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Let's Solve Water

8 steps to GMP compliant Mapping of storage rooms

Pharmaceutical finished and intermediate products have to be distributed and transported worldwide due to increasing globalization. The global distribution of COVID-19 vaccines has shown the importance of **maintaining the cold chain** for the quality and efficacy of pharmaceutical products.

This depends on a number of important factors, such as a qualified courier, the right packaging and a reliable logistics system, as well as optimal control and monitoring.

The requirements of the **worldwide GMP (Good Manufacturing Practice) regulations** regarding storage and logistics are unanimous in one point.
When it comes to **monitoring storage rooms and halls**, it must be proven where the weak points are located with regard to temperature distribution.

WHO cites the following phrase in this regard: „Temperature mapping should show uniformity of the temperature across the storage facility. It is recommended that temperature monitors be located in areas that are most likely to show fluctuations."[1]

Especially with regard to increasingly temperature-critical pharmaceuticals, it is all the more important to be able to rely on qualified (intermediate) storage facilities and a proven uniform temperature distribution within these storage facilities.

„The requirements of the worldwide GMP regulations regarding storage and logistics are uni ted in one topic!"

Supporting the validation of the storage areas, a mapping has to be performed and a **uniform and constant temperature and humidity distribution** has to be proven.

For this purpose, we have prepared a **step-by-step guide** to provide you with important aspects of mapping and an internationally recognized **GMP compliant** procedure for qualifying your storage areas.

A step-by-step approach helps the successful planning and execution of the **mapping**. It ensures that the most important aspects of the validation, especially the risk assessment with regard to weak points in the temperature and humidity distribution, are identified.

This allows **GMP compliance** to be demonstrated during a regulatory audit.

Fig. 1: Typical high-bay warehouse. Can the uniform temperature distribution be guaranteed?

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1. Creating a validation plan

Already during the creation of the validation plan or the validation master plan, it must be determined how you want to approach **qualification and validation topics** within the company.

This should already include how sensitive products and materials are to be stored and how the **required specifications** can be met. A risk-based approach has proven to be effective here.

The validation plan should define at least the following aspects:

- Which **areas** are to be validated within which **time schedule** and who has to take over **which tasks**?
- Which **activities** regarding processes, equipment and premises have to be performed?
- Which **specifications** must be met and what measures will be taken if deviations occur during validation?

Once these questions have been clarified, you can start planning the actual mapping.

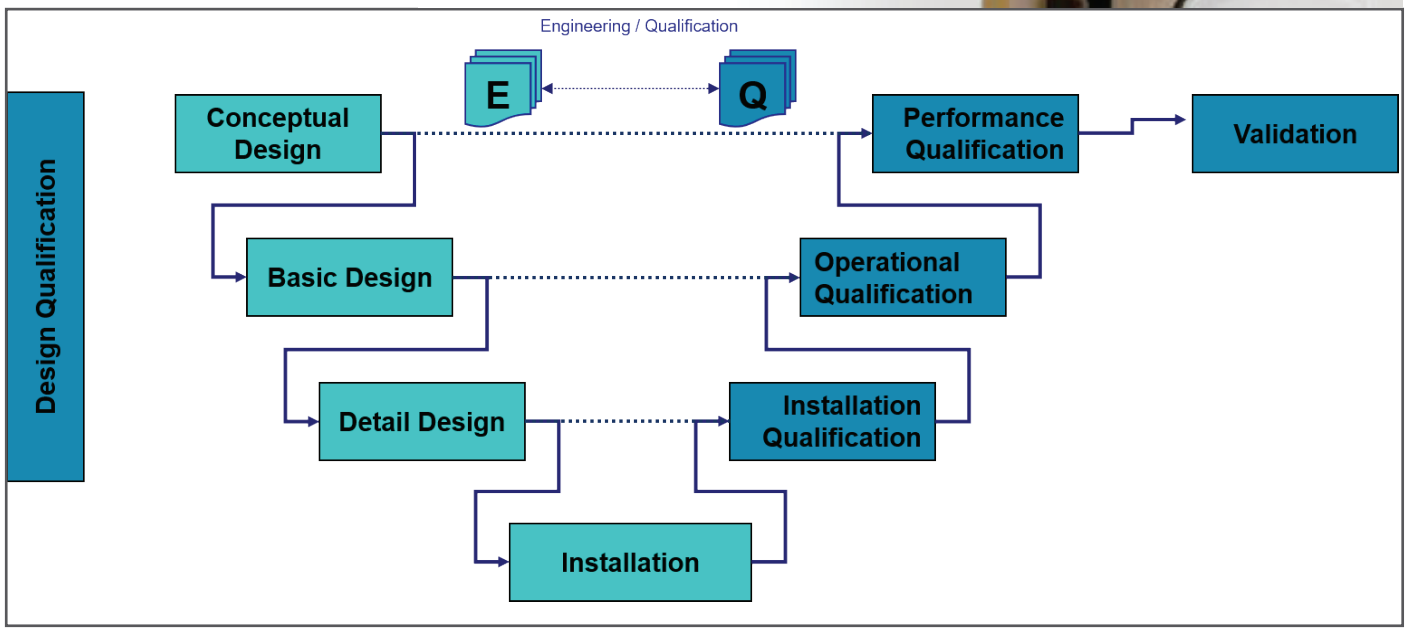


Fig. 2: The V-model of qualification according to EU GMP Annex 15 shows all necessary steps of qualification up to the start of validation. This is the minimum requirement for all equipment used during temperature mapping. Work closely with the engineering department to successfully complete the relevant tests.

2. Identifying the critical areas and the spatial distribution of the loggers

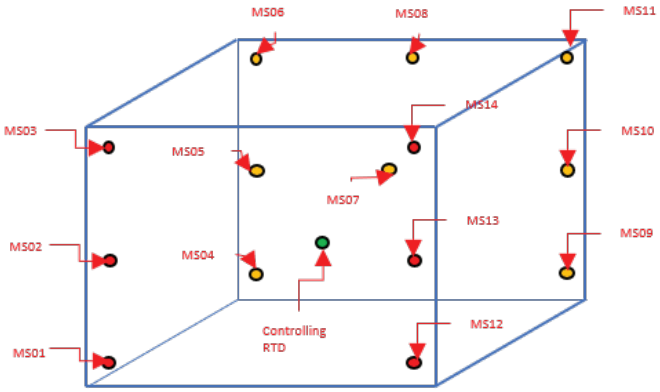


Fig. 3: Spatial distribution of loggers within a square room. Ensure that the loggers are evenly distributed depending on the size of the room.

Before starting the mapping of the storage areas, it is necessary to identify the **critical points** that may have an impact on the quality of the products. Be it due to diurnal or seasonal variations in temperature or relative humidity.

The following points play an important role:

- **How big is the warehouse?**
  The larger a warehouse, the more power the HVAC (heating, ventilation, and air conditioning) must apply to meet temperature requirements. However, this may result in a gradient between areas near and far from the facility within the room. Does the height of the hall affect the temperature distribution between the floor and ceiling?

- **Where are the HVAC sensors located?**
  The control will not respond to temperature increases if the associated sensors do not detect them.

- **Is the air moved by fans or similar?**
  Large installations such as high shelving have an impact on circulation, and therefore even distribution of air. Full shelves affect airflow differently than empty shelves. The installations themselves can also generate temperature and thus heat the air.

- **Are there areas that need special consideration due to seasonal variations, daily work or spatial conditions?**
  Rolling doors, windows or heaters have an impact on the temperature inside the warehouse. Insulation of the wall changes the heat transfer.

All this must be considered during a survey of the warehouse. It's best to have construction drawings on hand and talk to employees on site. This will help identify risks that might otherwise be overlooked.

When determining the correct **number of loggers** during mapping, care must be taken to ensure an even distribution within the premises and to include the height of the rooms. Typically, this involves distributing loggers evenly in all three dimensions and in addition at locations that are considered risky due to the design of the warehouse or due to fixtures.

A procedure should be defined that defines the distances between loggers.

Fig. 4: Distribution of loggers within a high rack. The height of the rack is monitored via loggers mounted at different heights. In the length of the rack this is repeated every 6 - 10 meters. In very long warehouses, the distance can be increased even more. [2]

Even though loggers can theoretically be hung in free space, in the end they should represent the places where products are ultimately stored.

The loggers used will not change the temperature distribution within the warehouse. Therefore, a **large warehouse** can also be mapped in **several steps**, so that a **complete study** can be performed even with a smaller number of loggers.

However, this will stretch out the study in terms of time, which in turn can also lead to costs.

3. Logger specifications

Now it has to be decided **which loggers** and **which evaluation software** should be used for the study.

There is equipment now available that is specifically designed for mapping. Make sure that the reports are presented both graphically and in tabular form and that the software meets the requirements of **FDA 21 CFR part 11 and EU GMP Guidance Annex 11**.

The following specifications must be defined:

- The measurements should be carried out with a **measurement uncertainty** that is as low as possible.
- The loggers should have a **high accuracy** across the relevant measuring range.
- Even small fluctuations should be detectable. Therefore, loggers with a **short response time** should be selected.
- The loggers must **measure stably** during the entire time.
- **Calibration** must be traceable to a **national standard**. The corresponding records must be clear and understandable.

4. Creating the mapping protocols

Once the points to be monitored are defined, you need to consider what data should be collected during the mapping and what aspects should be covered. For this purpose, a protocol is created that contains at least the following information:

- **Which measured variables are to be recorded and which measurement interval is realistic?** If it is mainly the temperature that is critical or if it is a deep-freeze warehouse, it may not be necessary to measure the relative humidity. On the other hand, for warehouses in warm areas with high humidity, relative humidity measurement plays a major role.
- **How many loggers should be used and what is the distribution within the warehouse?**
- **How long should the study take and what are the requirements for the reports?** The study should cover both routine operation and rest periods, for example at weekends. Think about what deviations are acceptable during mapping.
- **What are the calibration requirements for the loggers?** Define the logger calibration requirements in terms of calibration interval, standard and norm, and tolerance or similar.

Once these issues are resolved, you can release the logs. From this point on, deviations must be recorded and evaluated.

Fig. 5 und 6: The EBI 25-TH temperature data logger with wireless technology, for example, combines the very good measuring accuracy of ±0.5K (-20 °C ... +40 °C) and functionality of a data logger with the possibility of monitoring up to 48 loggers via one interface. With the FDA compliant software Winlog.web it is possible to visualize all measured values live on one screen. In addition, the alarm function guarantees the possibility of a quick reaction in case of temperature or humidity deviations.

5. Preparing the mapping equipment

Considering the mapping scheme, you have selected the number of loggers.

Now it is a matter of preventing any mistakes during the preparation of the study. Therefore, a **checklist** should be created that can be worked through in advance.

The following points in particular should be considered:

- Recording the calibration data of the loggers. **Who calibrated them and when? Does the calibrated range cover the planned measurement range?**
- **Has the equipment been qualified and all relevant processes validated?**
- **Is the software installed correctly? Have user levels been defined and set up?**
- **Are the loggers recognized by the software? Is the audit trail activated?**
- **Have all loggers been programmed with the same measurement interval and across the same time period?**

Once you have considered all aspects, the loggers can be distributed according to the mapping protocol and the preliminary study can begin.

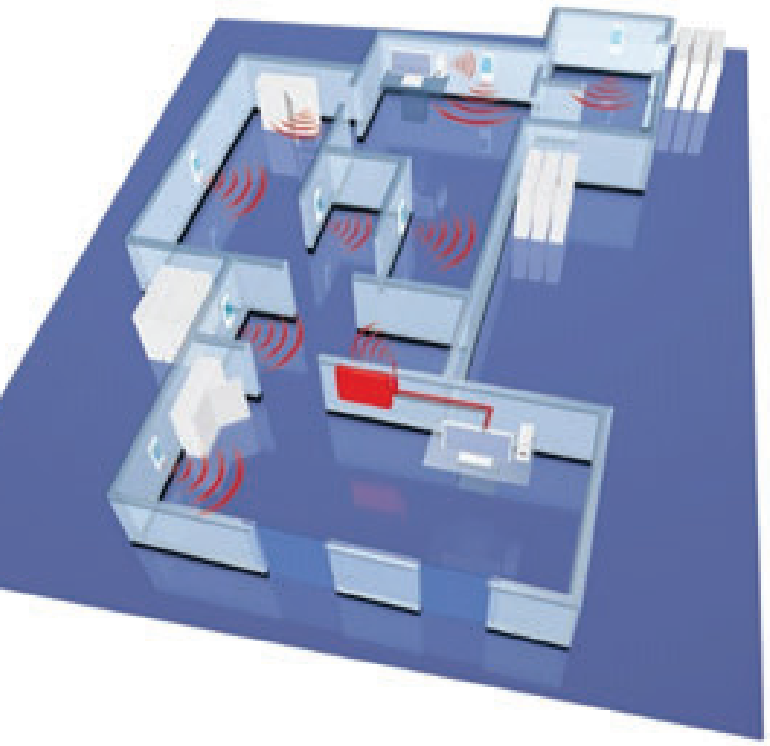


Fig. 7: Installation example of radio and temperature monitoring with EBI 25 data loggers.

6. Evaluation of the pre-study

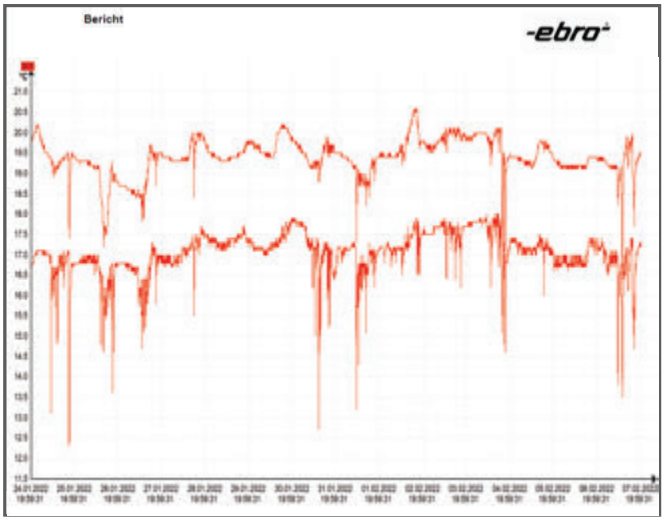


Fig. 8: If the graphs of all loggers are superimposed, the extreme values of the temperature distribution can be quickly identified.

When you have recorded all the data, the evaluation can begin. Make sure that the data of all loggers are read out and displayed in the same way. This way, the data can be superimposed and you get a first **overall view**.

Fluctuations can be evaluated in relation to the overall curve and outliers are quickly identified.

The following information must be visible on the documents:

- Raw data including time and date
- Calculated values such as maximum, average and minimum values of temperature and relative humidity
- Graphical representation of all curves
- Calibration data
- Instrument settings
- Time and date of the study

Subsequently, the results of all loggers can be displayed individually to allow a more precise and **detailed examination of the individual measuring points**.

This allows investigation of whether fluctuations and spikes are systematic problems or only occur when there are interactions with other activities. For example, when gates are opened or closed or equipment is operated from routine operations.

Once all measurement points have been evaluated, resulting modifications may occur.

7. Adjustments to the measurement results

When enough information on the individual measuring points is available and an evaluation has been completed, changes must be made to start the actual **mapping study.**

For this purpose, it must be estimated for each measuring point whether there could be risks for the product or whether areas of the warehouse must be modified or blocked.

For example, if there were slight deviations, the area may only be blocked for very temperature-critical products. Perhaps, the HVAC or high-bay storage scheme will need to be adjusted again.
If this is not possible, parts of the warehouse must be blocked and marked to prevent storage in the unspecified area. These locations must be recorded and adjusted in the validation plan and mapping protocol.

8. Planning and execution of the Validation study

All decisions made previously also apply to the **validation study**. The adjustments and modifications of the measuring points are included in the validation plan. Now the execution of the validation study is started. It is important that all previously identified risks are also considered in this study.

- Should the whole warehouse be mapped over a **long-term study** or several sections one after the other?

- Are there a lot of windows and radiators? If so, make sure that the temperature distribution of the warehouse is considered at both high and low outdoor temperatures. This should already be specified in the **validation plan**.

- Are there differences between regular operation, special service, maintenance or cleaning phases and weekends or holidays? Then the study should definitely look at all aspects.

Already at this stage, consider at what interval you would like to repeat the study. An **annual review of the warehouse** has proven to be effective.

However, this interval can also be extended by means of a **risk assessment** taking into account historical data. However, modifications within the warehouse, such as rearrangements of the high racks, adjustments of the HVAC settings or similar, necessarily lead to a reconsideration of the temperature distribution within the warehouse.

In this case, the mapping must be repeated for the corresponding areas.

[1] World Health Organization WHO Technical Report Series, No. 957, 2010; Annex 5 WHO good distribution practices for pharmaceutical products.

[2] Temperature mapping of storage areas Technical supplement to WHO Technical Report Series, No. 961, 2011; May 2015; Annex 9: Model guidance for the storage and transport of time- and temperature-sensitive pharmaceutical products.

Summary

A **successful mapping study** requires extensive planning and collaboration among all affected areas.

Consider from the outset what **risks** may arise within your warehouses. Talk on site with the personnel who work or will work there every day. This will enable you to identify weak points with certainty.

Clearly define what **requirements** you have for **technology and documentation** so that all relevant information is actually available later.

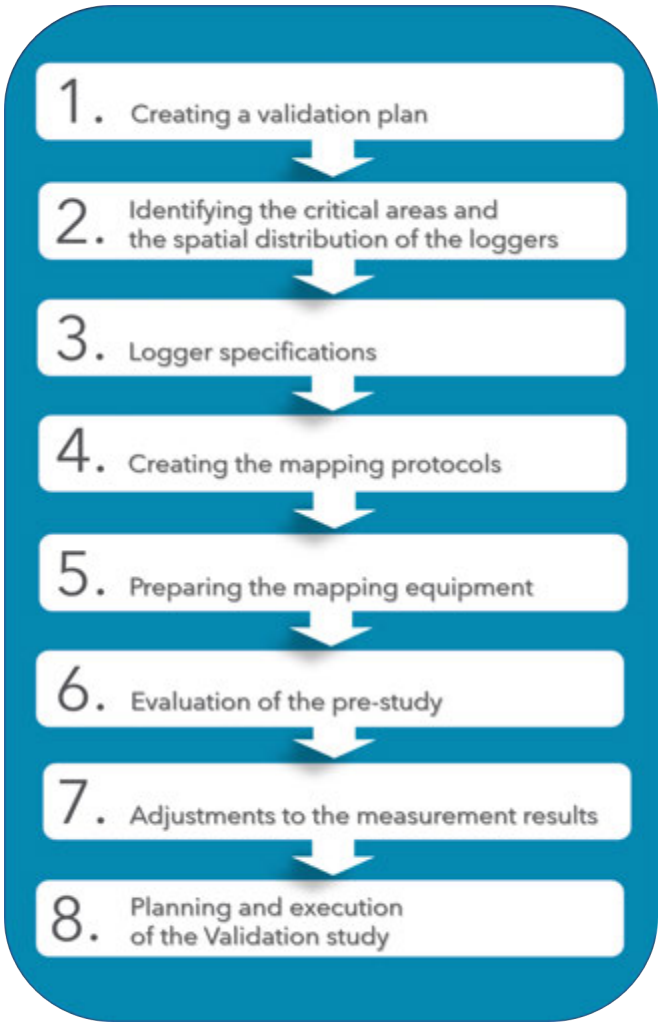
Be honest when **evaluating your preliminary study**! At this stage, modifications and adjustments can still be made without incurring immense costs.

Regularly **review your records** and revalidate your bearings in case of fluctuations or interventions.

Do you still have questions? I will be happy to assist you with advice and the necessary technology.

Please also feel free to contact me about our **service offer for qualified temperature and humidity mapping for warehousing in pharmaceutical companies.**

In 8 steps to GMP compliant and successful mapping of storage rooms:



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Cold chain and process monitoring with the EBI 25 radio data logger system

EBI 25 Data logger

- Highly accurate measurement of temperature and humidity (depending on logger type)
- Very long range up to 500 m in the open field
- Max. Range of 100 m in buildings (depending on building structure)
- Long battery life
- Easy installation

Base station: Interface IF 400

- Collects and stores the data of all connected EBI 25 loggers
- Connection of up to 48 loggers per interface possible
- Stores up to 576 measured values per logger
- Direct connection of any number of interfaces to PC or network
- Alarm message possible (with optional alarm box)

Evaluation software: Winlog.web and Winlog.wave

Winlog.wave:
Basic version for single users

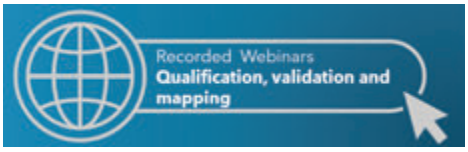
Winlog.web:
Professional version for multiple users

General technical specifications: valid for all EBI 25 data logger types*

Resolution: Temperature	0.1 °C (0.2 °F) in a range of -99.9 °C ... +199.9 °C (-147.8 °F ... +391.8 °F) 1 °C (2 °F) of the remaining measurement range
Resolution: Humidity (humidity data loggers only)	0.1 % rH
Total memory capacity	288 measurement values (per channel)
Sampling rate	1 min. to 24 hours, adjustable
Radio frequency	868 MHz in EU
Battery	3.6 V lithium (user replaceable)
Battery lifetime	Up to 2 years, depending on measurement and transmission rate
Storage temperature	-40 °C ... +85 °C (-40 °F ... +185 °F)
Operating temperature	-30 °C ... +60 °C (-22 °F ... +140 °F)
Measurement mode	Endless measurement
Housing material	ABS
Weight	Approximately 65 g

** Please find the exact technical data of each EBI 25 data logger type on the following pages.*

Further information:



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