Healthcare Cold Chain Management & Solutions and Thermal Mapping Requirements

ISPE 2022 Webinar

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Introduction of Resource Persons

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Career to date:

- Degree as chemical and biological engineer in Erlangen, Germany
- 7 years experience as a consultant in a GMP controlled environment
- Projects in the areas of calibration, qualification and validation for pharmaceutical manufacturers throughout Europe

Introduction of Resource Persons

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Product Manager
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Career to date:

- Biochemist; Thermal Process Authority (TPA), US FDA Recognized
- 21 years in the Validation field; Food and Pharma
- 4 years as Product Manager for Xylem Analytics (Ebro) in the Asia-Pacific Region

Webinar Topics / Outlines

1. The Essentials in Cold Chain (Warehouse/Logistics) Management
2. Stability, Quality and Efficacy of Healthcare Products

    ** From Material / Raw Material Receipt and Management*

    ** To Production and Distribution / Logistics*

3. The Applicable Norms and Regulations
4. Thermal Mapping

A Validation Excerpt:

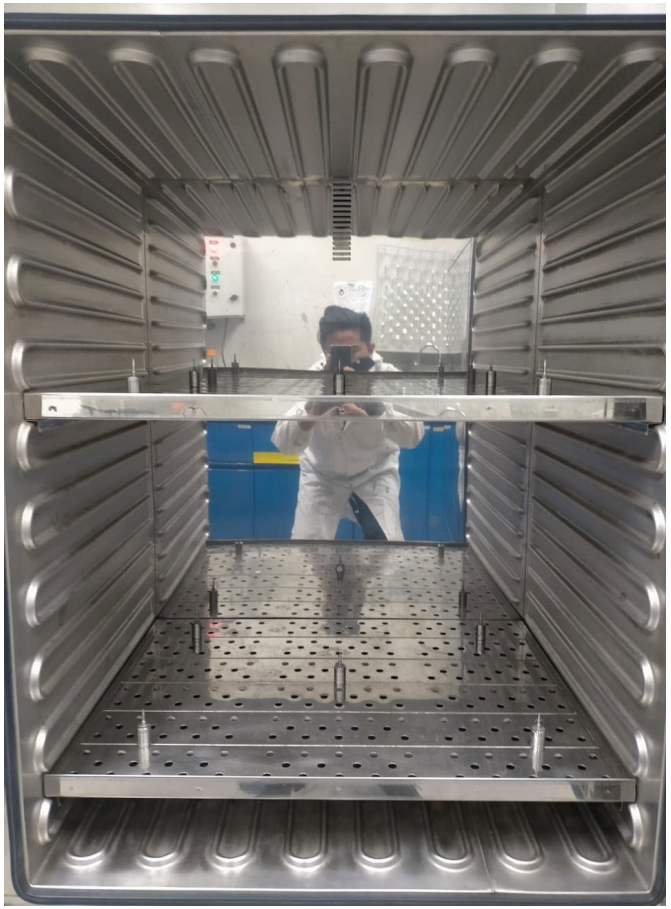
The Pharma / Healthcare Validation Requirements

Pharmaceutical Processes that Typically Require Validation

1. Moist Heat Sterilization
2. Dry Heat Sterilization
3. Ovens / Vacuum Ovens
4. EtO Sterilization
5. H_2O_2 Sterilization
6. Depyrogenation
7. Freeze Drying
8. Stability Cabinets / Rooms

9. Warehouse and Storage Area Monitoring and Control

Our Main Topic For Today's Meeting



Pharmaceutical Processes that Typically Require Validation

Most Popular:

Autoclaves / Sterilizers

Clean Rooms

Warehouses

Others:

Refrigerators
Incubators
Climate /Environmental Chambers
Freezers

1

Cold chain Process

The Cold chain Process

The Critical Purpose of Cold Chain Logistics in the Pharmaceutical Industry:

- **Ensure proper handling of temperature-controlled products safely and securely in the supply chain**

The Cold chain Process

- Determine how to protect your pharmaceutical shipments from temperature excursions and other environmental conditions

- Knowing the key criteria for storage and later for distribution

Everything you need for your Cold Chain and Logistics Process

Taking Vaccine Products as example:

For Storage Facilities and Storage Areas, Temperature and Humidity measurements are very necessary.

Temperature and Humidity, when outside the required limits, have
Great and adverse effects to the following:

- **Raw Materials**
- **Intermediate Products**
- **Final Products**
- **Retained Samples**

Storage conditions must correctly determine and exclude negative impacts on the goods and therefore needs to be monitored.

- **Raw Materials** → *Placebo*

Includes Packaging or Packing Materials
Ex. *Capsule Shell*

excipients → *Active*

- **Intermediate Products**

Compounds or drugs used as materials for the production of APIs and bulk drugs
Ex. Temozolamide

- **Final / ~~Finished~~ Products**

Healthcare Products in all Forms

Improving the Cold chain Process

- Knowing the solutions to improving operational flexibility

- Building Long-Term brand resilience

- Reduce Supply Chain Costs

2

Storage Control & Management

Environmental and Storage Influence on Stability, Quality and Efficacy of Healthcare Products

Environmental and Storage Influence on Stability, Quality and Efficacy of Healthcare Products

The proper storage is important right from the drug manufacturing facility to the pharmacy stores and until it reaches the consumers.

Storage and Transit Controls are therefore one of the most important aspects of the TOTAL DRUG CONTROL SYSTEM which will result to loss of potency if mismanaged and which could adversely influence the efficacy and safety of the pharmaceutical products.

Environmental and Storage Influence on Stability, Quality and Efficacy of Healthcare Products

Proper Environmental Control should include:

- Suitable but Adequate Lighting in the facility
- Correct Storage Temperature
- Acceptable Humidity/ %RH Levels
- Conditions of Sanitation
- Air Flow and Ventilation
- Segregation

Environmental and Storage Influence on Stability, Quality and Efficacy of Healthcare Products

Environmental Control Varies according to Medicine Types:

Tablet – Cool & dry place; protected from light & Moisture
Capsule – almost the same as Tablet's requirements
Emulsion – Cool/dry place or in an air-tight container
Suspension – Cool/dry place but not in the Fridge and NEVER in Freezers; Store below 25.0^{o}C protected from Moisture
Injections / Injectables – Storage conditions on Label; Always protected from light

Healthcare products that must be stored under defined conditions require appropriate storage instructions.

Storage requirements are written in labelling instructions:

Conditions on the Label	Meaning
Do Not Store Over 30.0°C	From +2.0°C to +30.0°C
Do Not Store Over 25.0°C	From +2.0°C to +25.0°C
Do Not Store Over 15.0°C	From +2.0°C to +15.0°C
Do Not Store Over 8.0°C	From +2.0°C to +8.0°C
Do Not Store Below 8.0°C	From +8.0°C to +25.0°C
Protect From Moisture	<60.0% **RH** in Normal Storage Condition

• Raw Materials

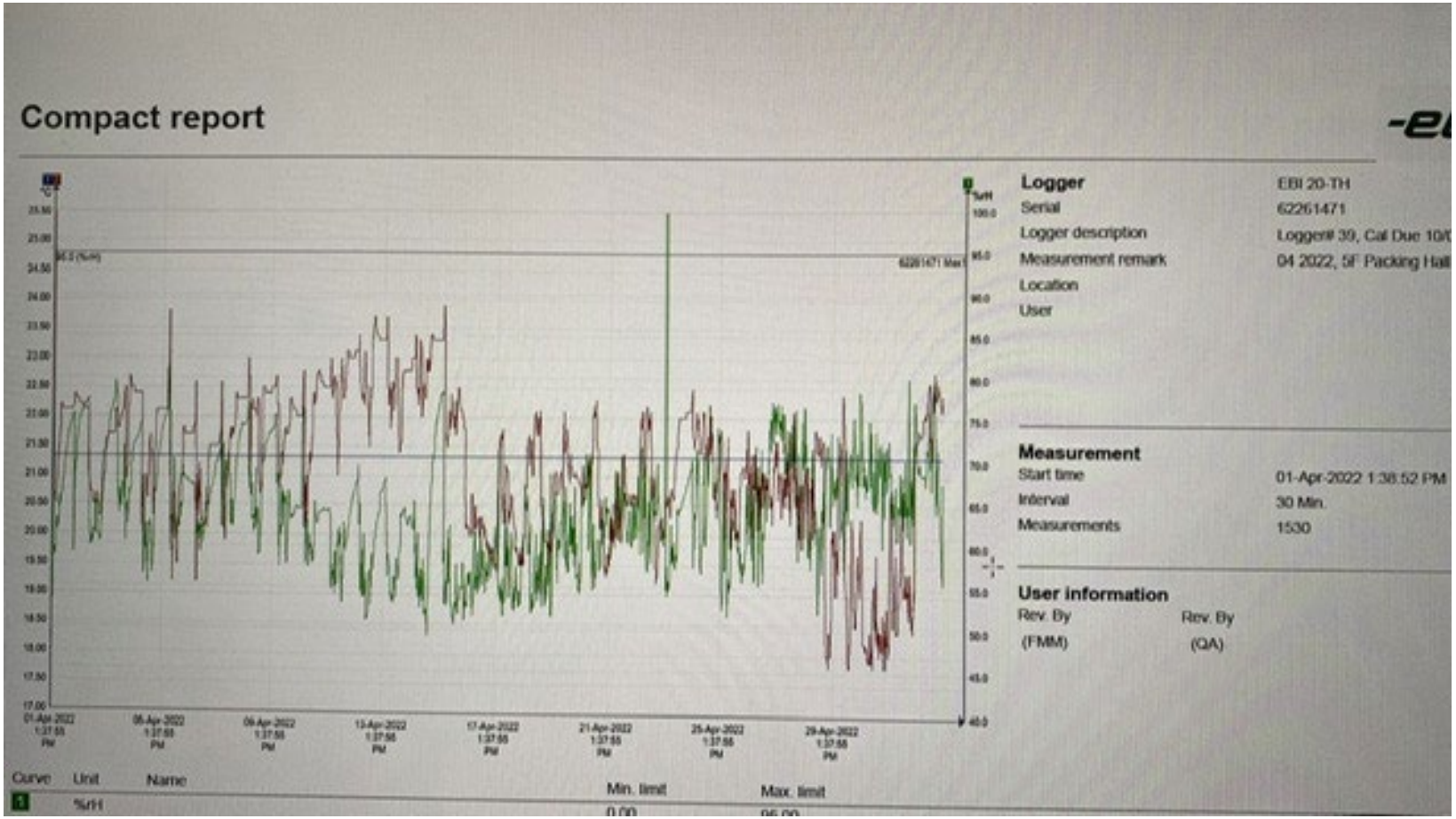
Storage Conditions for Pharmaceutical Raw Materials

Storage Condition	Pharm. Eur.	USP
Cold	8°C – 15°C	<8°C
Cool	8°C – 15°C	8°C – 15°C
Room temperature	15°C – 25°C	temperature prevailing in a work area
Controlled room temperature	–	20°C – 25°C excursions between 15°C and 30°C are allowed

Storage Conditions According to Different Pharmacopoeias

Storage Condition	Pharm. Eur.	WHO	USP	JP
Deep Freeze	> -15°C	> -20°C	-	-
Refrigerator	2.0°C to 8.0°C	-	-	-
Cold	8°C to 15°C	2.0°C to 8.0°C	< 8.0°C	1°C to 15°C
Cool	8°C to 15°C	8°C to 15°C	8°C to 15°C	-
Room	15°C to 25°C	15°C to 25°C	Temp. prevailing	1°C to 30°C
Controlled Room	-	-	20°C – 25°C excursions between 15°C and 30°C are allowed	-

Monitoring and Control



Monitoring and Control

3

The Applicable Norms and Regulations

Why do we need cold chain validation and temperature mapping?

GMP regulations increasingly focus on storage and distribution.

-> Away from **“quality through regulation”**

-> towards **“quality through design”** with an eye on risk minimization and patient safety.

Other causes are

- the increased need for **storage space** due to globalization
- increasing **numbers of temperature-sensitive** products
- technological developments

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FDA PART 211 - CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS

§ 211.142 Warehousing procedures.

Written procedures describing the warehousing of drug products shall be established and followed. They shall include:

(a) Quarantine of drug products before release by the quality control unit.

(b) Storage of drug products under appropriate conditions of temperature, humidity, and light so that the identity, strength, quality, and purity of the drug products are not affected.

§ 211.208 Drug product salvaging.

Drug products that have been subjected to improper storage conditions including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures shall not be salvaged and returned to the marketplace. […]

WHO - GOOD DISTRIBUTION PRACTICES (GDP) FOR PHARMACEUTICAL PRODUCTS

8.10 Where special storage conditions (e.g. temperature and relative humidity) are required during transit these should be provided, checked, monitored and recorded. All monitoring records should be kept for a minimum of the shelf-life of the product distributed plus one year, or as required by national legislation. Temperature mapping of vehicles (where applicable) should support uniformity of the temperature across the vehicle. Recorded temperature monitoring data should be available for review.

8.11 Equipment used for monitoring conditions within vehicles and containers, e.g. temperature and humidity, should be calibrated at predetermined intervals.

10.8 Methods of transportation, including vehicles to be used, should be selected with care, taking into consideration local conditions including the climate of the region and any seasonal variations experienced. Delivery of products requiring controlled temperatures should be carried out by the fastest practical means.

11.3 Where special storage conditions are required (e.g. temperature, humidity) these should be provided, monitored and recorded.

EMA - Guidelines of 5 November 2013 on Good Distribution Practice of medicinal products for human use

3.2.1. *Temperature and environment control*

Suitable equipment and procedures should be in place to check the environment where medicinal products are stored. Environmental factors to be considered include temperature, light, humidity and cleanliness of the premises.

An **initial temperature mapping** exercise should be carried out on the storage area before use, under representative conditions. Temperature monitoring equipment should be located according to the results of the mapping exercise, ensuring that monitoring devices are positioned in the areas that experience the extremes of fluctuations. The mapping exercise should be repeated according to the results of a risk assessment exercise or whenever significant modifications are made to the facility or the temperature controlling equipment. For small premises of a few square meters which are at room temperature, an assessment of potential risks (e.g. heaters) should be conducted and temperature monitors placed accordingly.

3.3. Equipment

All equipment impacting on storage and distribution of medicinal products should be designed, located and maintained to a standard which suits its intended purpose. […]

Equipment used to control or to monitor the environment where the medicinal products are stored should be calibrated at defined intervals based on a risk and reliability assessment.

Government of Canada - Guidelines for environmental control of drugs during storage and transportation (GUI-0069)

4.1 The role of environmental controls

Environmental controls are essential to maintaining drug safety, quality and efficacy. Drugs must be stored and transported according to labelled storage conditions or specific transport conditions supported by data.
Temperature is one of the most important parameters to control. You must transport, handle and store drugs in a way that reduces the risk of exposure to temperatures outside the labelled storage conditions—also known as “temperature excursions”.
Temperature excursions may be acceptable for brief periods if stability data and scientific or technical justification show that product quality is not affected.
In addition to temperature, storage conditions limiting humidity, exposure to light, or limits to physical stress may occasionally be stated on the label. Measures need to be taken during storage and transport to abide by these required conditions. This document includes primarily temperature related guidance and examples, but the same principles should be applied when controlling other environmental conditions.

5.1 Warehousing and storage

1.Store all drugs according to the conditions described on the label of the product. Ensure any controls for conditions that are specified on the label (e.g. temperature, humidity, light, etc.) are in place. […]
2.Design or adapt storage areas to ensure good conditions. Make sure they are clean and dry, with enough air circulation. Ensure they are kept within all acceptable temperature limits and ensure they are qualified […]
3.Monitor the area to demonstrate storage conditions indicated on the label are being met and keep a record of your findings (refer to Section 5.5 Documentation). Use calibrated monitoring devices to control and monitor temperatures.

United States Pharmacopeia:

- USP Chapter 1079 Good Storage and Distribution Practices for Drug Products
- USP Chapter 1118 Monitoring Devices – Time, Temperature, and Humidity

Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme:

- PIC/S GMP Guide Part I: Guide to GMP for Medicinal Products Section 3.19
- PIC/S GMP Guide Part II: Guide to GMP for Medicinal Products Sections 7.42 and 10.1

International Conference of Harmonisation:

- ICH Q7 – GMP Guidance for Active Pharmaceutical Ingredients
- ICH Q9 – Quality Risk Management
- ICH Q10 – Pharmaceutical Quality System

And of course…

International Society for Pharmaceutical Engineering:

- ISPE Good Practice Guide – Controlled Temperature Chamber Mapping and Monitoring

Regulatory Summary:

1) The requirement to control the environmental conditions during transport or storage can be found in virtually all regulations

2) Equipment used for monitoring should be calibrated

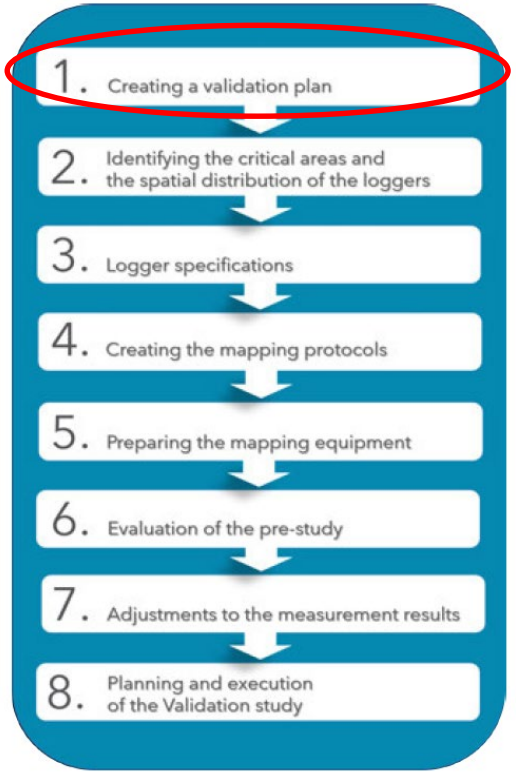
3) An initial temperature mapping exercise should be carried out on the storage area before use, under representative conditions.

4

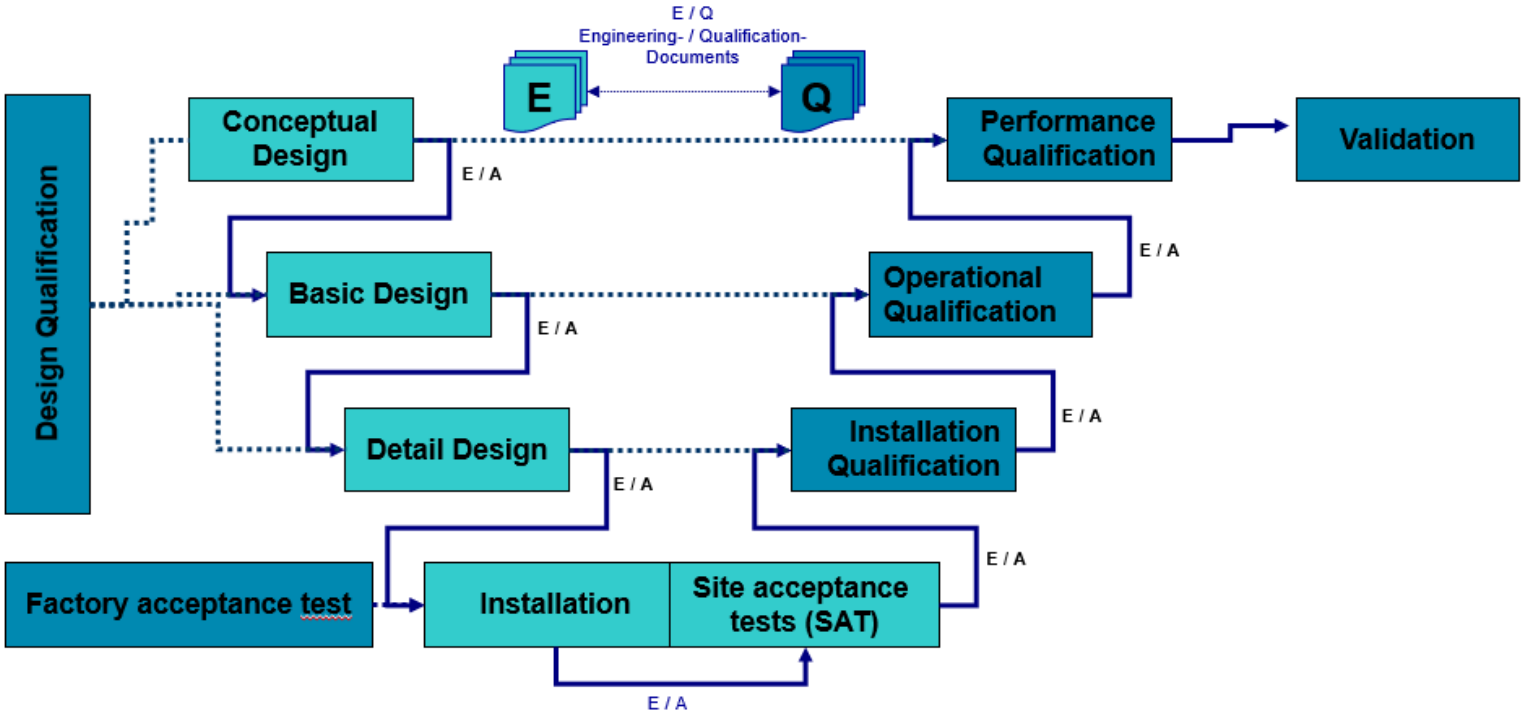
Thermal Mapping

Thermal Mapping Procedure

2. Think about what validation needs to be done!

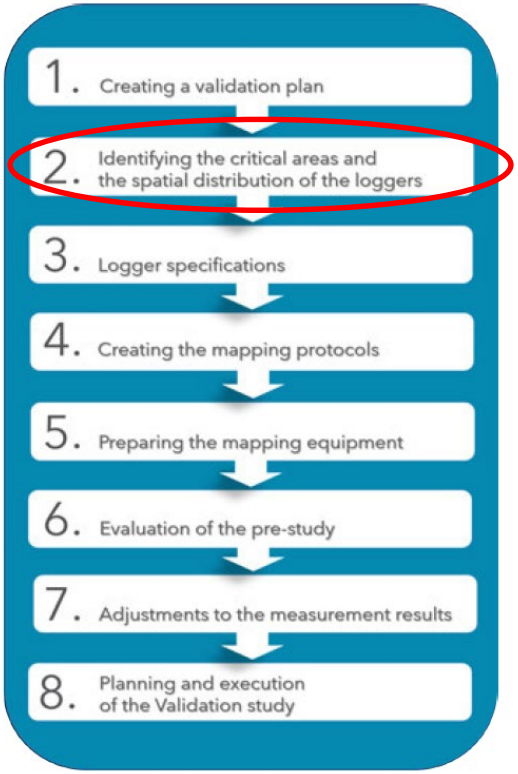


Thermal Mapping Procedure



Thermal Mapping Procedure

2. Identify the critical areas and define the spatial distribution of the loggers



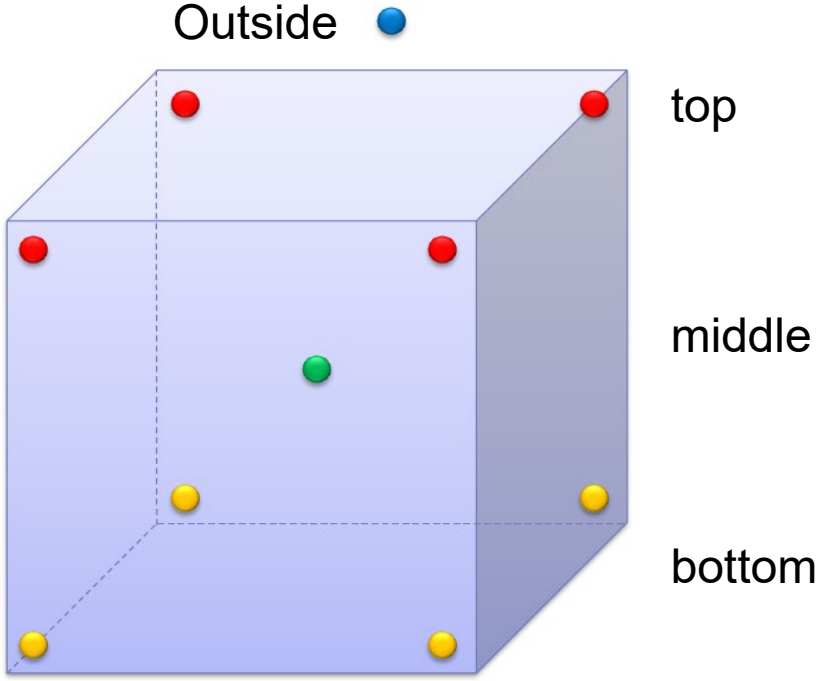
Thermal Mapping Procedure

Sensor distribution (according to WHO)

Chambers ≤ 2m³
- ISPE Guidelines
- According to AS2853 and WHO

•Defines the minimal number of loggers

• Rule of 9 + 1



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Thermal Mapping Procedure

Chambers ≤ 2m³ -> For example Refrigerators

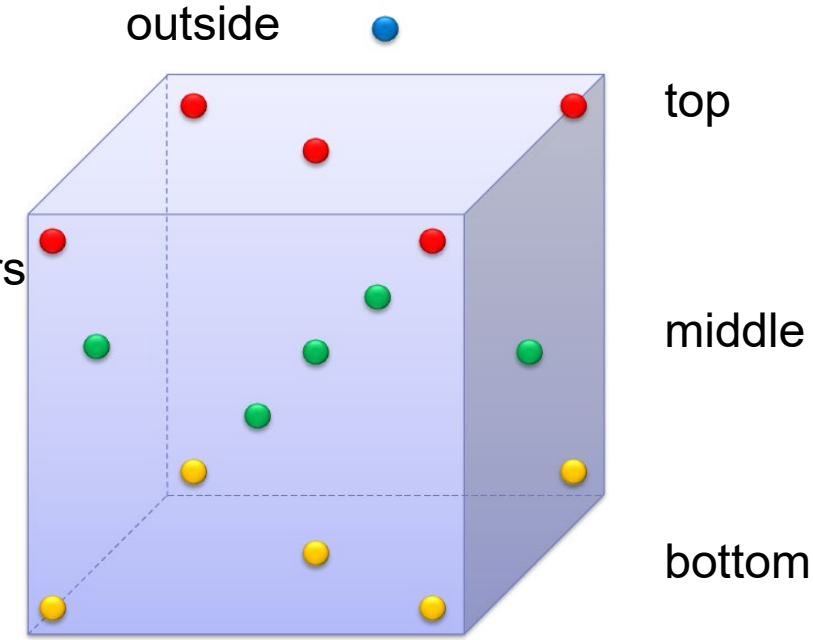
Thermal Mapping Procedure

Sensor distribution (according to WHO)

Chambers >2m³ and ≤ 20m³
- ISPE Guidelines
- According to AS2853 and WHO

•Defines the minimal number of loggers

• Rule of 15 + 1



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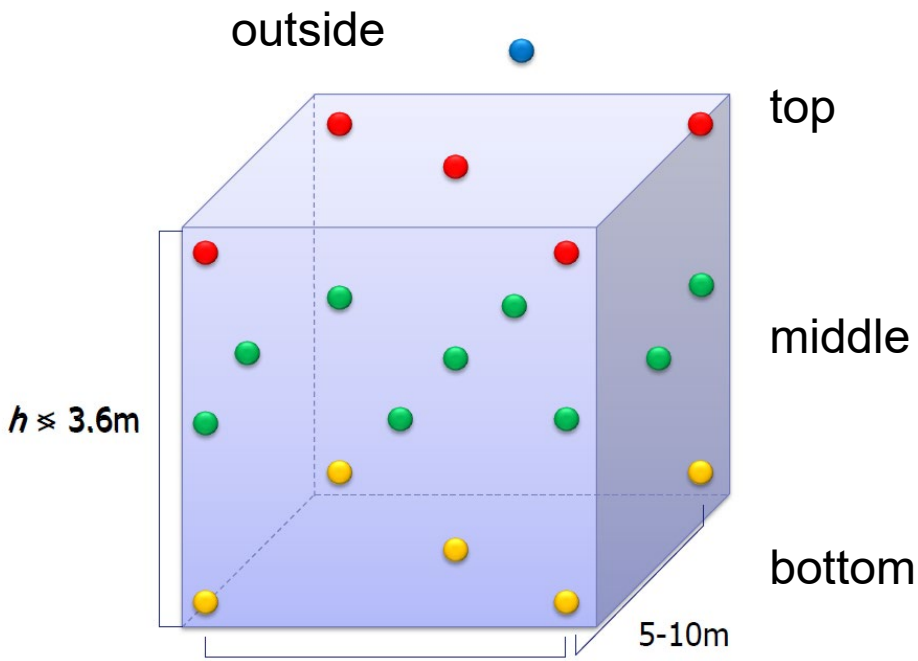
Sensor distribution (according to WHO)

Chambers >20m³
- ISPE Guidelines
- According to AS2853 and WHO

•Rule of 19 + 1



Sensor distribution (Technical supplement to WHO Technical Report Series, No. 961, 2011)

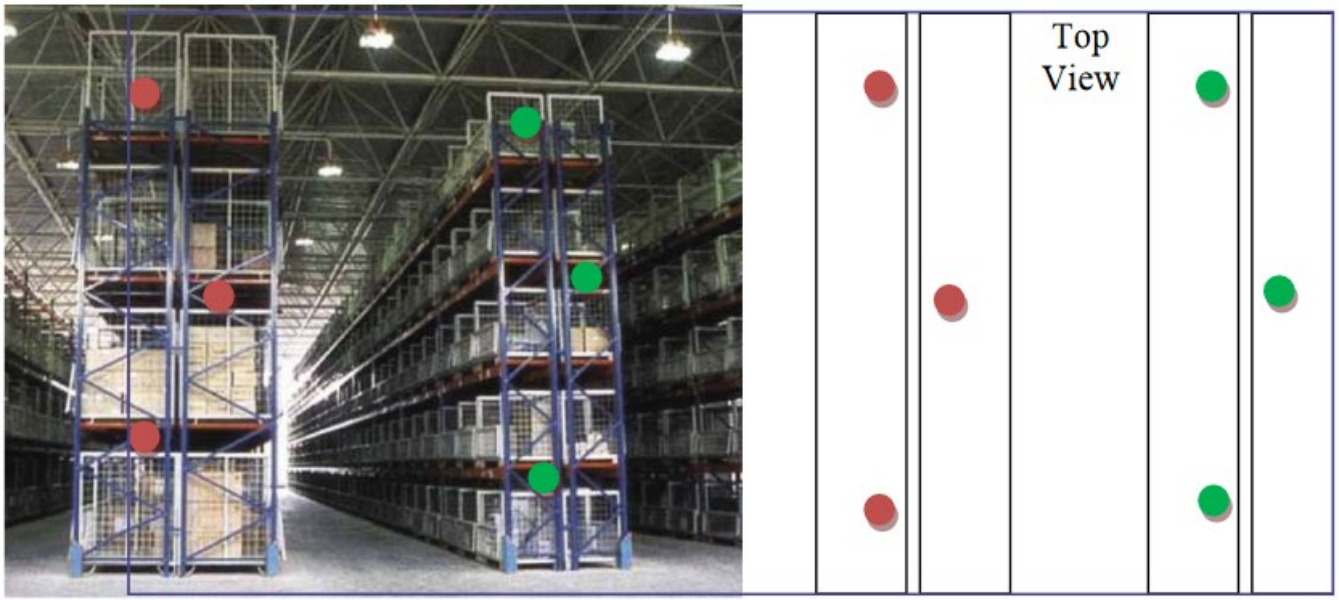
If the ceiling height is 3.6 m or less, position the loggers directly above one another at high, medium and low level
-> floor level, one at 1.2 m and one EDLM at 3.0 m

If the ceiling height is greater than 3.6m, loggers can be arranged at the bottom, middle (multiple) and top of the space.
For instance, for a storage area 6 m in height
-> 0.3m, 1.8m, 3.6m and 5.4m.

Sensor distribution (Technical supplement to WHO Technical Report Series, No. 961, 2011)

Loggers should be arranged in a grid fashion along the width and length of the area, with loggers located every 5–10 m

In very large facilities, this can be up to 20 or 30 m.



Thermal Mapping Procedure

Identifying the high-risk areas

- Volume of space.
- The capacity of diffusers or fans to adequately circulate air.
- Temperature gradients between the cooler floor and warmer air near the ceiling.
- Independent energy sources, such as space heaters, air conditioners, and fans, which create warm or cold pockets.
- Layout of racks, shelves, and pallets, which obstruct airflow.
- Location of HVAC control sensors.
- Locations near sources of heat or cold
- High-traffic areas where product or equipment is moved.
- Seasonal temperature changes or unusual weather events.

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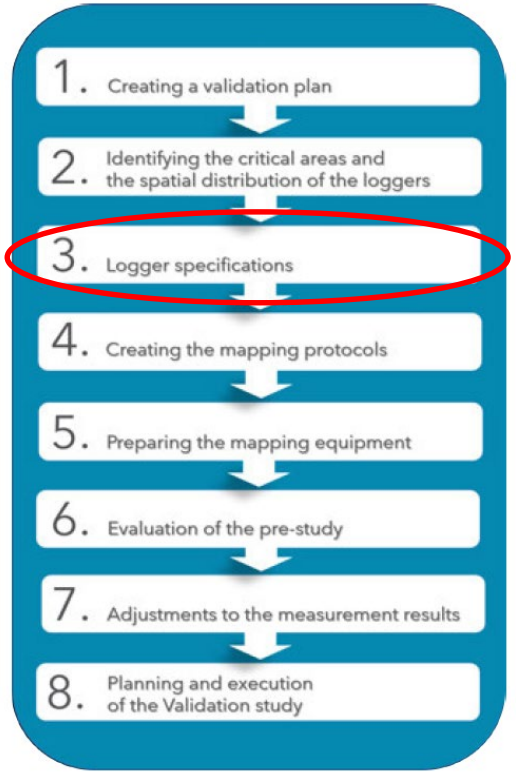
Thermal Mapping Procedure

2. Choose the correct logger specifications



Thermal Mapping Procedure

Select suitable technology

MINIMUM SOURCES OF ERROR

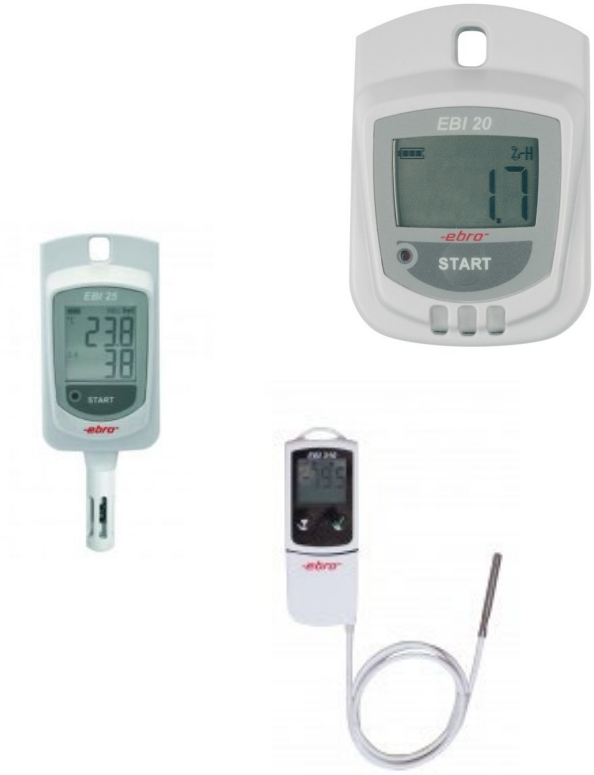
SENSITIVITY TO SMALL TEMPERATURE CHANGES

LONG-TERM STABILITY,.

HIGH ACCURACY IN THE RANGE OF USE.

TRACEABLE CALIBRATION PERFORMED WITHIN THE MEASUREMENT RANGE

CLEAR, COMPREHENSIVE, AND ACCESSIBLE CALIBRATION RECORDS.



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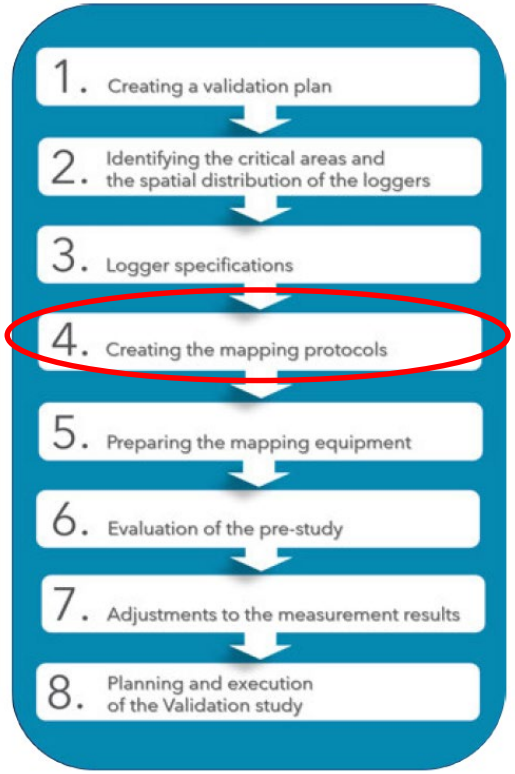
Thermal Mapping Procedure

2. Summarize the information in a Mapping protocol



Thermal Mapping Procedure

Develop protocol information

- TYPES OF DATA TO BE GENERATED
- NUMBER OF SENSORS TO BE USED
- MAP OF SENSOR LOCATIONS.
- DURATION OF STUDY.
- CALIBRATION REQUIREMENTS OF THE DATA LOGGERS
- ACCEPTABLE RANGE OF VARIATION OVER TIME AND ACROSS THE SPACE, WHICH WILL DEPEND ON THE PRODUCT STORED.
- ACCEPTABLE LIMITS FOR TEMPERATURE OR RELATIVE HUMIDITY EXCURSIONS.
- REPORTING REQUIREMENTS.

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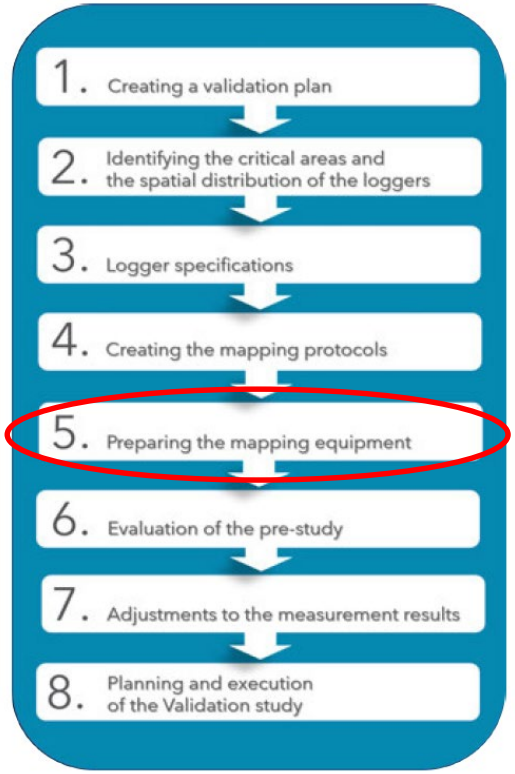
Thermal Mapping Procedure

2. Prepare the mapping equipment and start the mapping study



Thermal Mapping Procedure

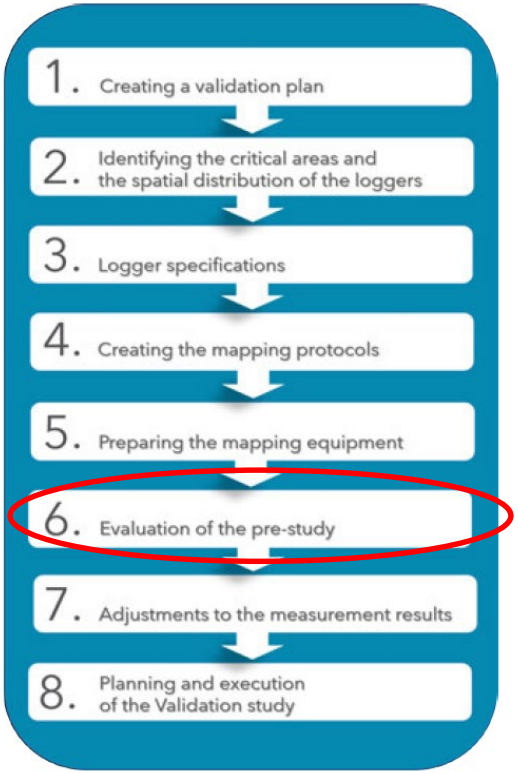
Set Up Mapping Equipment

- Equipment has been calibrated
- Equipment has been validated.
- Program access has been secured and authenticated.
- Software reads and records hardware and firmware model, version, and serial number
- The warehouse area under test has been precisely described.
- Data logger locations are precisely described
- Regular sample intervals have been determined.
- Test duration has been determined
- Data loggers have been positioned in defined locations.

Set Up Mapping Equipment

Thermal Mapping Procedure

2. Read out the loggers and evaluate the mapping study



Conduct test and review data

You'll need to establish the reporting information you'll use to evaluate the test.

When the test is complete, software will read the secure files from the data loggers, show recorded data, perform calculations, and graph the results selected for the mapping report

Thermal Mapping Procedure

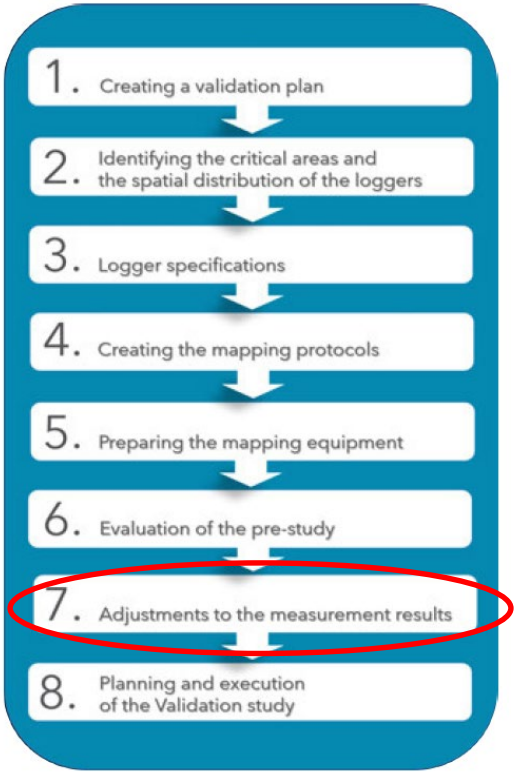
The following information must be visible on the documents:

- 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

Thermal Mapping Procedure

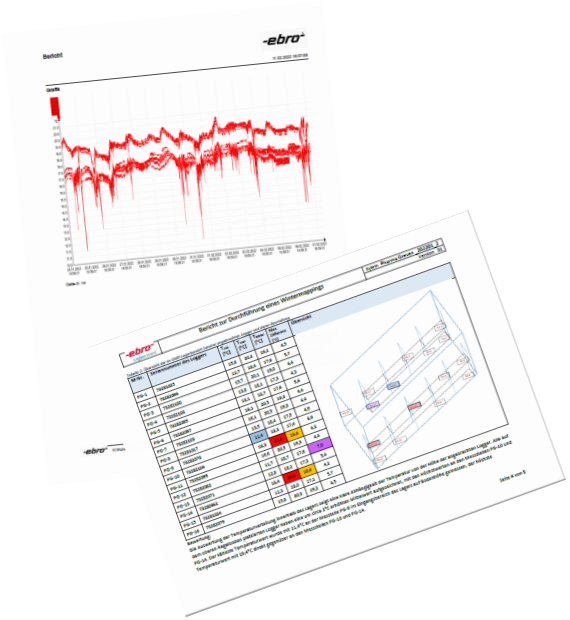
2. Make adjustments, if the results of the pre-study are out of tolerance

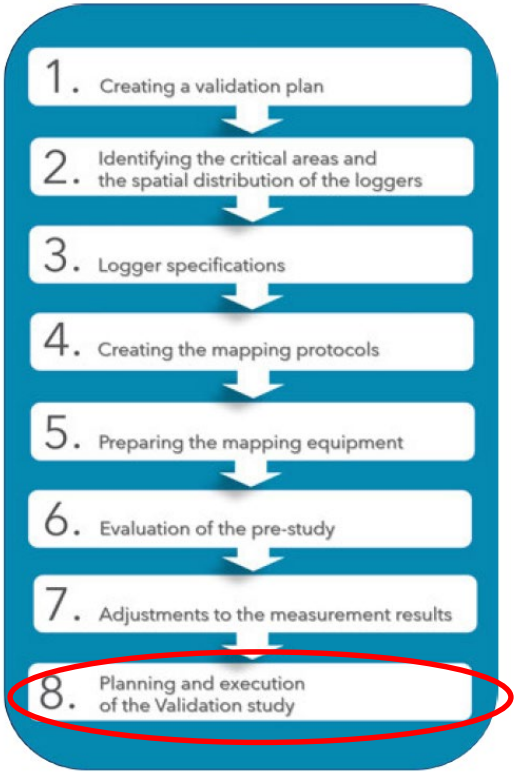
For this purpose, it must be estimated for each measuring point whether there could be risks for the product or whether areas of the warehouse must be modified or blocked.



Thermal Mapping Procedure

2. Summarize the results in the validation protocol and start the validation





Summary

A **successful mapping study** requires:

- Extensive planning and collaboration among all affected areas.
- Clearly defined **requirements** for **technology and documentation**
- Being honest when **evaluating the preliminary study**!

Case Study 1

Description of the premises

A large warehouse near a major airport in Germany.

Specifically, it is an area of a large warehouse separated by a high rack, approximately 7mx11m and 7.5m high.

The wall is adjacent to the office floors and the windows face north. Direct sunlight into this area is not expected. Light hatches are installed on the ceiling of the hall, and air conditioning is provided by a heater (blower) installed on the ceiling side.

The area is used for storage of raw materials and finished products of pharmaceutical production. It was specified for an ambient temperature of 2°C and 25°C.

Case Study 1

Selection of measurement technology

Calibrated PDF data loggers of the EBI 300 series with external TPC 300 probes were selected as temperature loggers to perform the study.

The measuring range is -35°C...+75°C with an accuracy of ±0.5K in the relevant measuring range of -20°C...+40°C.

1 minute was selected as the measurement interval.

Two weeks (fourteen days), including two weekends, were chosen as the duration of the study.

Case Study 1

Result of the study – No modifications necessary

M-Nr.	Seriennummer des Loggers	T_{min} [°C]	T_{max} [°C]	T_{Mittel} [°C]	Max. Differenz [°C]	Übersicht
PG-1	73281025	15,8	20,3	19,2	4,5	
PG-2	73282096	12,7	18,4	17,6	5,7	
PG-3	73282100	15,7	20,1	19,0	4,4	
PG-4	73282106	13,8	18,1	17,3	4,3	
PG-5	73282095	13,1	18,7	17,6	5,6	
PG-6	73282097	16,1	20,5	19,3	4,4	
PG-7	73282103	16,1	20,5	19,3	4,4	
PG-8	73281017	13,5	18,4	17,5	4,9	
PG-9	73282078	11,4	18,3	17,4	6,9	
PG-10	73282104	16,3	20,6	19,4	4,3	
PG-11	73282099	16,6	20,5	19,3	4,4	
PG-12	73282082	11,7	18,7	17,6	7,0	
PG-13	73282071	12,8	18,2	17,3	5,4	
PG-14	73280962	16,4	20,6	19,4	4,2	
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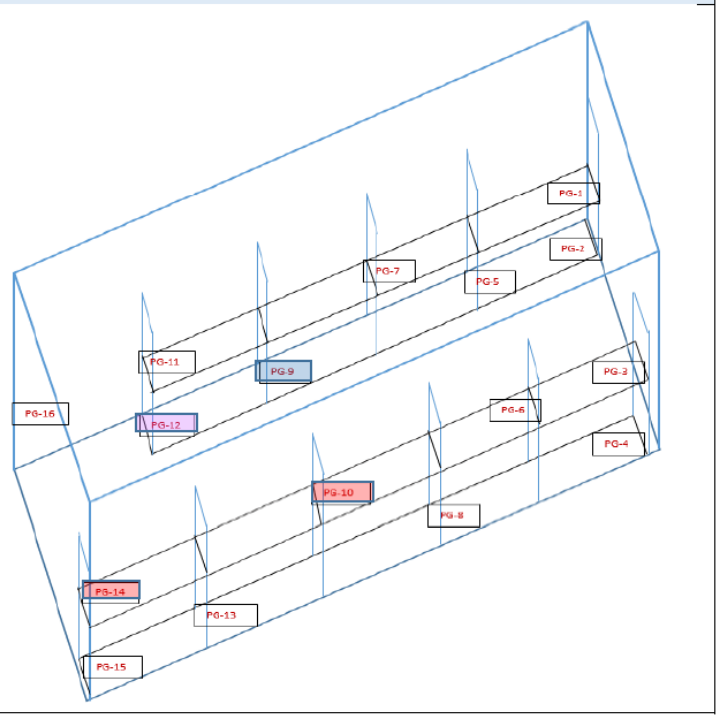
PG-16	73282079	15,8	20,3	19,2	4,5	



Case Study 2

Description of the premises

Specifically, it is a large warehouse measuring approximately 17mx34m and 7.5m to 5.8m high.
The space is separated longitudinally by movable high shelves.

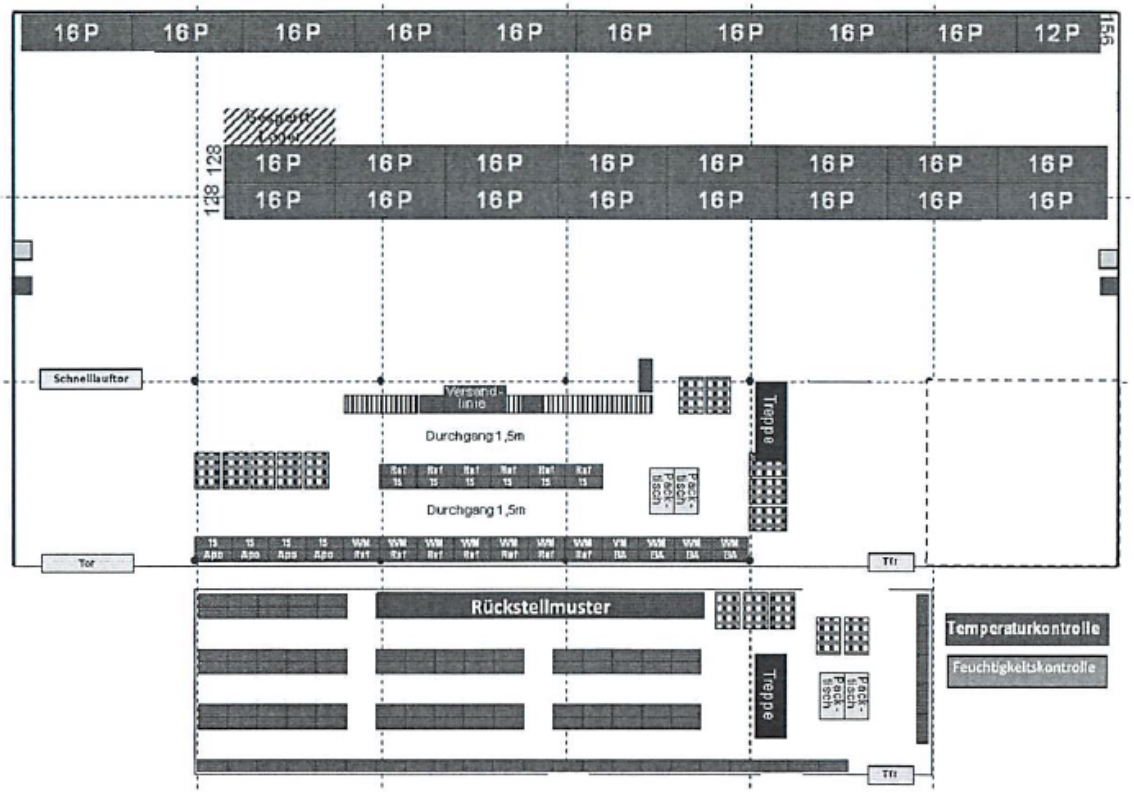
One wall is adjacent to the storage area, office space is accessible via a staircase.

Windows are located on each of the short sides of the warehouse. Direct solar radiation into this area is therefore to be expected. Light hatches are installed on the ceiling of the hall, air conditioning is provided by a heater (blower) installed on the ceiling side.

The area is used for storage of raw materials and finished products of pharmaceutical production. It has been specified for an ambient temperature of 15-25°C and a maximum relative humidity of 60%rH

Case Study 2

Description of the premises



Case Study 2

Selection of measurement technology

- PDF data logger of the EBI 300 series with external TPC 300 as pure temperature logger Measuring range: -35 °C...+75°C.
Accuracy: ±0.5K in the relevant measuring range of -20 °C...+40 °C.

- EBI 25 TH logger for temperature and humidity measurement
Measuring range: -30 °C ... +60°C and 0%rH ... 100%rH
Accuracy: ±0.5K in the relevant measuring range of -20 °C...+40 °C and ±3 % in the measuring range 10% to 90%rH.

Case Study 2

Description of the measuring point selection

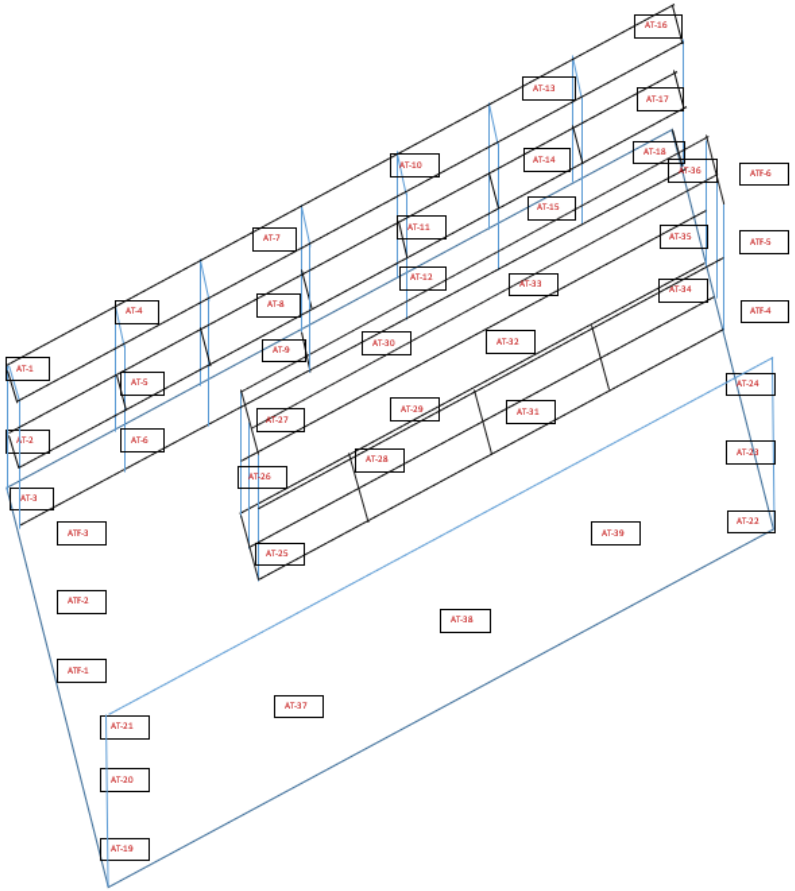
The entire large warehouse is to be mapped.

The humidity and temperature loggers already installed on the short sides of the warehouse at three heights are to be included in the measurement and are used to measure relative humidity.

In addition, temperature data loggers will be distributed evenly in all corners of the warehouse and on three levels of the high racks where temperature-critical goods are to be stored during routine operation

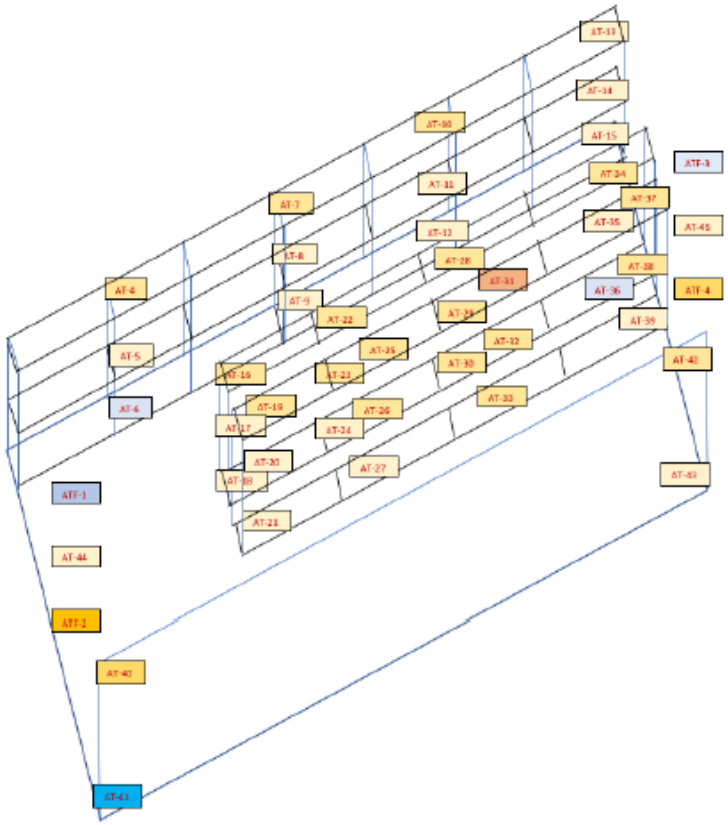
Case Study 2

Description of the measuring point selection



Case Study 2

Result of the study – No modifications necessary



Temperaturbereich [°C]	Farbmarkierung
18,5 - 19,0	
19,1 - 19,5	
19,6 - 20,0	
20,1 – 20,5	
20,6 - 21,0	
21,1 – 21,5	
21,6 - 22,0	
22,1 – 22,5	

THANK YOU VERY MUCH