GMP Warehouse Mapping

/ STEP-BY-STEP GUIDELINES FOR VALIDATING LIFE SCIENCE STORAGE FACILITIES

VAISALA

Good manufacturing practice (GMP) regulators in the United States, Canada, European Union, Japan, Australia, and China have sharpened their focus on warehouse storage and distribution practices. Driving this trend is a shift in regulatory thinking from quality-by-test to quality-by-design systems with emphasis on level of risk to product quality and patient safety. Other drivers include greater demand for storage facilities due to globalization of manufacturing, increase in temperature-sensitive biopharmaceuticals, and changes in technology.

Regulators in these countries require "mapping" the temperature and relative humidity profile of warehouses for environmentally sensitive life science products. This step-by-step guide describes how to map a warehouse to comply with internationally recognized GMPs, including many that have been published or revised recently. (See Regulations and Guidance at the end of this paper for more detailed citations of GMPs.) This guide, intended for use by any organization involved in the storage and distribution of products sensitive to temperature and humidity in a GMP-compliant environment, draws on Vaisala's extensive customer experience throughout North America and Europe. Indeed, Vaisala's environmental and industrial measuring and monitoring products are used in more than 140 countries.

Step by Step – Good Practice Warehouse Mapping

Vaisala recommends a nine-point process for successful mapping of a warehouse or other regulated storage space:

1. Create a validation plan
2. Identify areas at risk
3. Develop protocol information
4. Determine sensor distribution
5. Select suitable technology
6. Set up mapping equipment
7. Conduct test and review data
8. Make modifications
9. Document and schedule mapping tests

These nine steps will help you design and execute a successful mapping plan. They will ensure that you take into consideration the most important elements of validation, especially understanding where temperature and humidity pose risks to product quality. Following these steps will go a long way in demonstrating to a regulatory inspector that your company is GMP compliant.

Step 1: Create a Validation Plan

The validation plan, or validation master plan, is the document used to specify the company's commitments and decisions about qualifying every aspect of the facility, equipment, and people to maintain a GMP-compliant environment. The plan should take a risk-based approach, with a rationale based on science and verifiable measurements. The plan should focus on where environmentally sensitive products and materials will be stored and whether environmental controls can meet specified storage requirements.

The plan is also a starting point for regulators to evaluate the rationale for the company's goals and methods.

The master validation plan should –

- State the validation objectives.
- Identify roles and responsibilities of quality, metrology, and other working groups in the process.
- Identify validation activities, including processes, equipment, and space.
- Develop documentation and procedures, including the company's response should a temperature or humidity excursion occur.
- Define a validation schedule.
- Specify the management approval process, especially for adverse events such as out-of-temperature deviations.
- Identify change-control protocols so it's clear when changes such as maintenance, new construction, and reconfiguration of racks require revalidation.

Regulatory Note: GMPs require maintaining temperature and humidity within storage recommendations printed on product labels or provided by raw-material suppliers. These recommendations are derived from known chemical properties and stability testing.

Step 2: Identify Areas at Risk

To map a warehouse or other storage space, you first must identify areas where product quality may be at risk because of unacceptable variations in temperature and humidity. Many factors affect the control or variability of your space. (Because relative humidity is dependent on temperature, variations in temperature will affect humidity as well.) Considering each of these factors will help you pinpoint risk:

- Volume of space. A large warehouse has different control burdens than a small storage area, with greater demands on the HVAC system and the potential for greater variations in temperature and humidity at various locations.
- 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. For example, a thermostat located near a source of heat or cold may cause the temperature of the space to fluctuate excessively.
- Locations near sources of heat or cold, such as the roof and exterior walls, windows, and loading dock.
- High-traffic areas where product or equipment is moved.
- Seasonal temperature changes or unusual weather events.

Regulatory Note: You can achieve GMP compliance through good science and sound justification of your approach to identifying risk. The more considerations the validation master plan addresses, the better your compliance rationale is likely to be.

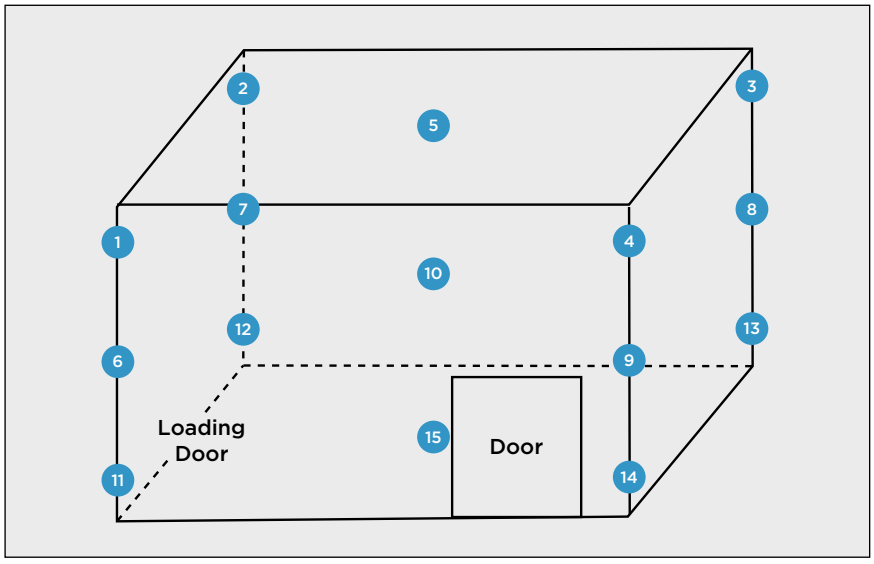


Figure 1. *The even distribution of 15 sensors is a typical pattern for three-dimensional mapping of a small space.*

Step 3: Develop Protocol Information

Once you've identified areas of risk, develop a protocol for the mapping test that describes the following, with justifications for each decision:

- Types of data to be generated – for example, temperature, relative humidity, and measurement intervals. Five-minute intervals offer more data to evaluate trends and modify the warehouse setting (see Step 8). Once you are satisfied that temperature and humidity are relatively stable, 15-minute intervals may be adequate for the final mapping.
- Number of sensors to be used (see Step 4: Determine Sensor Distribution).
- Map of sensor locations.
- Duration of study. Your rationale and protocol may support a series of tests, each lasting two days during normal operations and into a weekend. A different and equally defensible protocol might specify a single run over a two-week period to account for a variety of activities, such as opening loading dock doors, in the warehouse.
- Calibration requirements of the data loggers (specified by the manufacturer).
- 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.

Regulatory Note: Once you develop a protocol, follow it consistently. If the protocol changes, document the reasons.

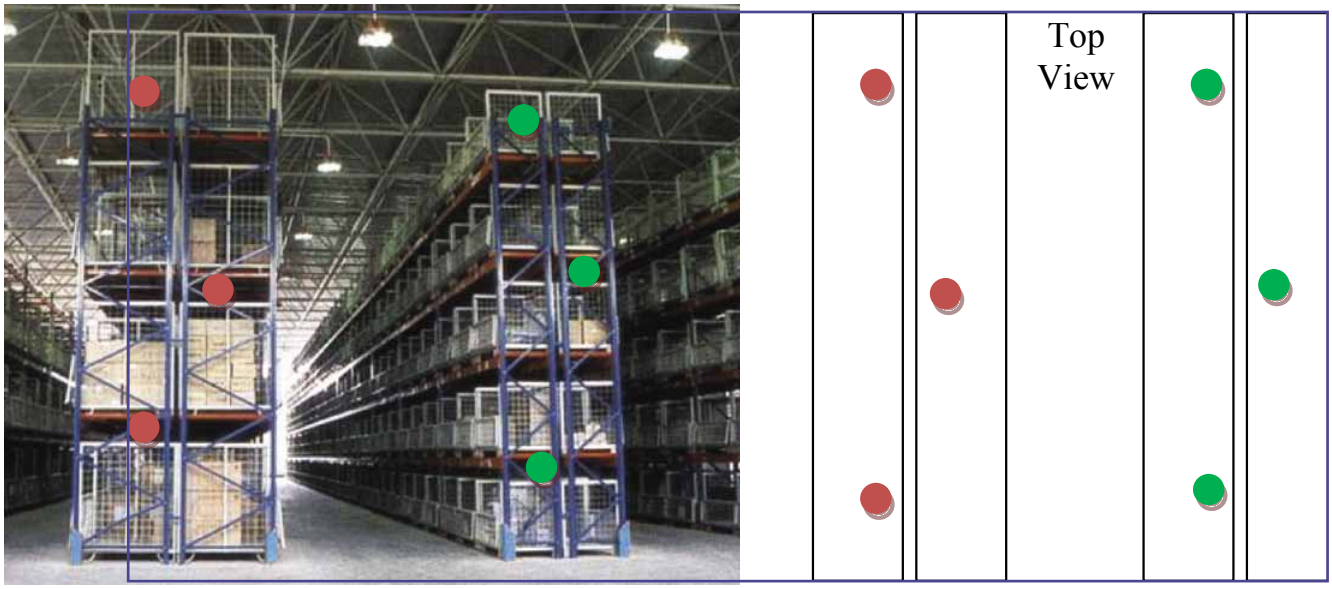


Figure 2. *Sensors placed in the middle of racks reflect actual product temperatures. In this example, nine sensors are located on each double rack in this warehouse measuring 30 meters by 30 meters by 15 meters.*

Step 4: Determine Sensor Distribution

How many sensors will you need to map a particular space? Where will you put them? There are no formulas or pat answers. Sensor distribution must be adequate to assess temperature uniformity. Good practice demands you use a sufficient number to understand your environment, especially problem areas where risk is greatest.

You'll need to place sensors in a uniform pattern in all three dimensions of your space – top to bottom, left to right, front to back. Add additional sensors where you suspect cool or warm areas may exist, as well as near the control sensors and monitoring sensors. Placement of temperature and relative humidity sensors is a function of the considerations and risks you evaluated earlier in Step 2.

A walk-in chamber or small warehouse is often mapped in three dimensions with 15 sensors. The protocol should set bounds on the distance between sensors, such as no greater than 6 meters.

In mapping a large warehouse, set sensors as far as 60 meters apart, with additional sensors in vulnerable areas affected by drafts from loading docks, heat or cold from external walls, solar heating from windows, heat generated from artificial lights, air circulation from traffic or the HVAC system, temperature extremes in poorly insulated areas, localized effects of space heaters and air conditioners, and drafts from typical warehouse activity. Anticipate that airflow and temperature gradients may vary depending on whether shelves are empty or stocked with product. Taller racks will be subject to wider temperature gradients, requiring more sensors top to bottom.

You can mount sensors in open areas (outside of racks or aisles, for example) where they are convenient to set up. But convenience mustn't take precedence over effectiveness. Sensors must measure the conditions to which your products or material are exposed.

If you don't have the sensors you need to map an entire warehouse in one test, you may choose to map one section at a time. Mapping in sections takes longer, and you may want to extend the mapping time for each section to compensate for the uncertainty of mapping the space piecemeal. To decide, weigh the equipment savings from a sectional mapping approach against the additional time needed to complete the project.

If high or low relative humidity can adversely affect product or material quality, then you should map for relative humidity as well as temperature. There are two approaches to determining the number and location of relative-humidity sensors.

The first approach is to use comparatively few humidity sensors distributed throughout the warehouse (as few as one for every six temperature sensors) and to rely on temperature uniformity to make the case that humidity is also within bounds. This approach relies on a history of temperature mapping in different seasons with consistent results. With this history, a specialist with an understanding of humidity measurement science can effectively make the case to an auditor or inspector that humidity measurements are not needed at all data points. If you decide to follow this strategy and cut back on the number of humidity sensors, it's crucial to place the few sensors you do use in areas with poor air circulation, between HVAC fans or diffusers, and where temperature is most variable.

Such a strategy is not without risks.

Compared with temperature sensors, relative humidity sensors are far more prone to to lose accuracy, or "drift," over time. Drift may be caused by poor design, poor calibration, or contamination from water-vapor saturation or chemical vapors. A single errant reading at recalibration time will call attention to your decision to skimp on humidity sensors. Starting with fewer humidity sensors creates the risk of nonconformance, because if one fails or is out of specification, that single sensor will represent a high percentage of your total humidity measurements. Deducing humidity compliance through temperature uniformity will require that a company employee with this specialized knowledge meet with the compliance inspector. Ideally, your company should minimize the number of contacts needed during an inspection as a way to streamline the process and reduce the possibility of a misstatement.

If you're concerned about relative humidity, a more defensible mapping strategy is to track temperature and humidity at all locations with data loggers that record both measurements. It's important to use high-quality loggers that remain demonstrably accurate.

Mapping with integrated temperature and relative humidity sensors offers several advantages over deducing humidity from temperature. Mapping both temperature and humidity at all sensor locations provides a quantitative map of the entire storage space for inspectors and auditors to easily comprehend without detailed explanation. And relative-humidity excursions (caused, for example, by fire sprinkler activation or other unexpected moisture) will be easier to identify and explain if you measure relative humidity directly.

Regulatory Note: Understanding environmental variability is essential to successful mapping outcomes and managing risk in a GMP storage space.

Step 5: Select Suitable Technology

Use equipment designed for mapping. Sensors should be integral with modern electronic data loggers. Data loggers measure, store, and record data throughout the validation test. Software that accompanies the data loggers is used to set up the equipment and download data. Software should produce tabular and graphical reports that meet all requirements of 21 U.S. Code of Federal Regulations Part 11 and comparable international standards, such as European Commission Annex 11, and those contained in European Union GMP Chapter 4. (See Regulations and Guidance for details.)

When choosing data loggers, look for the following features:

- Minimum sources of error – that is, low measurement uncertainty.
- Sensitivity to small temperature changes. The more rapid the response, the more closely the data point can be associated with the time of the measurement.

- Long-term stability, particularly for relative-humidity sensors, which are more prone than temperature sensors to drift. Low-quality equipment may need to be calibrated before and after every use. Stable, high-quality data loggers demonstrated to be accurate for 12 months or more between calibrations will save time and produce better results by eliminating the need to calibrate before and after every use.
- High accuracy in the range of use. Vaisala loggers, for example, are accurate to 0.10°C (0.18°F) in an operating range of -90 to 85°C (-130 to 185°F), and to 1 percent relative humidity.
- Traceable calibration performed within the measurement range – that is, calibrated with equipment using an unbroken chain of comparisons to an internationally recognized standard such as that of the National Institute of Standards and Technology. The logger's calibration certificate should document all of the data above.
- Clear, comprehensive, and accessible calibration records.

Regulatory Note: GMPs require written procedures for calibrating, inspecting, and checking automated, mechanical, and electronic equipment (21 CFR 111.25). International standards such as ISO/IEC 17025:2005 General Requirements for the Competence of Testing and Calibration Laboratories are recognized best-practice references for calibration.

Step 6: Set Up Mapping Equipment

After you've identified likely risk areas and determined sensor distribution, it's time to set up mapping equipment and conduct a mapping test of the storage space. The purpose of this initial test is to determine where risky (that is, variable) conditions exist, and where temperature and humidity are uniform and suitable for product storage.

Work through the following checklist, making sure each step is completed and documented:

- Equipment has been calibrated – by whom, when, next calibration date, and calibration confirms that the logger performs within the limits of stated uncertainty.

- Equipment has been validated. Installation qualification and operation qualification (IQ/OQ) is typically provided by the equipment supplier.
- Program access has been secured and authenticated. Access privileges or permissions restrict who is allowed to set up the equipment and use the application.
- Software reads and records hardware and firmware model, version, and serial number. Software can identify each unique piece of equipment.
- The warehouse area under test has been precisely described.
- Data logger locations are precisely described. A pictorial map helps ensure consistent sensor placement in subsequent tests.
- Regular sample intervals have been determined. Intervals typically run between five and 15 minutes.
- Test duration has been determined. All data loggers are set to begin and end at the same time.
- Data loggers link to an audit trail file for traceability. This is an essential requirement to show that documentation is trustworthy.
- Data loggers have been positioned in defined locations.

Regulatory Note: GMPs require the use of calibrated equipment and records to show maintenance to acceptable standards. If you gathered data in electronic form, these records must meet regulations for electronic records as defined in 21 CFR Part 11, in EC Annex 11, and in European Union GMP Chapter 4. (See Regulations and Guidance for details.)

Step 7: 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. The test document will typically show the following information:

- Raw data with times and dates.
- Calculated values such as temperature minimum, maximum, and average.
- Graph of all sensors over the test period.
- Instrument settings.
- Calibration information.
- Date and time of the test.
- Space for review and approval signatures.

Overlay traces from each sensor can be compiled onto a single graph to provide a quick look at any temperature and relative-humidity extremes. Preset lines, such as acceptable minimum and maximum limits, can aid the analysis.

The measured data become part of the secure record. This record can help identify high-risk locations, especially where problems occur sporadically. For example, a temperature spike may be linked to a time when loading

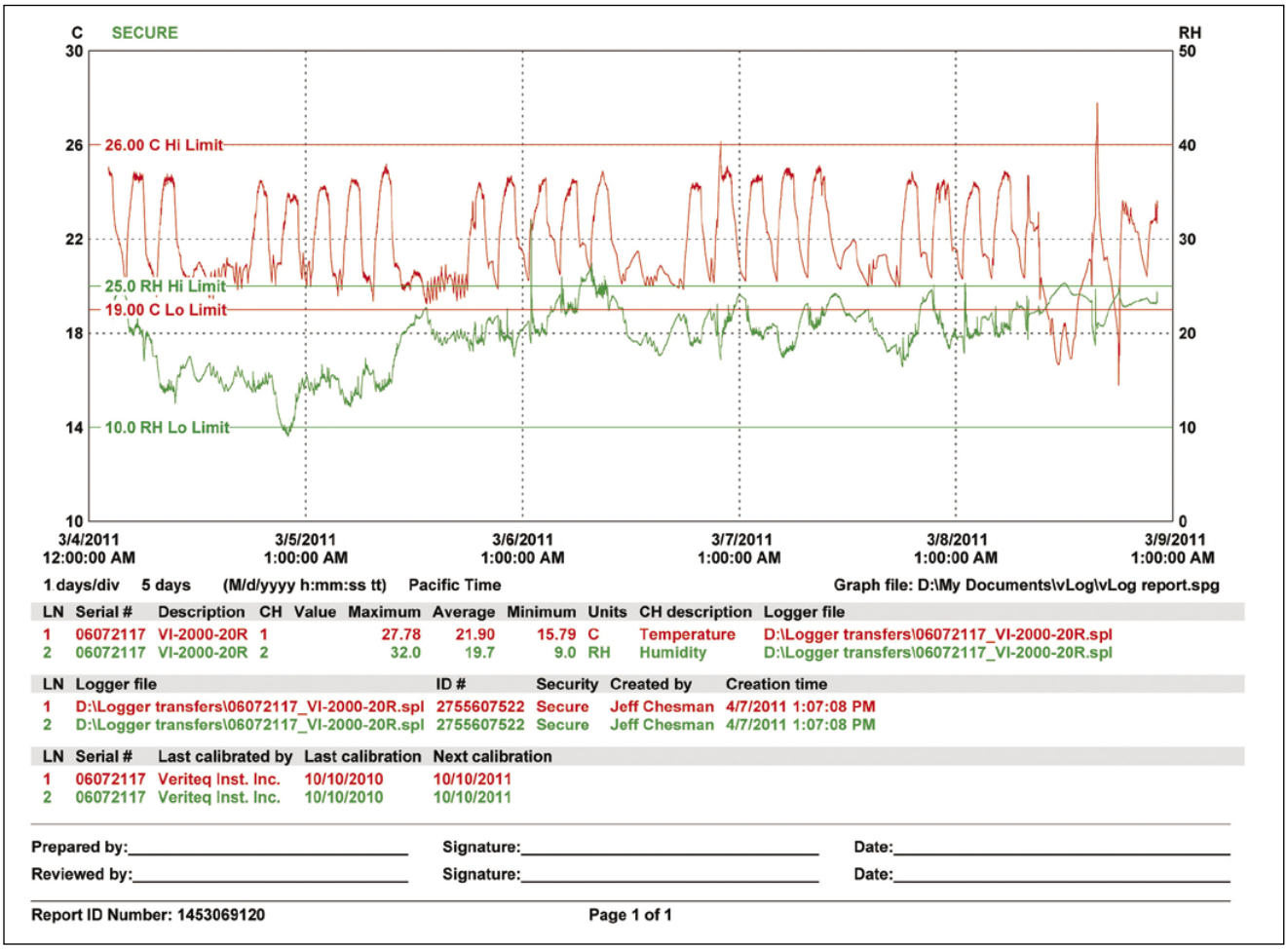


Figure 3. *The mapping report can show high and low limits to quickly visualize acceptance criteria.*

doors were open. Such a variation might indicate a risk from routine workplace activity or suggest the need for a buffer zone.

Regulatory Note: 21 CFR Part 11 and EC Annex 11 require that computerized records be available, readable, reliable and secure. It's better to present a summary graph with an easy-to-draw conclusion than a difficult-to-read report that may generate additional questions.

Step 8: Make Modifications

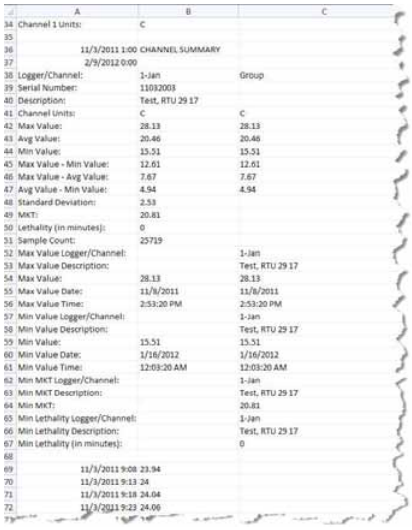
Use the results from the initial test to identify locations where the product would be exposed to unacceptable extremes of temperature or humidity. Then make adjustments—for example, to the storage racks or HVAC system—to correct this variation. Or simply decide where products will not be stored. For example, many warehouses have a mezzanine level designated off-limits to raw materials or finished goods because HVAC controls are ineffective there. Name and describe these nonstorage locations and modifications in the validation plan. Modify your validation protocol in light of the results from your initial mapping test.

Regulatory Note: Modifications to a newly commissioned warehouse don't need to appear in the inspection record. But once your company approves a validation master plan, then the plan must document all subsequent changes.

Step 9: Document and Schedule Mapping Tests

After you adjust for environmental variability in the warehouse, it's time to conduct and document a mapping test for approval.

How long should mapping last? Just as with your initial mapping test, there's no fast rule. Your rationale and protocol may support a single long test, or a series of shorter tests. Either way, it's important to measure the environment during a range of different work activities in the warehouse, such as loading, moving product, and periods such as weekends when little activity might occur.



	A	B	C
34	Channel 1 Units:	C	
35			
36		11/3/2011 1:00 CHANNEL SUMMARY	
37		2/9/2012 0:00	
38	Logger/Channel:	1-Jan	Group
39	Serial Number:	11032003	
40	Description:	Test, RTU 29 17	
41	Channel Units:	C	C
42	Max Value:	28.13	28.13
43	Avg Value:	20.46	20.46
44	Min Value:	15.51	15.51
45	Max Value - Min Value:	12.61	12.61
46	Max Value - Avg Value:	7.67	7.67
47	Avg Value - Min Value:	4.94	4.94
48	Standard Deviation:	2.53	
49	MKT:	20.81	
50	Lethality (in minutes):	0	
51	Sample Count:	25719	
52	Max Value Logger/Channel:		1-Jan
53	Max Value Description:		Test, RTU 29 17
54	Max Value:	28.13	28.13
55	Max Value Date:	11/8/2011	11/8/2011
56	Max Value Time:	2:53:20 PM	2:53:20 PM
57	Min Value Logger/Channel:		1-Jan
58	Min Value Description:		Test, RTU 29 17
59	Min Value:	15.51	15.51
60	Min Value Date:	1/16/2012	1/16/2012
61	Min Value Time:	12:03:20 AM	12:03:20 AM
62	Min MKT Logger/Channel:		1-Jan
63	Min MKT Description:		Test, RTU 29 17
64	Min MKT:		20.81
65	Min Lethality Logger/Channel:		1-Jan
66	Min Lethality Description:		Test, RTU 29 17
67	Min Lethality (in minutes):		0
68			
69		11/3/2011 9:08 23.94	
70		11/3/2011 9:13 24	
71		11/3/2011 9:18 24.04	
72		11/3/2011 9:23 24.06	

How often should you map a space? Some protocols call for mapping every three months while others can justify mapping yearly or even less frequently. The validation plan should anticipate the many variables that can change storage temperatures after completion of a mapping project. Warehouse construction, major HVAC changes, and similar modifications to the warehouse environment require additional mapping. Seasonal changes and extreme weather may justify mapping the warehouse with greater frequency or rescheduling a test for a more "seasonable" temperature. For example, the validation plan may call for a test in July, when temperatures are typically hottest. But if July is unseasonably cool, it may make sense to delay mapping until a warm spell in August. The validation plan should provide enough flexibility to capture weather extremes. For example, depending on the climate in your area, your plan might call for mapping when summer temperatures exceed 30°C and winter temperatures fall below 0°C.

Regulatory Note: Maintaining useful records is integral to meeting GMPs. Records must be stored securely but retrieved easily for review. They must be gap-free. They must provide an audit trail. Records may be paper, electronic, or a combination. If they are electronic records, they must meet the requirements of 21 CFR Part 11 or EC Annex 11.

Summary

The keys to successful warehouse mapping include creating and following a validation plan and protocol, with logical, scientific justification for each step. Document changes to the plan and protocol.

Identify areas of risk in your warehouse to determine the distribution of sensors and duration of the mapping.

Select reliable technology suitable to the task.

Modify your storage space to make sure you can validate a controlled environment.

Document and schedule mapping tests to account for changes in the warehouse environment. Keep records in a manner that they are both secure and available for review.

Document that your protocol was followed consistently, and re-evaluate your procedures periodically.

Regulations and Guidance

Warehouse mapping regulations, such as CFR Title 21 and comparable European standards, require documented evidence that an environment is in a state of control, suitable for the products stored there. Regulatory agencies and independent organizations also issue nonbinding guidance documents, which provide greater detail than regulations do in defining GMPs and current regulatory thinking. However, even these guidance documents lag behind advances in technology. In a race to keep up, regulatory agencies and industry groups worldwide constantly revise their interpretations of GMPs, developing new regulations and guidance documents. So it's imperative to keep abreast of the changing standards.

A selected list of regulations and guidance for mapping appears below. It's intended to be useful but not comprehensive.

International Conference on Harmonisation:

- ICH Q10 Pharmaceutical Quality System (2009)

United States Pharmacopeial Convention:

- USP Chapter 1079 Monitoring Devices – Good Storage and Shipping Practices (under revision 2011)
- USP Chapter 1118 Monitoring Devices – Time, Temperature, and Humidity

International Society of Pharmaceutical Engineering:

- ISPE Good Practice Guide – Cold Chain Management (2011)

Parenteral Drug Association:

- PDA Technical Report No. 52 – Guidance for Good Distribution Practices for the Pharmaceutical Supply Chain (2011)

European Commission:

- EC Guidelines on Good Distribution Practice of Medicinal Products for Human Use (under revision 2011)

Pharmaceutical Convention Inspection and Pharmaceutical Inspection Cooperation Scheme:

- PIC/S GMP Guide Part I: Basic Requirements for Medicinal Program Sections 3.19 and 4.9
- PIC/S GMP Guide Part II: Basic Requirements for Active Pharmaceutical Ingredients Sections 7.42 and 10.1

U.S. FDA Code of Federal Regulations Title 21:

- 21 CFR 820.150 Storage

Health Canada:

- GUI 0069: Guidelines for Temperature Control of Drug Products During Storage and Transportation (2011)

The following are other relevant sources for regulations, guidance and standards.

U.S. FDA Code of Federal Regulations Title 21:

- 21 CFR Part 210 cGMPs for Manufacturing, Processing or Holding of Drugs
- 21 CFR Part 211 cGMPs for Finished Pharmaceuticals
- 21 CFR Part 820 cGMPs for Medical Devices
- 21 CFR Part 600 cGMPs for Blood Products

- 21 CFR Part 111 cGMPs for Dietary Supplements
- 21 CFR Part 11 cGMPS Electronic Records & Signatures
- 21 CFR 211.46, .68, .142, .194 Ventilation, Air Filtration; Electronic Equipment, Warehousing; Laboratory Records

European Commission:

- Eudralex Volume 4 Good Manufacturing Practices – Medicinal Products for Human and Veterinary Use, Annex 11: Computerized Systems (2011)

U.S. FDA:

- Guidance for Industry: Quality Systems Approach to Pharmaceutical cGMP Regulations (2006)
- Pharmaceutical CGMPs for the 21st Century – A Risk-Based Approach (2004)

International Conference on Harmonisation:

- ICH Q8 – Pharmaceutical Development (2006)
- ICH Q9 – Quality Risk Management (2006)
- ICH Appendix 2.4 Human and Organizational Errors and Criticality of Records

International Society of Pharmaceutical Engineering:

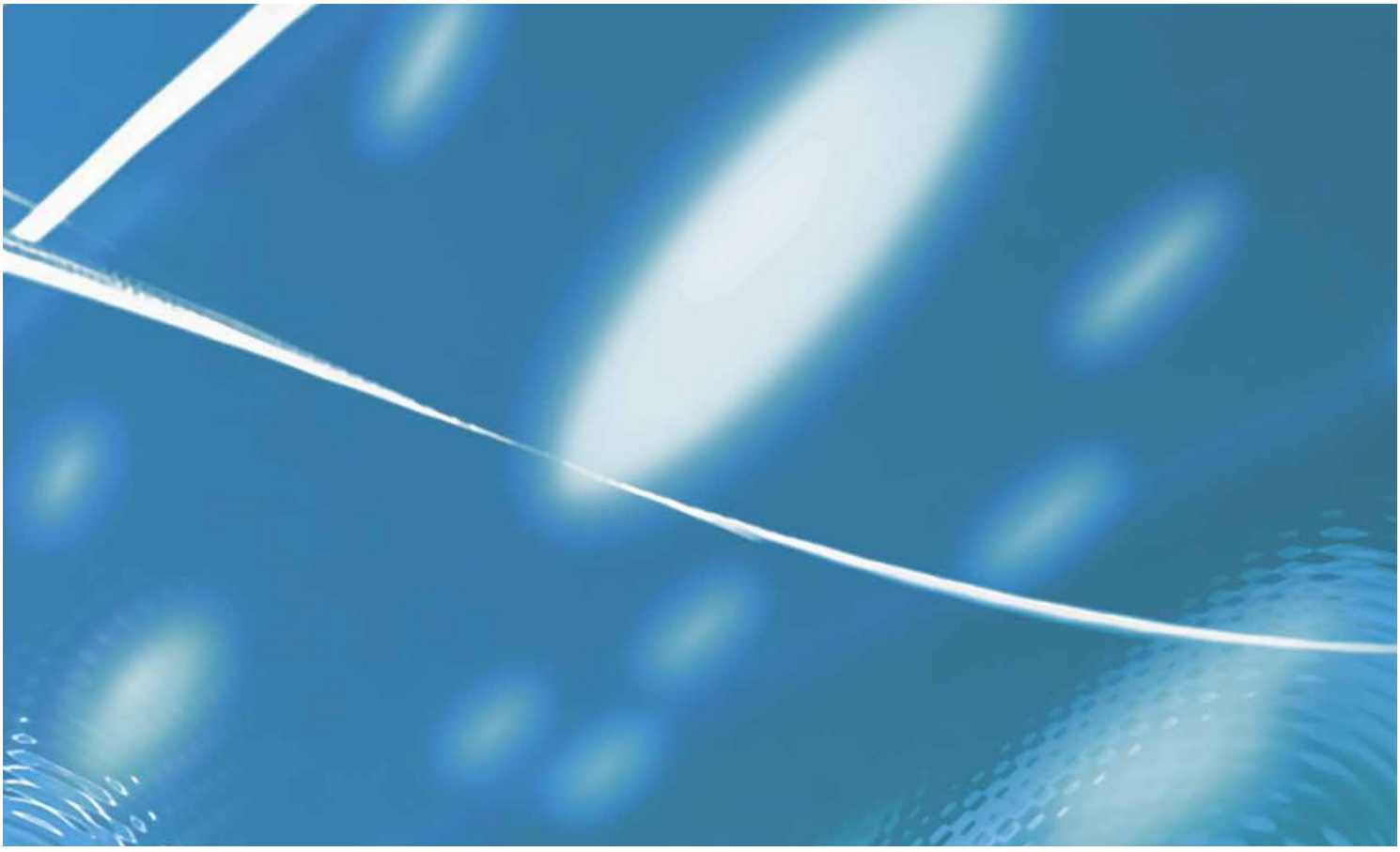
- ISPE GAMP® 5: A Risk-Based Approach to Compliant GxP Computerized Systems

World Health Organization:

- WHO Report 908 Appendix 2 ASTM (formerly American Society for Testing and Materials):
- ASTM E2500 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment (2007)

International Organization for Standardization:

- ISO/IEC 17025:2005 General Requirements for the Competence of Testing and Calibration Laboratories
- ISO 10012:2003 Measurement Management Systems
- ISO 14971:2007 Medical Devices – Application of Risk Management



VAISALA

For more information, visit
www.vaisala.com or contact
us at sales@vaisala.com