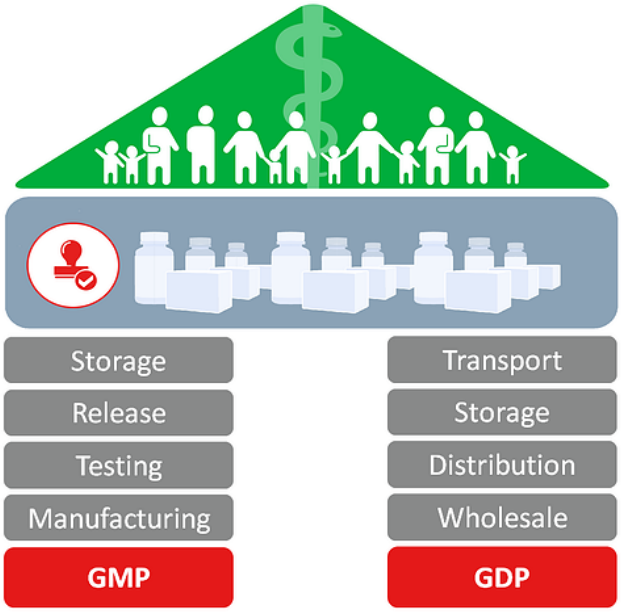
1.6. The regulatory environment of pharma companies

If a company wants to research, produce, store, transport or sell pharmaceutical products, they are subject to regulatory requirements. The laws and regulations are specific to each country and typically include a national or

international authority like the FDA (in the United States), EU (in Europe) or Swissmedic (in Switzerland). All are coordinated by the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use).

In addition to official regulations, there are a number of important associations issuing guidance documents supporting and detailing the regulations and their application in specific situations. Some of the most influential organizations relevant to the pharmaceutical supply chain industry are the ISPE (International Society for Pharmaceutical Engineering), the USP (United States Pharmacopeia), the PDA (Parental Drug Association) and the WHO (World Health Organisation). The regulatory framework is, therefore, a living organism that changes almost daily with new laws becoming effective and new guidance documents published.

1.7. GMP vs. GDP – what are the differences?



From a drug supply chain perspective, the cornerstones of the regulatory framework are the Good Manufacturing Practice system (GMP) and the Good Distribution Practice system (GDP), often jointly referred to as GxP. While GMP lays its focus on activities around manufacturing (including testing, release and storage); GDP focuses on the distribution including transportation, storage and wholesale of pharmaceuticals products. Both, GMP and GDP aim to increase public health by ensuring the product quality.

1.8. How GMP and GDP developed (a brief history)

GMP and GDP guidelines developed over the past 80 years. The following list shows some of the most important milestones in development of GMP and GDP.

Year	GDP or GMP Milestone
1937	The so-called "Sulfanilamid-Disaster" causing the death of 107 people (mainly children) is the main motivator for the US congress to pass the "Federal Food, Drug and Cosmetic Act" in 1938. This was the foundation for the FDA (Food and Drug Administration). [1]
1962	The American congress passes the "Kefauver-Harris Drug Amendment" increasing the requirements to drug safety. For the first time the law requires evidence of the drug efficiency, forming the foundation for clinical trials.[2]
1969	WHO forms their first GMP guidelines ensuring traceability of any produced drug or active ingredient during production and thus production documentation. [3]
1970	In Europe, the Pharmaceutical Inspection Convention (PIC) was established which, in turn, passed a directive on the proper testing of medicines. [4]
1978	The GMP rules are anchored in the Code of Federal Regulations (CFR). [3]

1987	The Federal Law Announcement, dated November 20, 1987, publishes the first German Federal Operational Regulation for Wholesale Pharmaceutical Companies of November 10, 1987. This Regulation became effective on 1 January 1988. The regulation establishes (very general) rules on the storage and transport of medicinal products. The regulation is renamed in the 2010s the "Regulation on the wholesale and drug distribution - pharmaceuticals regulation."
1989	While many European countries had their own laws, for the first time the European Union issues their EU GMP guideline. [6]
1989	All major regulators for the pharmaceutical industry around the world come together and form the International Conference on Harmonization (ICH). [5]
1994	Guidelines on good distribution of medicinal products for human use (94/C 63/03) are published in the Official Journal of the European Communities March 1, 1994. These guidelines are based on Article 10 of Council Directive 92/25 / EEC of March 31, 1992 on the wholesale marketing of medicinal products for human use.
1994	The European Medicines Agency (EMEA), today called EMA, is founded in London. [5]
2004	For the first time, the version of the German Federal Operating Regulation for Pharmaceutical Wholesalers (Betriebsverordnung für Arzneimittelgroßhandelsbetriebe, BetrV) of July 30, 2004, referred to 1987. Stipulates that companies and institutions must comply with the EU guidelines for good distribution practice of medicinal products.
2007	In June 2007, the first version of a Codex for the transport of medicines in Austria is published. Austria thus becomes one of the "GDP pioneers" in Europe, a position that the country still holds today.
2010	WHO issues the "Annex 5: Good Distribution Practices for Pharmaceutical Products," a comprehensive guidance document summarizing various aspects of the pharma supply chain.
2011	The Official Journal of the European Union of July 1, 2011 amends Directive 2011/62 / EU of the European Parliament and of the Council of June 8, 2011 amending Directive 2001/83 / EC on the Community code relating to medicinal products for human use penetration of counterfeit medicines into the legal supply chain. This "Falsified Medicines Directive" is the basis of many other rules on GDP.
2012	Since 12.06.2012 the new pharmacy operating regulations (Apotheken (Apothekenbetriebsordnung - ApBetrO)) are mandatory for pharmacies in Germany. This results in new requirements for pharmacies in Germany, i.e. temperature monitoring of bearings (rooms, fridges, etc., refer to §16 of the ApBetrO).
2012	The IPEC Good Distribution Practice (GDP) Audit Guideline for Pharmaceutical Ingredients has been revised and the new version released. The previous version was released in 2008. The original version dates back to the year 2000. The new document, in the form of a questionnaire, is intended to help evaluate the practices and quality systems of traders who sell, store and/or repackage pharmaceutical excipients. The audit guideline is intended to be used as the audit tool to assess GDP compliance of distributors of excipients. The standard used for the assessment is the IPEC GDP guideline for pharmaceutical excipients (2006). [9]
2013	In March 2013, the Commission published Guideline on Good Distribution Practice for medicinal products for human use. The document has been revised several times since the first version was released; a substantial amendment of the German version will be made in November 2013 (document number 2013 / C 343/01).
2014	The US Congress passes the "Drug Quality and Security Act" (DQSA) including the "Drug Supply Chain Security Act" (DSCSA), which outlines steps to build an electronic, interoperable system to identify and trace certain prescription drugs as they are distributed in the United States.
2015	In 2015, a Commission guideline 2015 / C 95/01 on the principles of good distribution practice for medicinal products for human use is published. For the first time, GDP requirements are set for the distribution of active substances within the EU.
2016	PZ Pharmazeutische Zeitung is alarming in release 35/2916: A journey full of risks. Since 2013, the European guideline for a good distribution practice of pharmaceuticals applies. For public pharmacies, the monitored distribution channel is an important quality criterion, but increasingly complex supply chains highlight critical shortcomings in storage and distribution systems. [7]
2018	Drug scandal: Brandenburg withdraws Lunapharm operating permit permanently. The allegations against the pharmaceutical company Lunapharm are heavy: Trafficking in illegal, stolen and inferior drugs should have been operated by the company. Now the GMP licence was withdrawn.[8]
2019	In Germany the "Law for more safety in the supply of pharmaceuticals (GSAV)" came in force as of 16.08.2019. The quality and safety of the drug supply are significantly improved. This is the goal of the Safer Drug Supply Act (GSAV).

Sources:

[1] Kleist P, Zerobin Kleist C: Eine Kurzgeschichte der klinischen Studie. In: Schweizerische Ärztezeitung, 2005, 86, Nr. 44, Seite 2476

[2] US FDA. Milestones in U.S. Food and Drug Law History, https://www.fda.gov/about-fda/fdas-evolving-regulatory-powers/milestones-us-food-and-drug-law-history (22.05.2019) (letzter Aufruf: 22.05.2019).

[3] Wenzel J: Arzneimittelproduktion in den USA. In: Pharm. Ind., 1995, 57, Nr. 2.

[4] Feuerhelm K: GMP – Was ist das? In: PTS Training Service, 2000.

[5] Peither T, Rempe P, Büßing W: Qualifizierung. In: Maas & Peither AG, 2008, Tab. 1-1.

[6] Schnettler R: Basistraining Validierung. In: Kursunterlagen PTS Training Service, 2008, Seite 8.

[7] Biermann, Andreas: Eine Reise voller Risiken, erschinen in PZ Pharmazeutische Zeitung, Ausgabe 35/2016, https://www.pharmazeutische-zeitung.de/ausgabe-352016/eine-reise-voller-risiken/ (31.08.2016), letzter Aufruf 28.08.2019

[8] Märkische Allgemeine Zeitung vom 15.01.2019, Patrick Pleul, dpa, https://www.maz-online.de/Brandenburg/Lunapharm-Skandal-Brandenburg-entzieht-Betriebserlaubnis, zuletzt aufgerufen 04.09.2019

[9] IPEC Press release 03.01.2012; https://www.gmp-navigator.com/gmp-news/ipec-veroeffentlicht-gdp-audit-richtlinie-fuer-pharmazeutische-hilfsstoffe (zuletzt aufgerufen 04.09.2019)

1.9. Summary: compliance in the context of the pharmaceutical supply chain

If storage or transport of pharmaceutical products needs to comply with GMP and GDP guidelines, one must:

- produce, handle, store and transport products in qualified facilities
- ensure the temperatures are monitored by a compliant monitoring system (audit trail)
- ensure the sensors are calibrated regularly

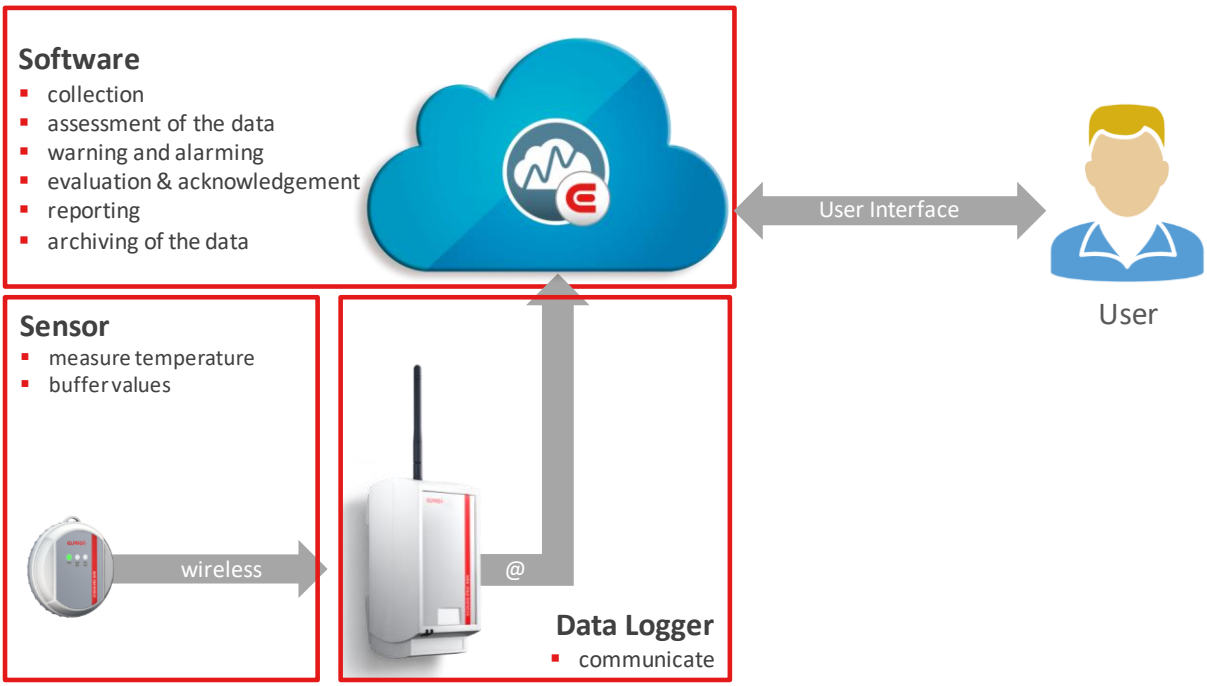
The same applies to the transportation, but with more focus on the requirements of fleets, containers, boxes and single-use equipment.

2. All About Monitoring Solutions

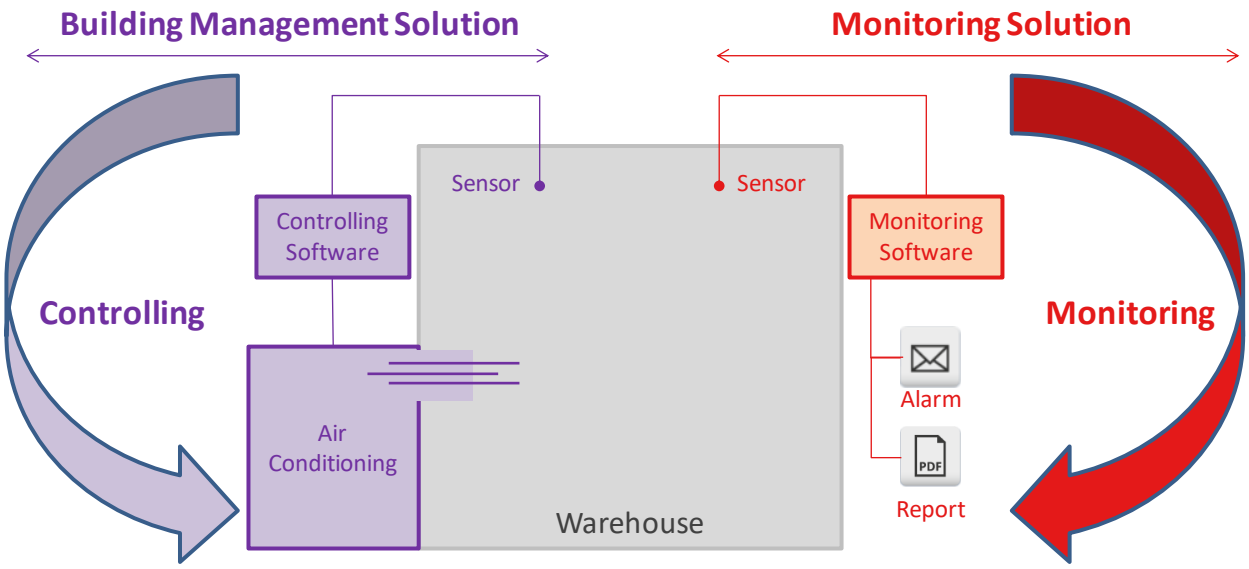
The history of monitoring solutions started more than 30 years ago with autonomous temperature data loggers such as ELPRO's legendary HAMSTER. Driven by a battery, the data logger recorded temperature and humidity measurements and was able to transmit its internal memory to the analysis software through an interface. Since the autonomous temperature data loggers were compliant to the Hazard Analysis and Critical Control Point (HACCP) standards, the food and beverage industry, as well as heating, ventilation, and air conditioning companies, (HVAC) used early applications of autonomous data loggers. Soon after that, the pharmaceutical industry started to monitor refrigerators and cold rooms also. Temperature data loggers were first used in laboratories and production facilities. Storage and transportation facilities were later added to the scope.

2.1. Key Functions of temperature monitoring systems

A monitoring system typically consists of a sensor conducting measurements of temperature or other environmental data in a defined interval. The sensor transmits the values (wired or wirelessly) to a data logger, which acts as a communication bridge. The software collects the values in real time in order to perform various tasks (see below illustration).



2.2. Building management systems vs. temperature monitoring systems?



In any production environment and in many warehouses, state-of-the-art building management solutions (BMS) are installed to conduct measurements of temperature and environmental data (like humidity), and give commands to the air conditioning system. How is an independent Monitoring Solution different? Other than building management solutions, monitoring solutions never have control loops. Instead, they are fully independent from any control mechanism. The validated independence of a monitoring solution is an important requirement of any GxP guideline.

2.3. Parameters and sensors

Research, production, testing and filling of pharmaceutical products are often performed in cleanrooms. In this environment, various parameters such as temperature, humidity, pressure, pressure differentials, CO_2 and particles play an important role regarding the quality of the product. Therefore, monitoring solutions must be open to process evaluation and display numerous environmental parameters. As soon as product is placed into a bottle, blister pack, vial or syringe, temperature are the only relevant environmental data that are important to the quality of the product.

2.4. Placement of sensors

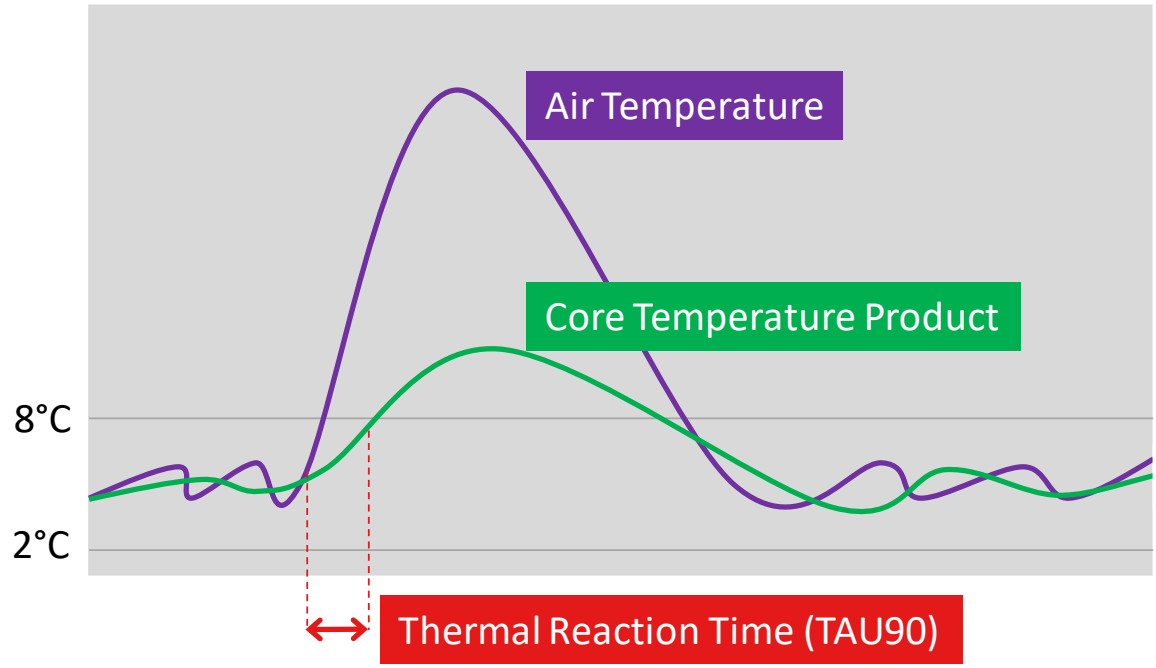
GMP and GDP guidelines require a qualification of the storage facility, refrigerator or transportation container. The most important part of the qualification is the thermal mapping process identifying the hottest and the coldest spots. Depending upon the specific situation and the requirements, the right sensors can be chosen and placed accordingly. Depending on the scenario, a mix between wired sensors (e.g. for 4 to 20mA transmitters) or wireless sensors (e.g. temperature and humidity) can be chosen.

2.5. Technologies of temperature measurements

To conduct temperature measurements electronically, there are different measurement technologies available. Each of them have advantages and disadvantages.

	Thermocouples	Resistance thermometers		
		NTC	PT 100	Digital Sensor
Physical principle	Two different electrical conductors (bi-metal) changing resistance with temperature	**N**egative **T**emperature **C**oefficient (resistance decreases as temperature rises)	**P**latinum Resistance **T**hermometer**s** (resistance increases as temperature rises)	Electronic microchip measuring & delivering a digital temperature value
Advantages	▪ Lowest cost ▪ Exchangeable standardized elements	▪ Low energy ▪ Very stable over time ▪ Low cost standard component	▪ Low energy ▪ Very stable over time ▪ Exchangeable standardized elements	▪ Low energy ▪ Very stable over time ▪ Low cost in large volumes
Disadvantages	▪ Drift over time	▪ Limited temperature range of each type	▪ Needs an additional converter (extra cost)	▪ Limited temperature range of each type ▪ Internal sensors only
Typical Application	Extreme temperatures (steel and iron industry)	-30 °C to +70 °C	-200 °C to +850 °C	-30 °C to +70 °C

2.6. Thermal reaction time



In a storage facility (i.e. a refrigerator) air temperature will change very fast through the opening and closing of the door. The thermal reaction time (Tau90) measures the time it takes to adjust to 90% of the temperature change. In other words, if a door of the refrigerator (5 °C) is open, it takes a lot of time until the temperature adjusts to the ambient temperature (20 °C). Since temperature sensors have a very small thermal mass, they immediately change temperature. Pharmaceutical products are normally well packaged or have significant thermal mass, meaning that the core temperature of the products will adjust significantly slower. This effect is called the thermal reaction time. Depending on the thermal mass of the pharmaceutical product and the packaging, this thermal adjustment might take 15 minutes to over and hour. To simulate this effect, thermal dampers (such as glycol bottles) or electronic damping mechanisms are used.

2.7. Technologies of humidity measurements

Humidity is relative to temperature. Relative humidity is a function of the ambient temperature and the water vapor pressure in the air. Humidity sensors use the dependency of the relative humidity and the amount of moisture pressure inside the sensing element as a physical measurement principle. For electronic measurement, there are two different technologies available. Each of them having their advantages and disadvantages:

	Capacitive	**Conductivity (Electrolytic)**
Physical principle	Plate condenser changing capacity with relative humidity	Tubes changing capillary height with relative humidity, therefore electrolyte changing conductance with relative humidity
Advantages	▪ High accuracy between 5% rF and 95% rH (relative humidity) ▪ Simple and cheap to build (low price) ▪ Not sensitive to vibration & shock (can also be used for transport monitoring)	▪ Very high accuracy between 5% rF and 95% rH (relative humidity) ▪ Good accuracy also in high-moisture environment (>95% rH) ▪ Less vulnerable to clogging of sensing element (due to air pollution), ▪ Minimal drift over time
Disadvantages	▪ More vulnerable to clogging of sensing element (due to air pollution) ▪ Small drift over time ▪ Depending on environment, yearly exchange of sensor might be needed	▪ Complex construction with many manufacturing steps (therefore expensive) ▪ Sensitive to shock and vibration (due to capillary tubes) 
Typical Application	▪ Warehouses and storage facilities ▪ Trucks, transport boxes and containers	▪ Incubators with high humidity ▪ Clean rooms (due to high accuracy & less sensitivity to clogging*)

*Clean Rooms have, by definition, very clean air with very few particles. However, they are regularly disinfected with different types of gases. Those gases may cause clogging of the humidity sensor (resulting in drift = loosing measurement accuracy over time).

3. Compliance in Temperature Monitoring Solutions

Why does a temperature monitoring solution need to be compliant? What do user management; data management; and audit trail have to do with it?

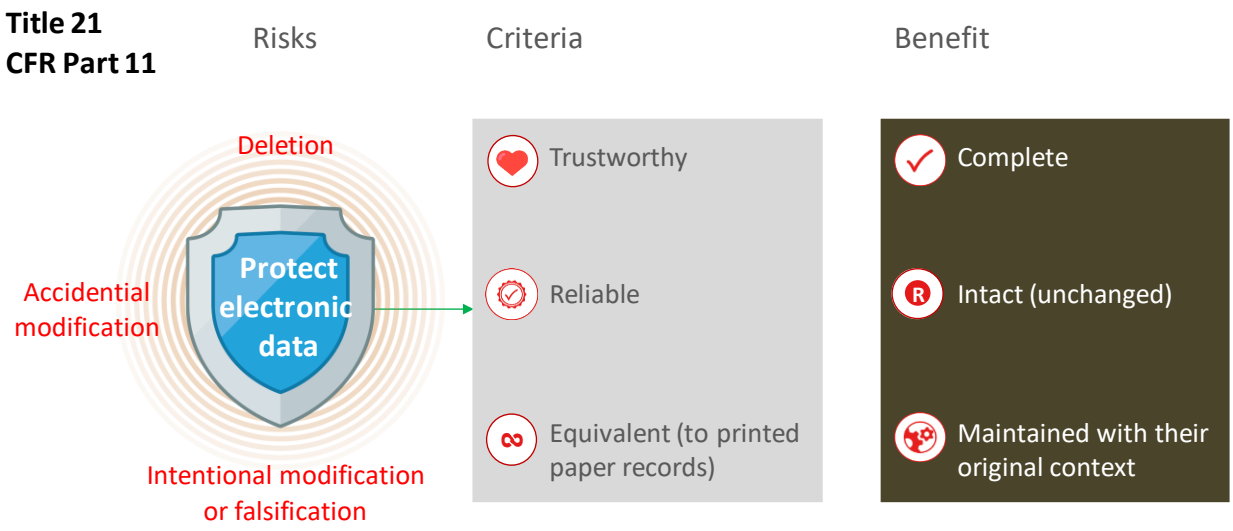
3.1. How is compliance in monitoring solutions defined?

If a company stores or transports pharmaceutical products and wants to comply to GMP and GDP guidelines it must produce, handle, store and transport the products in qualified facilities. Calibrated sensors need to be installed in those facilities, which report their temperature values to a compliant monitoring system. But what does compliance in combination with a temperature monitoring solution mean? In the following short summary we list all elements and features of a GxP-compliant temperature monitoring solution.

3.2. What is Title 21 CFR Part 11?

“Title 21 CFR Part 11” is the part of the Title 21 of the Code of Federal Regulations written by the United States Food and Drug Administration (FDA). Title 21 contains regulations on electronic records and electronic signatures. Part 11 defines the criteria by which electronic records and electronic signatures are considered trustworthy, reliable, and equivalent to paper records to ensure compliance.

A monitoring solution which stores electronic records which are critical to patient safety must be in compliance to Title 21 CFR Part 11. In order to do so, it is important to understand the main risks.



3.3. How does Title 21 CFR Part 11 apply to a monitoring solution?

Electronic data could be deleted, accidentally modified or intentionally modified. Title 21 CFR Part 11 defines criteria by which electronic data is trustworthy, reliable and equivalent to paper records and handwritten signatures executed on paper. If you follow those rules, your electronic records will be complete, intact, maintained in the original context and geared towards compliance.

- Complete Data – Monitoring temperature with the help of sensors, a communication bridge and the software solution, one of the main challenges is the completeness of data. Mechanisms need to be in place to ensure compliance, so that no data is lost on the way from the wireless sensors through the communication bridge to the monitoring software. Therefore, in case of a disconnection between the sensors and the radio bridge or the cloud storage, data must be buffered in the sensors until the cloud confirms that the connection has been re-established and the data have arrived.
- Intact Data – Although the risk for accidental or intentional modification is minimal, the integrity of data in a measurement chain can only be achieved by encrypting the data all the way from the measuring wireless sensor through the communication bridge to the cloud. Once the data has arrived in the software, it is important that no raw data can be deleted or modified. No user should be able to change the raw data; however it is possible to add certain types of additional information. For example, in order to add an interpretation of the data, certain comments or acknowledgements about the raw data can be added to the system. Furthermore, in order to create selective views on the raw data, reports can be created and exported.
- Maintaining electronic data in its original context – Keeping the data in one single source on a central cloud infrastructure makes sure that the data are kept in its original recorded context and the risk of misinterpretation is therefore eliminated. Warnings, alarms and reports should always refer to the unique sensor name, event number and time stamp.

3.4. Compliance in user management and authentication

There are many rules to follow when it comes to compliance in user management. Every user with access to the solution must be identified by a unique username and password and must have a clear role and rights. Additionally, every action taken by the user in the system must be identified and tracked. When conducting critical operations such as the acknowledgement of an alarm, the user even needs to confirm his action by inserting his

password a second time. In order to avoid unauthorized access, it is furthermore important to implement a time-out mechanism in case the user is not taking action for a longer time period.

3.5. What is an audit trail?

The result of the above mentioned tracking functionalities is a complete audit trail aligned with compliance: who has done what and why? Technically, the audit trail keeps track of every single automated event the system is generating and every single manual task a user is performing. So regardless from which perspective one takes a look into the system, a full audit trail could be:

- Sensors: Timeline of all events on a sensor like measurement values, statuses, setting changes, warnings, alarms and acknowledgments
- Warnings and alarms: Time stamps, statistics, who has commented on what, who has acknowledged something and when
- Reports: Sensor names, timeline, user which has created the report

3.6. Automated events in the audit trail

A temperature monitoring system typically executes the following different automated mechanisms and workflows:

- monitoring the system availability and performance (to trigger a system warning)
- monitoring the sensors (battery status, wireless connection, validity of the delivered data to trigger sensor warning)
- measuring, storing and evaluating temperature values and matching them with the defined limits to trigger high/low temperature warnings and alarms (for further information see section on "how to deal with temperature excursions")
- monitoring all settings and setting changes

3.7. Manual tasks in the audit trail

In addition to automated events, the system must keep track of every single manual task a user performs including the time stamps of each task. The following manual events can be tracked:

- Who is logged into the system and what are the roles and rights of this individual?
- Who has logged in/out and at which times?
- Who has changed settings, what were the settings like before and after the change?
- Who has commented or acknowledged a warning or an alarm?
- Who has generated a report?

3.8. How to deal with temperature excursions?

GMP and GDP standards define that pharmaceutical products must be stored and transported according to the required temperature conditions mentioned on the drug label to ensure compliance. Every excursion from these temperature conditions must be documented. The monitoring system should support the user in creating automated excursion reports to which the user can still add certain information. The following procedure gives an example of what questions a quality manager should ask, once a temperature excursion has occurred.

3.9. Excursion report

ALARM Goes Off

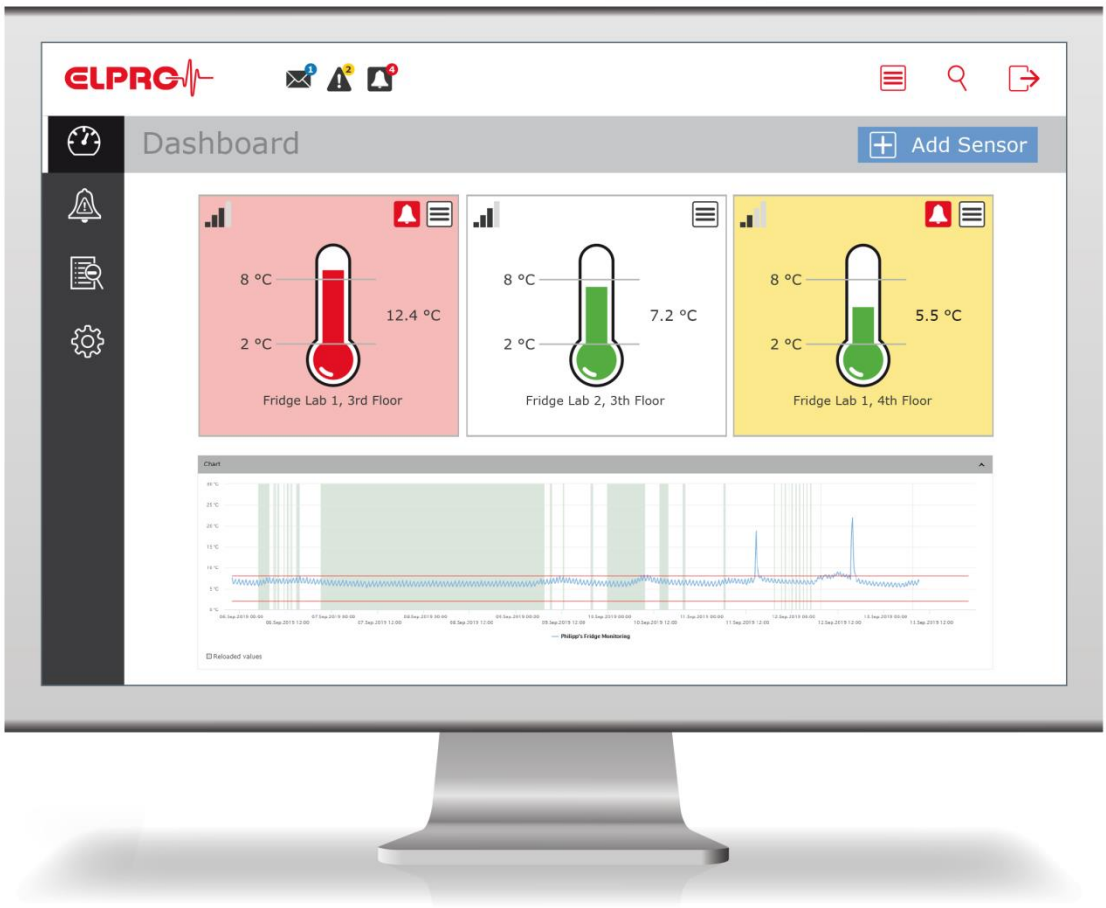
A temperature excursion triggers an alarm. The alarm can be seen on the sensor itself or the dashboard display and can be sent out via email or SMS containing an excursion report with the following information:

- Where did the alarm go off? Which facility, container or sensor had an excursion?
- When has the temperature excursion occurred and when were the drug label conditions re-established?
- How long has the product been exposed to temperatures outside the drug label conditions?
- What was the highest/lowest temperature measured?

Manual Information to be added by a user to the temperature monitoring system

- Affected Product? Which product, batch or pallet have been potentially affected?
- Risks? Is it likely that the core temperature of the product has been affected, thus damaging the product?
- Severity? Is there sufficient stability budget left to justify a release of the product or is a product recall necessary?
- Corrective actions needed? What is the cause of the temperature excursion and does it have to be corrected? Do people need to be informed about the findings?
- Preventive Actions needed? In case of high-risk and/or repetitive errors: Which preventive actions can be performed in order to avoid a repetition of the event? Are changes implemented?

3.10. Why is the dashboard important?



A dashboard gives a brief overview on the current status of each sensor. The sensors can be grouped in a meaningful way or placed on top of a floor plan to illustrate their physical location. The dashboard should show the currently measured value, show the alarm status, and give further meaningful information on the technical status of the sensor. The benefits of a dashboard are:

- Clear entry screen into the software and easy navigation from the dashboard
- Quick overview screen for operators to see if production is running smoothly or not

3.11. Why is a periodic reporting important?

Besides a clear alarming mechanism, it is vital to have a periodic reporting on all sensors of a system. Every report can have a different purpose and therefore every report will contain different content. If the report serves as an archive of data, the report should be a document with compliance regarding the ISO standards for long term archiving. If the report is sent to customers, it might be vital to combine various sensors together giving the ideal overview on their project. To sum it up, a few examples of regular reports could be:

- Monthly reports for each sensor (for archiving purposes)
- Weekly reports of various sensors combined (for customer reports)
- Daily reports for each sensor (for data exports to a batch system)

3.12. How are data archived?

Archiving is not clearly defined in GxP regulations and is left open to everybody's own interpretation. Many people have the rather unrealistic idea that, once data are archived, it should be available forever in the same way it was generated. Data archiving is the process of "moving data that is no longer actively used to a separate storage device for long-term retention. Archive data consists of older data that remains important to the organization or must be retained for future reference or regulatory compliance reasons." As a result, "archive data" has a different form than "process data".

Process Data

Process data are "fresh data" used to execute business decisions (e.g. data of a product, mean kinetic temperature calculation of a stability study). The service provider must ensure that for two years, process data are available electronically for visualizations (e.g. zoom, overlay), statistics (e.g. calculate MKT), reports (e.g. release decision) and exports of the data (e.g. to a higher batch management system). Furthermore, it must be possible to add comments related to the data in the system.

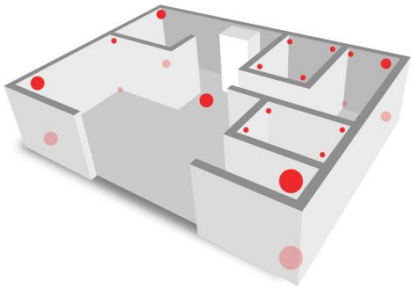
Archive Data

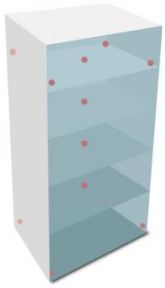
After the first two years, the data are not typically needed in business processes anymore and the location and form will be changed into archive data. The service provider must ensure that archive data are available for at least 10 years and fulfils the following requirements:

- Naming conventions clearly labelled (e.g. "monthly report Sensor A")
- Data must be stored as a record in a readable form, for example the "PDF/A" format, which follows the ISO 19005 standards for archived documents
- Data must be stored in a secured data archive

4. All You Need to Know About Qualification and Mapping

If you want to comply with GMP and GDP guidelines, you need to produce, handle, store and transport your products in qualified facilities. Read more about the formal requirements and industry best practices and become a qualification champion.



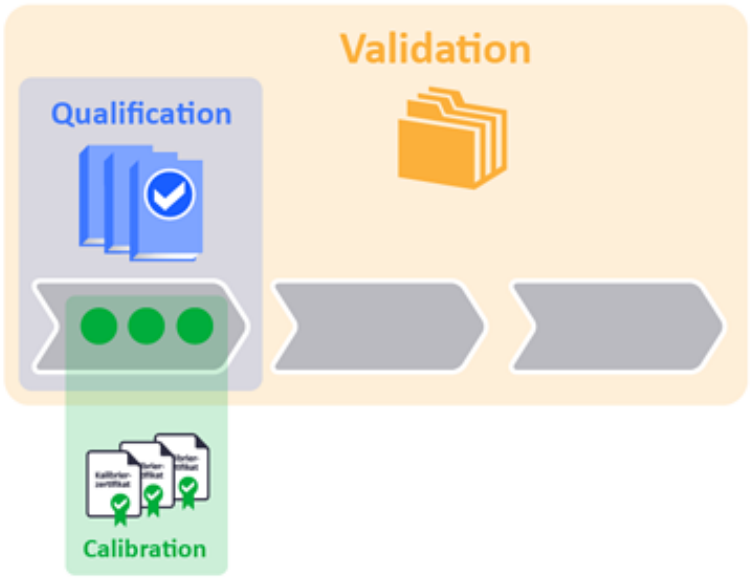


4.1. What is a validation?

A validation is (according to GMP/GDP) to check if a process or activity has the expected result. Validation is therefore about taking a closer look at a complete process. The GxP rules define that all quality relevant processes must be validated. The first part of the validation is to define the expected results; the second part is to verify and document that the process delivers the expected result. For example, to store products in a warehouse, you need the warehouse itself of course, but you also need employees, which are qualified to do their job, systems to support the process, and you might need other equipment to ensure the product is stored according to its needs. In a validation, all of the things mentioned above would be validated. Validation is only possible if all used elements are qualified upfront. Quality-relevant elements of the supply chain, which need qualification, are for example, storage facilities, cold rooms, containers, insulated boxes, reefer trucks, vans, data loggers, software for evaluation and archiving, etc. If all of these elements are qualified according to EU-GMP Guideline, Annex 15, one can start the validation of the process using all those elements.

4.2. What is a qualification?

Qualification is the process of proving that a room, system, facility, transport container, truck or supplier fulfills the intended purpose. In other words, a piece of equipment is used in some way to produce, handle, store or transport pharmaceutical products. Therefore, a qualification must demonstrate that the equipment is fit for that purpose. For example, a warehouse must to maintain 2 to 8°C in every area. The qualification certifies that the warehouse is fit for purpose and that the temperature range from 2 to 8°C is maintained.



As a result, the qualification therefore always starts with the definition of the intended purpose and then continues with an evaluation and documentation of whether the equipment is suitable to fulfill the intended purpose.

A simple rule to remember: whatever you can touch, you can qualify - the rest is validated.

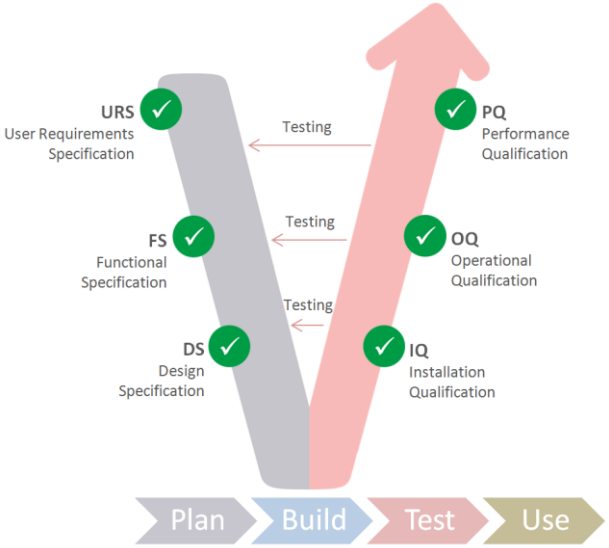
4.3. What are formal requirements for a qualification?

There are no detailed formal requirements to a qualification. Therefore, whoever performs a qualification is free to decide in what form and document structure the qualification is performed. However, regulation gives some hints and there is plenty of industry best practice:

- Documented proof: A qualification should follow the good documentation practice and therefore include clear document naming, versioning, change history and document ownership. Furthermore, a proof is only possible with evidence – which means that a test plan and clearly identifiable and reproducible test results must exist.

- Intended purpose stated: Clear requirements must be documented. What is the equipment, which is in the qualification process, supposed to do? By defining the intention, one automatically excludes all other non-intended purposes and effects and minimizes risks.

4.4. What is the Industry Best Practice for a Qualification?



In every GxP qualification, the so-called V-Model is applied. There are four phases: Plan, Build, Test and Use. It is easiest explained by a simple example of a Refrigerator.

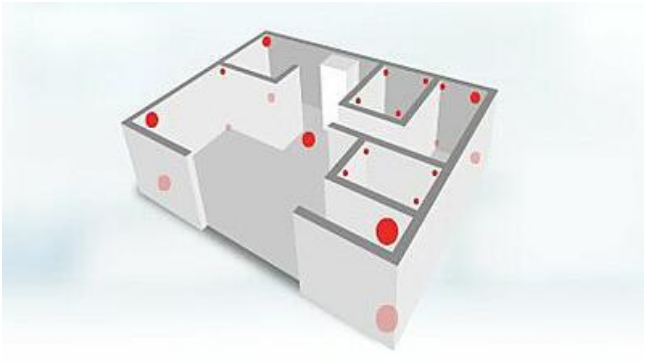
The same V-shaped principle works for any piece of equipment.

- User Requirement Specification (URS): The first document needed is a so-called URS. For a fridge, this could be simple and only contain a handful of points. For example: “Must maintain 2 to 8°C” and “must fit under a counter.”
- Risk Analysis: As a next step one conducts a risk analysis. In the risk analysis, you think about everything that could go wrong and decrease the patient's safety. In our fridge case, it could be “door open” and “power outage”. Each risk is now evaluated and rated in probability, severity and detectability.
- Design Specification: Since a power outage is a critical risk, you may define an uninterrupted power supply in your design specification for the fridge. Of course, you also define what type of fridge (model, manufacturer, etc.) you want to buy.
- Design Qualification: After the installation of the fridge, the design qualification checks if the right fridge was purchased and if the uninterrupted power supply is actually installed.
- Operational Qualification (Mapping): Now you can perform the first mappings. By conducting the operational qualification mapping, you test the functionality of the regulations and the ability to maintain a 2 to 8°C temperature range in the fridge. It is the dry run before you put the fridge into service.
- Performance Qualification (Mapping): Finally, in the performance qualification mapping, the regulations are tested to work in real operation, meaning with full load.

4.5. Summary of terms

Validation	Qualification	Mapping
The process of establishing documentary evidence demonstrating that a process carried out maintains the desired level of compliance at all stages.	An action of proving that equipment which is part of a validation is properly installed, works correctly and actually leads to the expected results.	An activity which is part of a Qualification which measures and documents the temperature distribution within a room by locating the hottest and coldest spot.

4.6. What is a temperature mapping exercise?

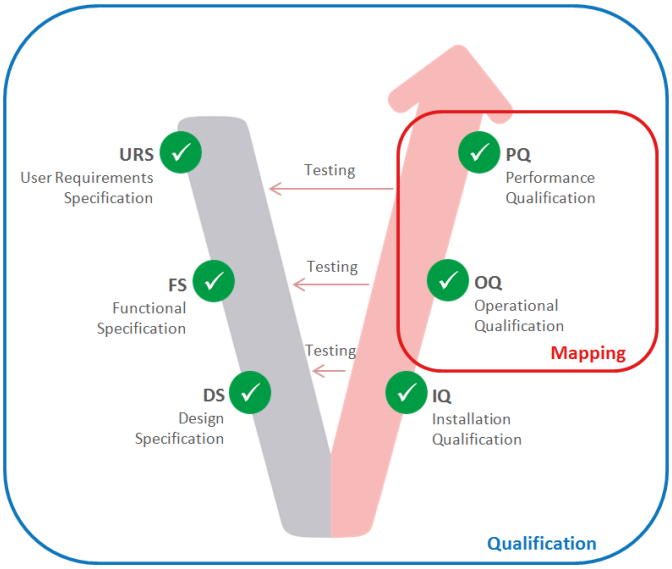


A mapping study is the activity to measure and document the temperature distribution within a room by locating the hottest and coldest spot. According to WHO, "mapping may also be used to identify zones where remedial action needs to be taken; for example by altering existing air distribution to eliminate hot and cold spots". A mapping study takes place for a defined time period, typically a few days or weeks, and monitors temperature in various defined locations inside the room (e.g. refrigerator, warehouse, box or container) forming the mapping grid. The mapping grid follows two principles:

- A 3-dimensional network of mapping points with consistent intervals in the x, y and z axes. WHO defines the expected distance between the mapping points.
- Additional mapping points being the expected hot and cold spot (which could be near the air outlet, door, seal or wall)

Following the mapping plan (floor plan), the calibrated mapping loggers are configured, clearly labeled, and placed at the defined mapping points. After the defined time period, all mapping loggers are collected, the measurement curves are overlaid and the hottest and coldest spot in the room are evaluated. The mapping is successful if no temperature outside the required temperature range has been found. The hottest and coldest spots are obvious places to install sensors of the monitoring solution, since a temperature excursion at those spots would be most critical first and therefore measured first.

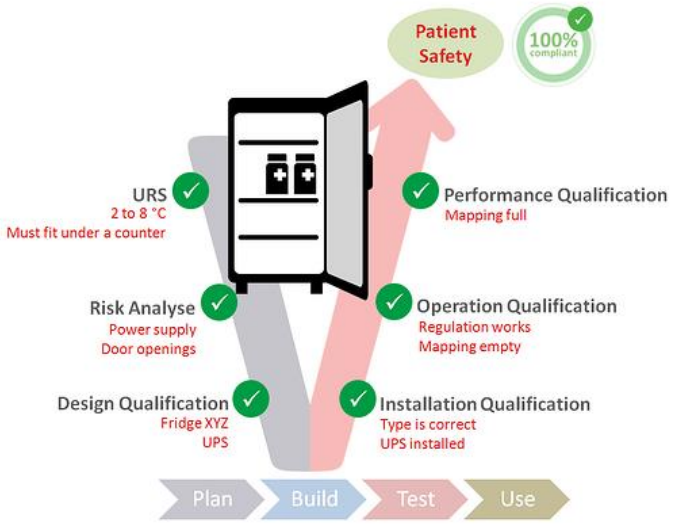
4.7. What is the difference between qualification and mapping



A mapping is always just the testing and proofing part of a qualification, so it is a sub-set of activities and documents. You could also say that the first part of the qualification is the theoretical part and the second part of the qualification is the mapping part, which is the testing part. The theoretical part of the qualification has its focus on describing requirements, evaluating risks and defining specifications, the testing part (mapping) is very practical with distributing mapping data loggers and analyzing measurement rows.

4.8. How to qualify and map a refrigerator

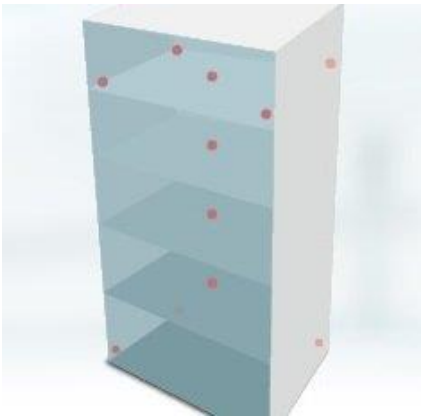
Qualifying a refrigerator, freezer or ULT-freezer is a rather simple type of qualification:



- Refrigerators are standard equipment purchased as stand-alone devices. Compared to other more complex and customized pieces of equipment (like warehouses, transport boxes), the risks are limited.
- Refrigerators operate in a controlled room temperature environment. The risks are limited to the following: air outlet blockage, power outage, wrong loading and door opening.

Companies usually operate many refrigerators, freezers, ULT-freezers or incubators. Therefore, qualifications are typically done as a so-called fleet or farm qualification, which is performed as follows:

1. Cluster the fleet of refrigerators into homogeneous groups, for example clustered by same supplier, same model and same size.
2. For each group apply the V-Model and work out:



a. User Requirement Specification: document temperature range and description of application.
b. Risk Analysis: evaluate placement, power supply and operational aspects like frequency and lengths of door opening, loading and cleaning patterns.
c. Design Specification: For each cluster of refrigerators, define exact purchased model and installation instructions (avoid blockage of air flow compressor, power supply).
d. Operational Qualification: One fridge from each cluster is mapped in detail following WHO guidelines in an empty status.

3. We can now perform the design qualification for one refrigerator per cluster group by simply checking if it is the right model, and does the airflow and power supply comply with the specifications?
4. Since one refrigerator per cluster group has already been mapped, it is now possible--for the remaining refrigerators of the same group--to leave out the dry run qualification and to directly perform a performance qualification (mapping of the full refrigerator) during normal operation. Of course, the mapping should be performed with data loggers that are calibrated and compliant.

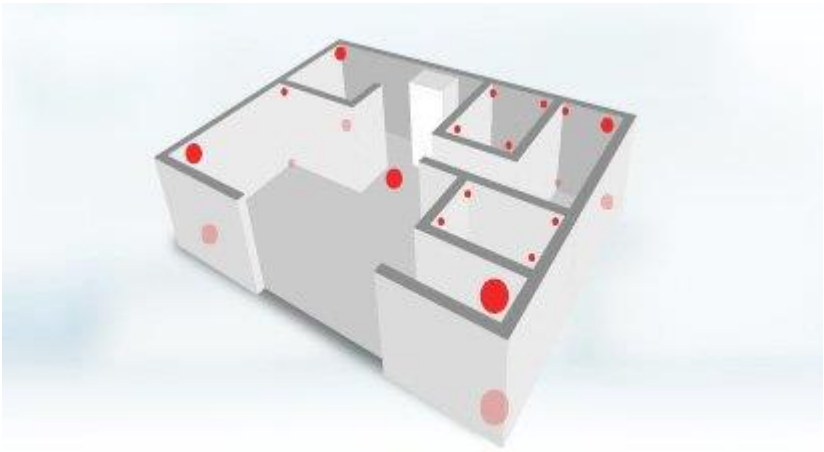
4.9. How to qualify and map a warehouse, cold room or storage facility

Qualifying and Mapping warehouses, cold rooms and storage facilities is much more complex than refrigerators, because they are not off-the-shelf products. Although built with standard components, they are engineered facilities with individual designs, layouts, air flows, doors and control systems. There are many different types of Warehouses, Cold Rooms or Storage Facilities with different temperature ranges and applications which have a major implication on the Qualification and Mapping strategy:

Type	Description (typical)	Temperature range (typical)	Implications on Qualification and Mapping
Warehouse	Large room/hall with open space or high racks.	15-25°C 2-8°C	Warehouses typically have outer walls directly exposed to ambient conditions and seasonal effects. Insulation of the building and the absence of windows and other openings is vital. Since we have influence from ambient conditions, a winter and summer mapping will be necessary. Same applies for the loading dock.
Cold Rooms	Smaller room/hall with open space or racks.	2-8°C -20°C	Cold rooms are typically rooms inside a building and the walls have no direct exposure to ambient conditions and seasonal effects. Often there is no need for performing a separate winter and summer mapping.
Other facilities and loading docks	Small room with racks	15-25°C 2-30°C <40°C	The stored/handled products, their required label condition and there lengths of stay will define the framework and complexity of the qualification and mapping.

Considering this leads us to the question of how to structure the qualification. In most cases, the planning and building phase is delegated to specialized engineering firms. Still the documentation of the qualification and mapping must be consistent in following these steps:

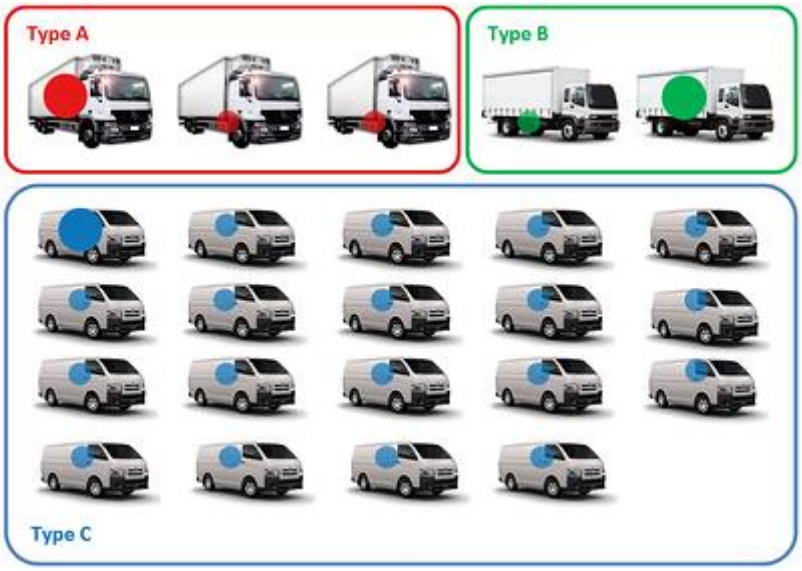
1. Define user requirement specifications describing the purpose of the warehouse, cold room or storage facility.
2. Perform detailed risk analysis describing all structural and operational risks
3. Define high-level design requirements (floor plan, equipment for temperature control, power supply)
4. Perform a simple design qualification: Has the facility been built as planned?
5. Perform an operational qualification: Mapping of the empty facility in winter and summer condition (perform only one mapping if seasonal effects can be fully excluded per above table).
6. Perform the performance qualification: Mapping with full load during normal operation.



4.10. How to qualify and map a truck or van

Companies typically operate many trucks or vans in one fleet. Therefore, truck and van qualifications are typically conducted as fleet qualification, which is performed as follows:

1. Cluster the fleet of trucks or vans into homogeneous groups. Example criteria can be: same brand, same model, same layout, same type and version.



2. For each group apply the V-Model and work out:
   - User Requirement Specification: Temperature range and description of application (lengths of trip, expected extreme ambient conditions, winter/summer profiles)
   - Risk Analysis: Power supply and operational aspects like loading/unloading, frequency and lengths of door opening.
   - Design Specification: For each type, definition of exact purchased model and set-up.
3. Now perform the design qualification for one truck/van per cluster group by simply checking the few points defined: Is it the right model with the exact same configuration and application range?
4. Since one truck or van per cluster group have already been mapped, it is now possible--for the remaining trucks/vans of the same group--to leave out the dry run qualification and to directly perform a performance qualification (mapping of the full truck) during normal operation. Of course, the mapping should be performed with data loggers that are calibrated and compliant.

4.11. How to qualify a transport box or container

Qualifying a transport box or container is much more complex than qualifying a refrigerator. Since the object to be qualified moves around in uncontrolled environments, we first need clarity on the planned purpose of the box and container by answering the following two questions: is it a road, air or ocean shipment? How long will the shipment take? The following picture shows an overview of different transport modes:

Furthermore, when performing a qualification of a transport box or container, another challenge is to come up with a realistic temperature profile to test against. How long will the shipment take? What temperatures will be expected at origin, on the way and at destination? Are there seasonal changes? There are two approaches to define the right ambient temperature profile:

1. Use empirical data: An often seen approach is to classify the shipment into shipment sections (origin-to-hub; hub-to-hub; hub-to-destination) or to cluster them by assigning climatic zones to the sections (e.g. cold, moderate, warm, hot) and to define extreme seasonal weather changes (e.g. cold-to-hot; hot-to-cold). The difficulty with this approach is to define the specific length of each shipment section (how many hours the product has in each section) and estimate a realistic average temperature within each climate zone.
2. Map the ambient temperature: The best way is to measure the temperature of the specific route in reality. This is done, for example, by performing several seasonal shipments and collecting the temperature data from each of the shipments. Afterwards, the average temperatures from each shipment section are calculated and used. This is the most elaborate method.

Last, but not least, there is a significant difference between passive insulated boxes using phase change materials (PCM) with insulation and active heating/cooling containers. From a qualification side, the difference of the two technologies is not so much performance but rather the involved risks which need to be considered. The following explains the difference between the two technologies including a high-level risk appraisal.

Passive box vs. Active container: Differences from a risk perspective

Technology	Passive Insulated Box	Active Container
Example	▪ Passive insulated 24 litre box	▪ Active Heating & Cooling Air Container ▪ Sea container
Technology used	▪ Thermal Packs filled with Phase Change Material (PCM) having a defined melting point (5°C melting point for 2-8°C shipments) ▪ Insulation materials such as Vacuum Panels	▪ Insulated container with air ventilation ▪ Heating and cooling unit (typically compressor cooling and electrical heating) ▪ Battery and charging unit
Process at origin	▪ PCM must be pre-conditioned and have the right temperature when loading ▪ To ensure the promised performance the box must be built-up exactly as designed: product surrounded by one (or several) layers of PCM, surrounded by one (or several) layers of Vacuum Panels, hold together by a cardboard box.	The battery must be charged before loading and the right set temperature must be defined.
Process during shipment	Make sure the shipment is not exceeding the defined shipment lengths (e.g. the box is built to keep temperature for 72 hours).	Re-charge the unit at hubs and airports. Prevent manipulation of the set temperature or door openings.
High-level risk appraisal	The highest risk is a packaging error (e.g. wrong conditioning of PCM). As soon as a shipment is on its way, the solution is very stable and there are only minimal risks.	While active containers are very easy to load, there are significant risks during shipment involving human error (no re-charging) and mechanical failure (heating and cooling containers consist of hundreds mechanical and electronic components which can fail)

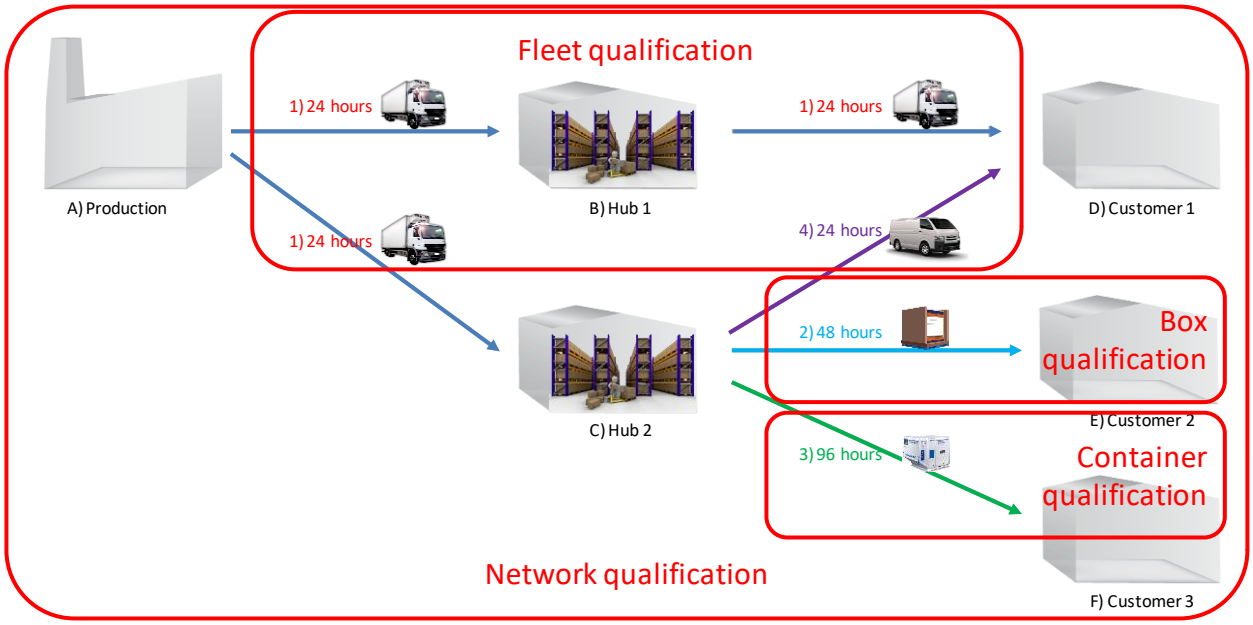
As soon as the box or container has been chosen, and the intended purpose is defined, qualification can start applying the steps of the V-Model:

1. Define specifications of the transport box or container describing the type transport box, loading volume, set temperature, shipment lengths of the transport box or container and specific temperature profiles.
2. Risk analysis describing all operational and technical risks of the transport box or container.
3. Operational qualification by testing the box in a climate chamber (mapping) running through all defined temperature profiles.
4. Performance qualification by performing test shipments (mapping) on a specified route (e.g. shipment from an extreme cold environment to an extreme hot environment).

4.12. How to validate a transport route or network

Validating a transport route or an entire network starts with qualifying all used equipment elements (warehouses, transport boxes or containers, trucks or vans). In order to be able to find the right subjects for qualification inside a network, a clustering must be performed. Clustering criteria of the transport elements can be:

- Transport mode (truck, van, rail, air, ocean)
- Secondary packaging (no secondary packaging, thermal cover, insulated box or active container)
- Truck or van type
- Trip lengths
- Trade-lane (Origin/Destination)
- Climate zones and seasons

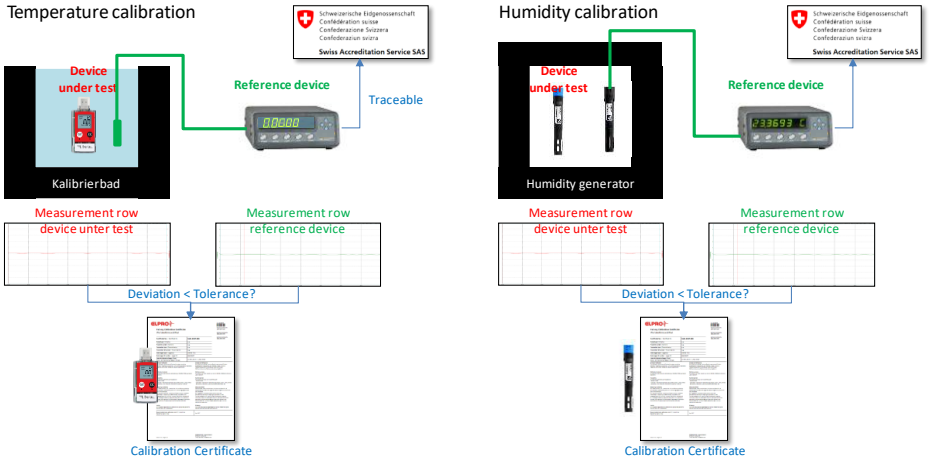


After clustering the network into homogeneous groups, now a high-level risk analysis can be performed. Cluster-specific risks are described and evaluated. The probability, severity and detectability form the risk rating. The higher the risk rating, the more focus must be given when defining mitigation measures. After performing the clustering and risk analysis, each “cluster element” must now be qualified.

Cluster/ Step	Risk	Description and Cause of Risk	Proba-bility	Severity	Deteca-bility	Risk Rating	Mitigation
1) Truck 24h	Wrong truck	Wrong truck type arrives from forwarder	low (1)	low (3)	high (1)	low (3)	Fleet Qualification
1) Truck 24h	Length	Trip takes longer than 24h due to traffic or customs issues	medium (2)	low (1)	high (1)	low (2)	Fleet Qualification
1) Truck 24h	Extreme °C	Extremely low temperatures in winter or extremely high temperatures in summer	high (3)	high (3)	medium (2)	high (18)	Fleet Qualification
2) Box 48h	Wrong packaging	Insulated boxes are wrongly loaded	medium (2)	high (3)	low (3)	medium (18)	Training of personnel
2) Box 48h	Length	Trip takes longer than 48h due to wrong routing by forwarder/ airline or customs issues	medium (2)	high (3)	high (1)	medium (6)	Book express freight
2) Box 48h	Extreme °C	Extremely low temperatures in winter or extremely high temperatures in summer	high (3)	high (3)	medium (2)	high (18)	Box Mapping, Monitoring

5. All You Need to Know About the Calibration of Sensors

5.1. What is a (factory) calibration?

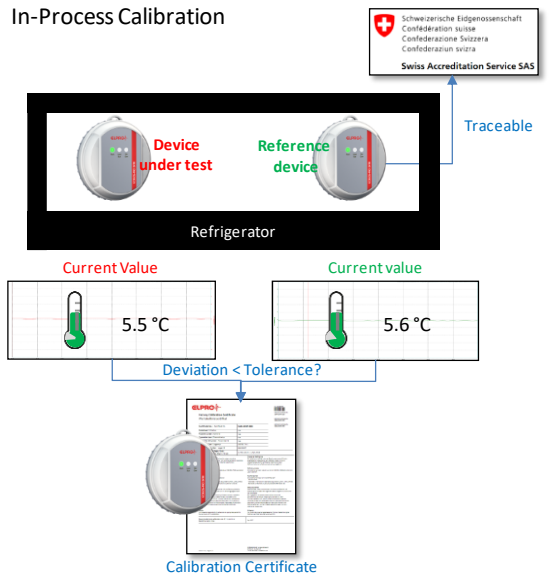


A calibration is a reliable, reproducible and documented comparison of a device under test (data logger, sensor) with a traceable reference. The reference is a high-precision instrument which is checked regularly by an accredited laboratory (Switzerland: SAS/SCS; USA: NIST; Germany: DaaKs; UK: UKAS). A calibration is always performed at one or several defined measurement points. To perform the calibration, a device/machine is needed to keep a stable environment:

- Temperature: calibration bath or a calibration block keeping a constant temperature to let the two devices adjust to the temperature point (e.g. for 30 minutes)
- Humidity: humidity generator or a reference solution (salt water) generating a defined humidity at a given temperature to let the two devices adjust to the relative humidity (e.g. for 2 hours)

The two measurement rows (device under test and reference device) are compared. If the device under test measures within the specification, the result is documented in a calibration certificate.

5.2. What is an “in-process calibration”?

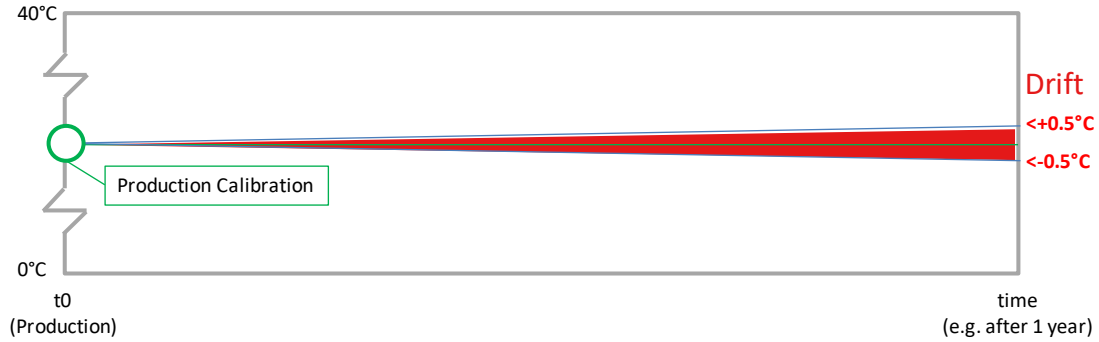


An in-process calibration is a faster, less reliable and cheaper way to calibrate. It is mostly used on temperature sensors and is typically performed on-site – without using a calibration bath or block. It simply compares the current reading of a device under test and the reference device. The reference is a high-precision instrument which is checked regularly by an accredited laboratory (Switzerland: SAS/SCS; USA: NIST; Germany: DaaKs; UK: UKAS). An in-process calibration is by definition only performed at one measurement point – the current process temperature. In-process calibrations do not have a very good reputation since the theoretical risks of measurement errors is higher. Still, they deliver a strong indication of the accuracy.

5.3. Why calibrate from a technical perspective

What is drift?

The core of each data logger is its measurement sensor. Each sensor type has a specific measurement range, accuracy, and different strengths and weaknesses. Before the sensors are built into a data logger, each sensing element is calibrated (tested on its accuracy and documented) and therefore is accurate within the defined specification. The change of the accuracy over time is known as “drift.” If we recalibrate a sensor after one year, we verify that the sensor accuracy is still within specification.



What causes drift?

Drift can happen due to physical effects and aging of components over time. The risk for drift is different for each sensor type since it heavily depends on the used measurement principle and how well the sensing element are protected.

	Temperature sensor		Humidity sensor	
Risk of Drift...	**NTC**	**PT100**	**Capacitive**	**Electrolytic**
...in Rooms	Minimal	Minimal	Small	Minimal
...in Incubators & hot cabinets (high humidity)	Minimal	Minimal	Moderate	Small
...during Transportation	Minimal	Minimal	Small	Moderate

Conclusion Temperature

Temperature sensors have a minimal risk of drift. In both applications (rooms and equipment; and transportation) they are long-term and stable over many years.

Conclusion Humidity

The risk for drift of humidity sensors depends on the application and the sensing technology. As a general rule, the following applies:

> Use capacitive humidity sensors for room temperature environments and transport

> Use electrolytic humidity sensors for hot cabinets, incubators, and high precision requirements (e.g. cleanrooms)

5.4. Why calibrate from a regulatory perspective

So why recalibrate temperature sensors after one year?

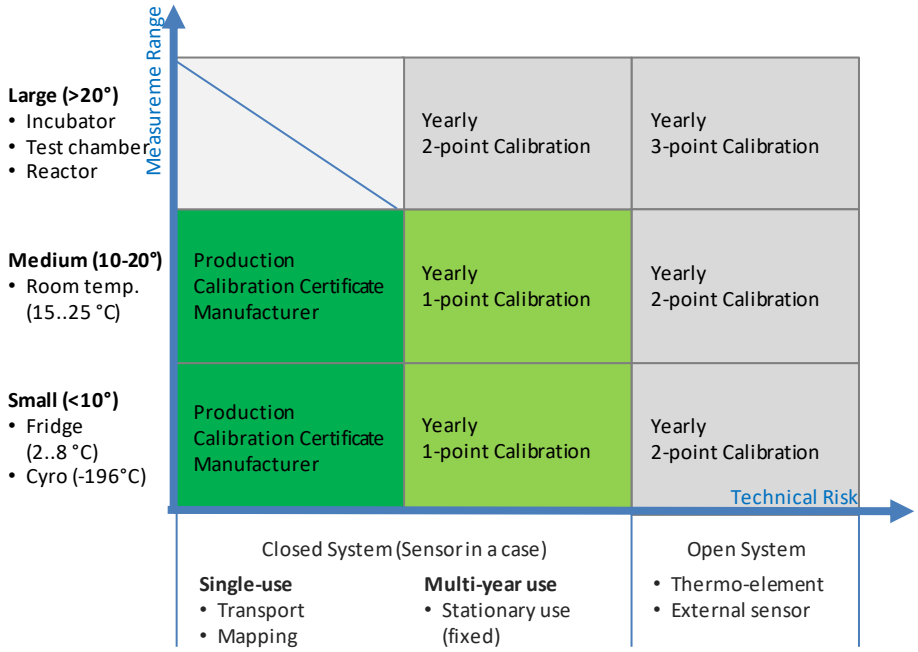
From a technical perspective, it makes little sense to recalibrate temperature sensors (using resistance thermometers like NTC, PT100 or digital sensors). The risk for drift is minimal. We have evidence showing that those sensor types are long-term stable over many years. So why exchange or recalibrate temperature sensors after one year? Because of regulatory requirements.

So why recalibrate humidity sensors after one year?

Depending on the application, it might or might not make sense to recalibrate humidity sensors. In particular in room temperature environment (warehouses, storage facilities), the risk for drift is minimal. We have evidence showing that the drift is minimal in 12 months. So why exchange or recalibrate a humidity sensor used in a room temperature environment after one year? Because of regulatory requirements.

What are the regulatory requirements for recalibration?

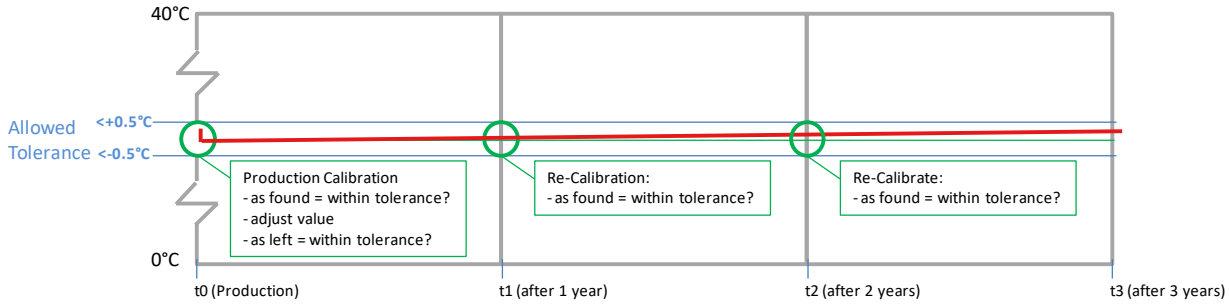
Regardless which guidance document in the GxP environment you consult (FDA, EU, PDA, ISPE, WHO, USP or ICH), in general they all require to work with “calibrated sensors.” While some guidance documents are more general, “calibrated sensors must be used,” others are more specific requesting “regular calibration” or even “yearly calibration.” Some auditors even tend to do an extreme interpretation of the regulations requiring ISO 17025 calibrated single-use sensors for transportation. Lately some pharma companies have received audit findings by Swissmedic about sensor calibrations not being in compliance to ISO 17025. There is no general rule what regulation requires, but in general, most auditors appreciate a risk-based approach considering the measurement range of the application as well as the type of the sensor used.



5.5. The life cycle of a data logger (or sensor)

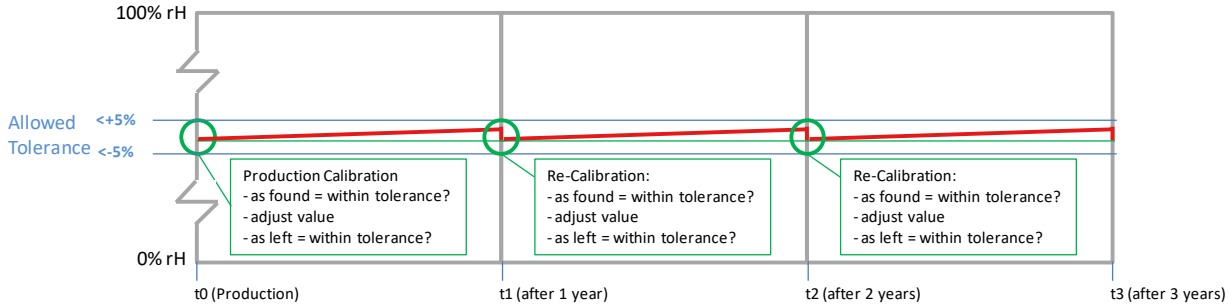
To understand the term calibration, it is vital to know about the physical and technological properties of a data logger and its life cycle. Calibration as such is not making a sensor more accurate. Accuracy is a quality built by design. During the engineering of a data logger the right sensor is carefully chosen and built into the device using the right algorithm. During production, each sensor is calibrated before it is built into the data logger. Afterwards several checks and sample tests are performed in order to verify that the product meets all requirements – including accuracy. So, when a data logger leaves the factory, it meets all requirements (which are often stated in a so-called validation certificate) and it has a production calibration certificate.

Recalibrating temperature: as found



During production, temperature sensors are tested (as found calibration), adjusted to match the expected temperature value at the test point and tested again (as left calibration). Since resistance thermometers (NTC, PT100, and digital temperature sensors) have a very small drift, they are typically not readjusted during recalibrations. If, during a recalibration (after one or several years), a temperature sensor is found to be outside tolerance, it is typically exchanged since it is very likely that it has been physically damaged.

Rexalibrating humidity: As found, adjust, as left



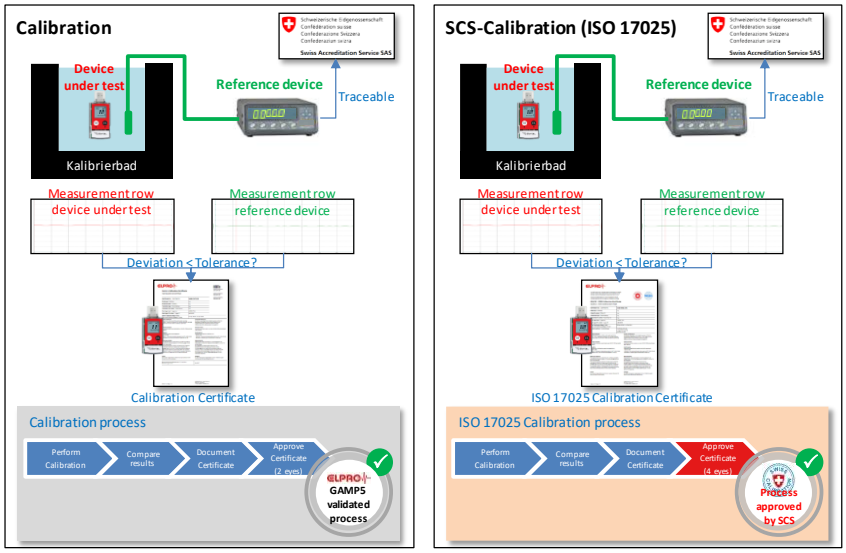
During production, humidity sensors are tested (as found calibration), adjusted to match the expected humidity value at the test point, and tested again (as left calibration). In comparison to resistance thermometers (temperature sensors), humidity sensors have a higher risk of drift. Therefore, they are typically adjusted during recalibration. The first calibration is called “as found calibration” and documents the status before adjustment. Then, the sensor is adjusted by the measured deviation. Afterwards the so-called “as left calibration” is performed to check if the adjustment has been successful. If a sensor is found to measure outside the allowed tolerance, it is typically exchanged since it has been polluted too much and/or is physically damaged.

5.6. What ISO 17025?

ISO 17025 is the international standard for calibrations. The general requirement to issue ISO 17025 certificates are:

- The company (and in particular the laboratory) must have an ISO 9001 certified quality management system – which means that all processes must be documented.
- The laboratory as such must be mapped and accredited by the local authorities (Switzerland: SAS/SCS; USA: NIST; Germany: DaaKs; UK: UKAS)
- The used calibration method must be documented, including the measurement uncertainties, and accredited by the local authorities.

What is the difference between a factory calibration and an ISO 17025 calibration?



Technically, the two calibrations are identical. The only difference is two additions for ISO 17025:

1. Not 2, but 4-eye approval
2. The entire process is not just GAMP5 validated, but also approved by the accreditation body

Although the main difference is the price (the exact same processes and devices are used, the same tolerances applied and the certificates look very similar), why is the ISO 17025 certificate to popular with auditors? Usually auditors have little specialty knowledge on calibrations. ISO 17025 is a known standard. Therefore, the mindset is: *"I can rely on this certificate, since the process has been approved by an official regulatory body."*

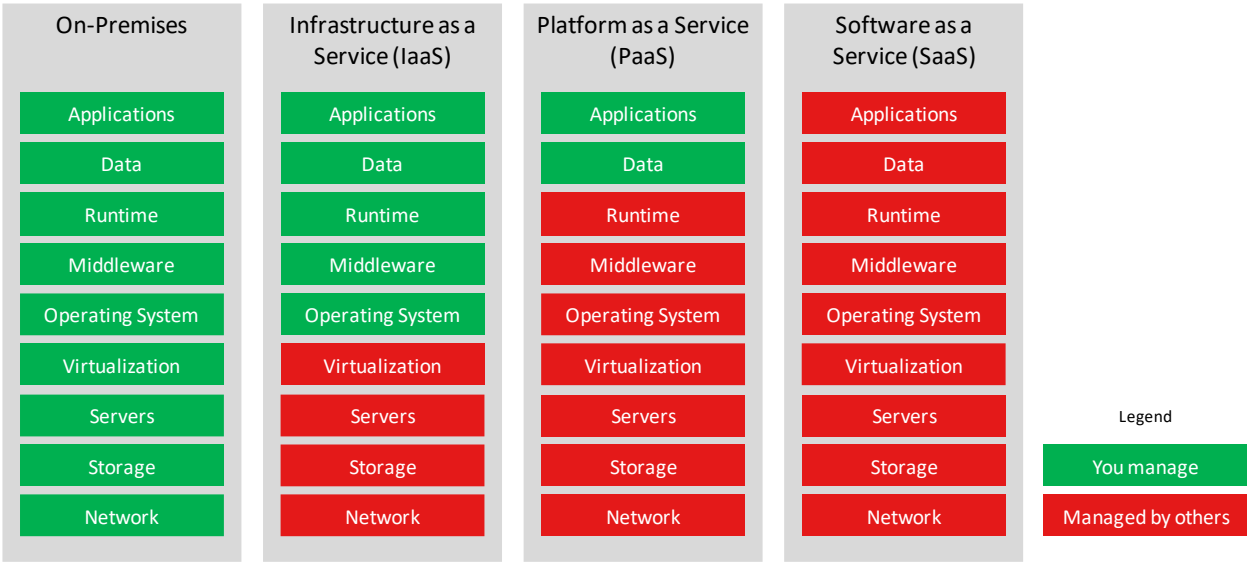
6. Cloud-based Temperature Monitoring

6.1. Where to host the temperature monitoring software?

A cloud-based temperature monitoring solutions consist of hardware collecting the temperature values and software evaluating the data, triggering alarms, performing reports and archiving the harvested data in a compliant manner. But where is this software running? While in the past “on-premise” was the usual answer, today more and more cloud solutions are being introduced. But what are the implications, risks and requirements of running a GxP-compliant cloud-based temperature monitoring solution?

What is “cloud computing”?

Cloud computing is a service using remote servers hosted in the Internet to store, manage, and process data, rather than running an application on a local server on premise. As a rule, a distinction is made between three cloud models, which differ in the outsourced areas of responsibility.



Software as a Service (SaaS), also known as cloud application services, represents the largest cloud market. SaaS delivers (business) applications that are typically accessed directly via web browser and do not require any downloads or installations on the client side.

What are the advantages of “cloud computing”

In the past years, cloud computing and cloud hosting has rapidly grown for business applications across different industries. This is due to obvious advantages:

- Know-how to run a data center is available and accessible at the cloud provider
- High security standards in facility, equipment, SW tools (e.g. firewalls), processes and personnel
- Fast and easy scalability of all resources (performance, storage space)
- Built-in backup and recovery functionalities
- Reduced maintenance efforts due to synergy effects

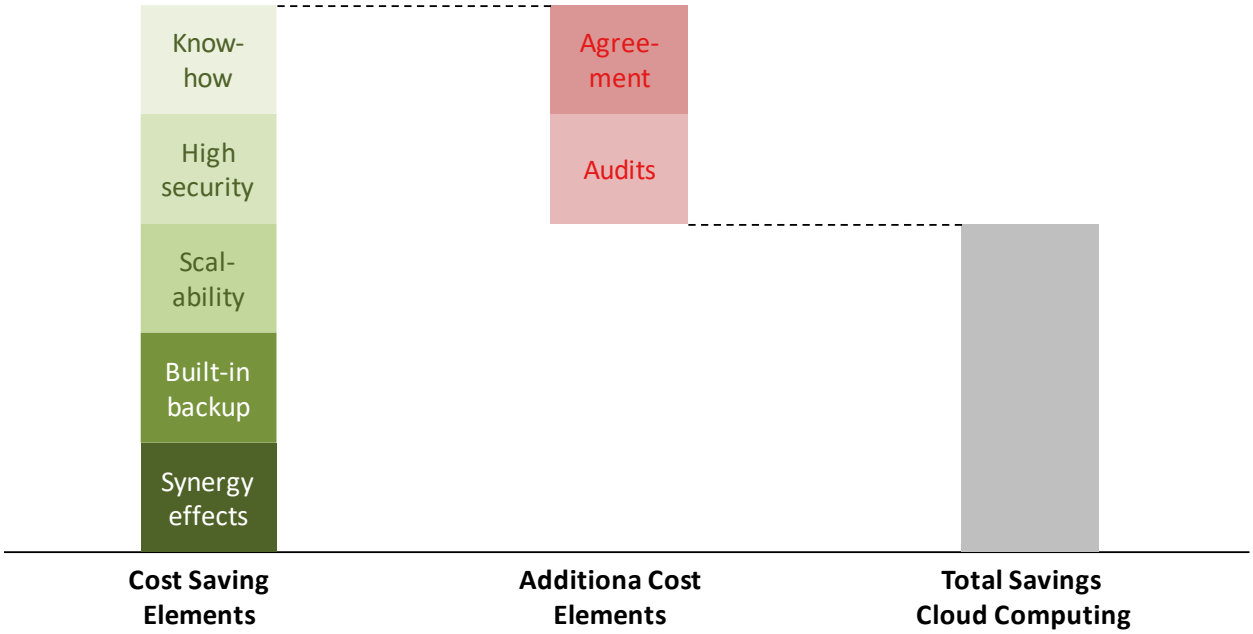
All those benefits usually lead to significant cost savings compared to running software on premise at the same security and performance levels.

What is the downside of "cloud computing"

Naturally, cloud computing also has downsides:

- Lock-in effects resulting in dependencies on the solution provider. This requires a clearly structured and detailed agreement with a well-defined exit scenario.
- Security concerns or delegation of control. This requires additional efforts to evaluate the right partner and regular audits.

However, in the end it is all about cost. What are the benefits (and cost savings) and what are the additional efforts (additional costs) in a cloud solution in comparison to running the software on premise?

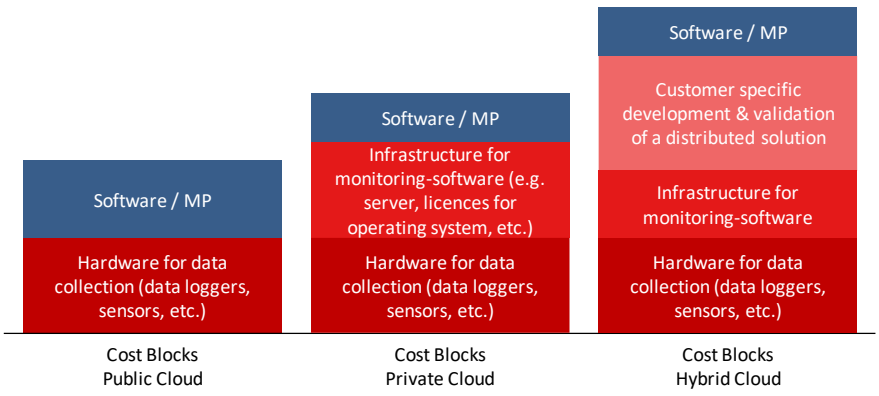


6.2. Public cloud vs. private cloud: what is the right SaaS model?

Cloud computing or Software-as-a-service (SaaS) has again three sub-types differentiating if the application is dedicated to one customer or if the application is shared by many.

- **Public Cloud**: Application is provided by SaaS provider and used by many customers with their own user names and passwords, but shared infrastructure and software.
- **Private Cloud**: Application is dedicated to a single customer. Compared to the public cloud, the private cloud is significantly more expensive since the resources need to be multiplied with each new customer.
- **Hybrid Cloud**: Mix of public and private cloud solutions. The resources are typically orchestrated as an integrated infrastructure environment. Hybrid Cloud takes "the best of both worlds," but is more complex to overlook and manage.

So, while a public cloud will deliver the lowest total cost per temperature measurement point (MP), the private and hybrid cloud result in higher costs.



6.3. What makes a cloud-based temperature monitoring solution GxP-compliant?

To ensure that a SaaS Public cloud-based temperature monitoring solution is GxP-compliant, a few requirements must be fulfilled:

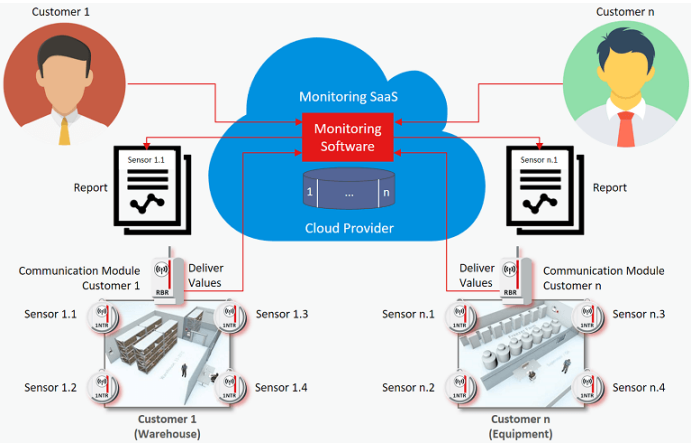
- The temperature monitoring solution, including the database, is a computerized system. To meet GxP requirements (e.g. GAMP5, Title 21 CFR Part 11), the computerized system must be validated (CSV).
- To ensure patient safety, data must be immutable and data integrity must be protected by a multi-layer application where data become attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring and available over their entire life cycle.

What is CSV (computerized system validation)?

A computerized system validation (CSV) is the documented process of assuring that a computerized system does exactly what it is designed to do in a consistent and reproducible manner. It follows the V-Model, which means requirements must be documented, validation and test plans written, risks evaluated in a written risk assessment, functionalities tested and documented according to the test plan and, finally, a validation report issued summarizing all validation efforts.

How to ensure data privacy in a SaaS public cloud-based temperature monitoring solution

In a multi-tenant infrastructure (SaaS Public Cloud), separate clients work on the same cloud-based temperature monitoring software using their own user names and passwords, which means they only have access to their own data and reports, guaranteed by low-level access rights. Therefore, each line in the database is only accessible to authorized customers.



6.4. What are the risks of hosting a cloud-based monitoring solution in the public cloud?

There are many risks related to hosting a GxP-compliant temperature monitoring solution in the public cloud. The following table provides an overview of the risks and proposed mitigation measures:

Risks of Public Cloud SaaS	Mitigation measures
Data Safety and Protection	▪ Implement security measures to protect data from unauthorized access. ▪ Back-up data to secure data from being deleted or lost. ▪ Align with privacy regulations (e.g. GDPR)
Validation	▪ Supplier must prove, that all hard- and software components have been validated according to the GAMP5 model including validation plan, risk analysis and validation reports. ▪ IQ documentation of the cloud software provided ▪ Provide efficient tools for qualification of customer-specific hardware components: o Installation Qualification (IQ): what measurement hardware have been installed? o Operational Qualification (OQ): does the measurement hardware and software configuration work together as planned?
Change Management	▪ Service Level Agreement (SLA) with clear definition of how to deal with upgrades, patches and changes: o Classification of changes (minor, major) o Notification, documentation and qualification of changes
Supplier Dependency	▪ Ensure that supplier SLA includes: o That supplier takes care of the maintenance and assurance of the accuracy, consistency and completeness of data over its entire life cycle. o Meaningful notice period prior to service termination. o The client remains owner of the data and that data is available for download before the service ends. ▪ Make sure to keep a copy of the data (e.g. a monthly sensor report) in a human readable format (e.g. PDF/A) at the client's premises (e.g. automated monthly email to in-house mail-account). ▪ Ensure that raw data (measurement values) cannot be changed or manipulated. ▪ Implement an audit trail keeping track of every change.
Business Continuity	▪ Ensure that supplier SLA guarantees the performance and availability of the solution and that the supplier monitors the availability and performance of the solution and provides reports thereof. ▪ Make sure that the system and data is backed up regularly and recoveries are exercised and documented regularly.
Data Archiving	▪ Process data is "fresh data" which is used for taking business decisions (e.g. MKT calculation of a stability study). For two years, the service provider must ensure that: o Process data is available electronically for visualizations (e.g. zoom, overlay) o It must be possible to draw statistics easily (e.g. calculate MKT), o It must be possible to add comments in the system and generate reports (e.g. release decision), o It must be possible to export the data (e.g. to a higher batch management system). ▪ After two years, data becomes "archive data." The service provider must ensure that archive data is available for at least 10 years and fulfils the following requirements: o Clearly labeled (e.g. monthly report per sensor) o "Human readable" form as a record (e.g. PDF/A report) o Stored in a secure archive (e.g. in a drive that is backed up regularly to a different physical location)

This e-booklet is an expert guideline to Temperature Monitoring of Pharmaceutical Products.

Most content can also be found on www.elpro.cloud/en/temperature-monitoring/. It discusses the requirements for monitoring solutions in a complex pharma supply chain and sheds light on compliance requirements, the process of qualification and mapping, and the different techniques of calibration.

If you have further questions about our monitoring solutions contact us today at online@elpro.com.

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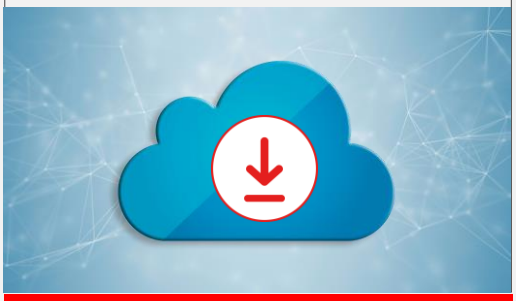
Checklist for cloud-based Temperature Monitoring



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