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White Paper

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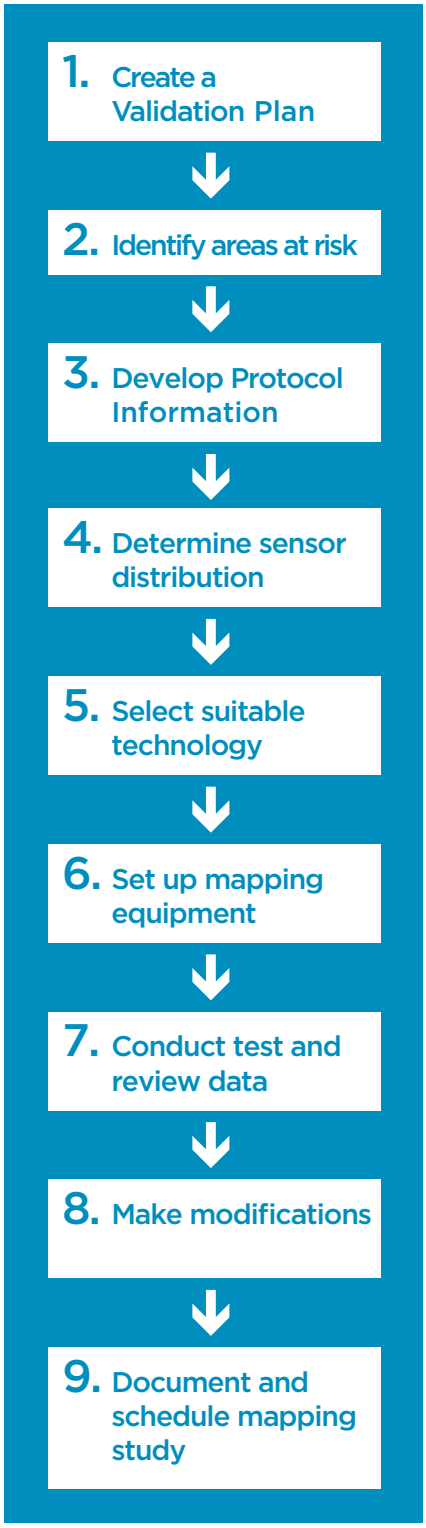
# GMP Warehouse Mapping Step-by-Step Guidelines for Validating Life Science Storage Facilities

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 profiles 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 the end of this paper for links to relevant regulations and guidance documents.)
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. Vaisala solutions are used in over 150 countries worldwide.

# Step by Step – Good practices for warehouse mapping studies

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




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 decisions about qualifying every aspect of the facility, equipment, and processes to maintain a GMP-compliant environment. The plan should take a risk-based approach, with a rationale based on verifiable data. 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 validation master 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 if a temperature or humidity excursion occurs.
- Determine a validation schedule.
- Specify the management approval process, especially for adverse events such as temperature deviations.
- Create change control protocols so it's clear when changes such as maintenance, new construction, and reconfiguration of racks will 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 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 identify risks:

- 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 floor and warmer air near the ceiling.
- Independent energy sources, such as space heaters, air conditioners, and fans, which create warm or cold spots.
- 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 docks.
- High-traffic areas where product or equipment is moved often.
- Seasonal temperature changes or unusual weather events.

*Regulatory Note: You can achieve GMP compliance through sound justification of your approach to identifying risk. The more considerations the protocol addresses, the better your rationale is likely to be.*

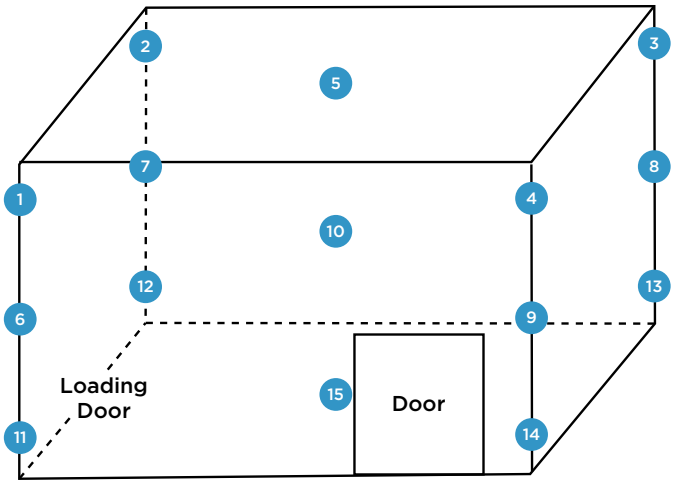



*Figure 1: . The even distribution of 15 sensors is a typical pattern for a three-dimensional mapping of a small space.*

## Step 3: Develop protocol information

Once you've identified areas of risk, develop a protocol for the mapping study 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).
- Schematic or diagram 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.
- 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.*

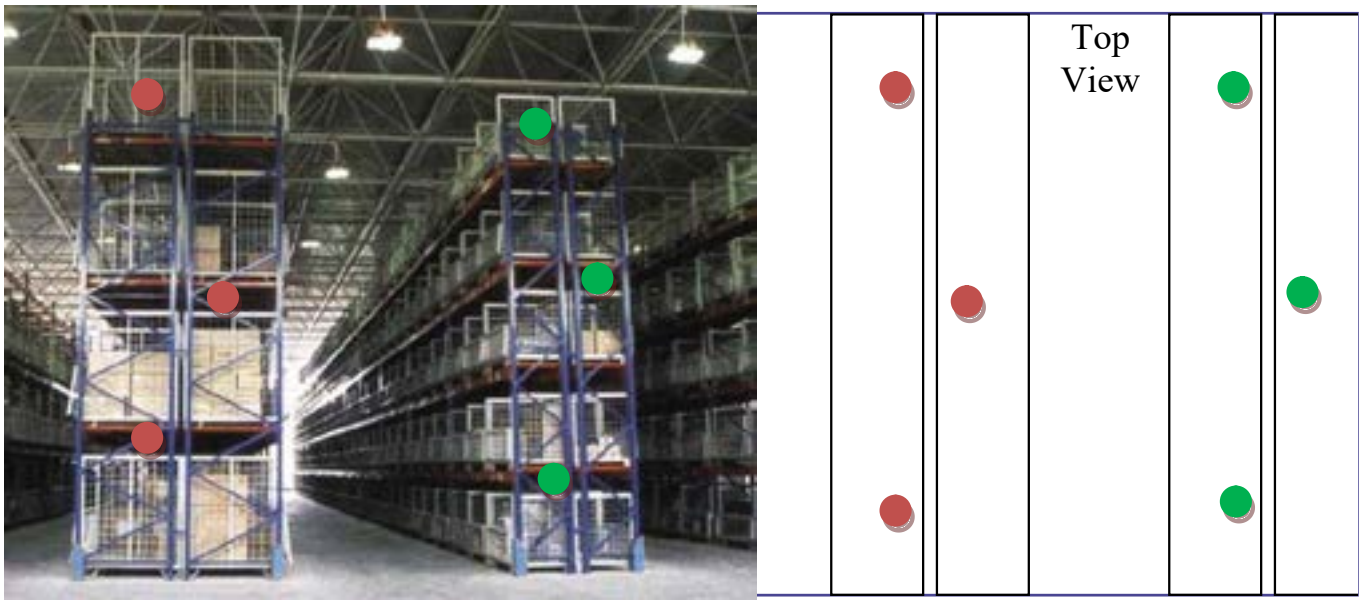



*Figure 2: Sensors placed in the middle of racks more closely reflect product temperatures. In this example, nine sensors are located on each double rack in this warehouse measuring 30 meters by 30 meters by 15 meters.*

## Step 4: Determine sensor distribution

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

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

A walk-in chamber or small warehouse is often mapped in three dimensions with 15 sensors (See Figure 1.) The protocol should include guidelines for the distance between sensors, for example, no greater than six meters.

In mapping a large warehouse, set sensors as far as 30 meters apart, with additional sensors in vulnerable areas affected by:

- Heat or cold from external walls, solar heating, windows, lighting
- Air circulation or drafts from entries, traffic, or the HVAC system
- Temperature extremes in poorly insulated areas
- Localized effects of space heaters and air conditioners

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 (for example outside of racks or aisles) where they are convenient to set up. But convenience must not take precedence over effectiveness. Sensors must measure the conditions that products are exposed to.

If you don't have an adequate number of sensors to map an entire warehouse in one study, you may 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 in sections. To decide, calculate 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 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.

## Determining humidity sensor density

The first approach is to use comparatively few humidity sensors distributed throughout the warehouse (as few as one for every six temperature sensors). In this case you will rely on temperature uniformity to make the case that humidity is also within bounds. This approach should be based on a history of temperature mapping in different seasons with consistent results. With this history, a specialist with an understanding of humidity measurement 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 humidity sensors you do use in areas with poor air circulation, between HVAC fans or diffusers, and where temperature is most variable.

## Considerations for humidity

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 use fewer 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. Interpolating relative humidity from temperature data will require that a company employee with this specialized knowledge meet with the auditor or 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 data loggers that are stable and regularly calibrated.

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 more quantitative map of the entire storage space for inspectors and auditors to easily comprehend without detailed explanation. And relative humidity excursions will be easier to identify with more humidity data points.

*Regulatory Note: Understanding the relationships between measured parameters is essential to successful mapping studies and managing risk in a GMP storage space.*

## Step 5: Select suitable technology

Use equipment designed for mapping. Software that accompanies the sensors is used to set up the equipment and download data. Software should produce tabular and graphical reports that meet all requirements of 21 CFR Part 11 and comparable international standards, such as European Commission Annex 11, and those contained in European Union GMP Volume 4.

When choosing data loggers, look for the following features:

- Minimum sources of error – that is, low measurement uncertainty.
- High accuracy in the measurement range. Vaisala DL2000 data loggers, for example, are accurate to ± 0.1 °C over +20 °C to +30 °C, with humidity accuracy of ± 1 %RH in 10 to 80 %RH.
- Sensitivity to small temperature changes (high resolution). 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. Low-quality equipment needs to be calibrated before and after every study.
- Traceable calibration performed within the measurement range and with equipment using an unbroken chain of comparisons to an internationally recognized standard such as that of the National Institute of Standards and Technology (NIST).
- Clear, comprehensive, and accessible calibration records.

*Regulatory Note: GMPs require written procedures for calibrating, inspecting, and checking automated, mechanical, and electronic equipment (21 CFR 211.68). International standards such as ISO/IEC 17025:2017 "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 risk areas and determined sensor distribution, it's time to set up mapping equipment and conduct a test of the storage space. The purpose of this initial test is to determine where variable conditions exist, and where temperature and humidity are uniform and suitable for product storage. Work through the following checklist and document each step:

- Equipment has been calibrated. Document by whom, when, and the next calibration date. This confirms that the data logger performs within the calibrated measurement range.
- Equipment has been validated. Installation qualification and operation qualification (IQ/OQ) is typically provided by the mapping system supplier.

- Ensure mapping software access has been secured and authenticated. Access privileges restrict who is allowed to use the application.
- Ensure the software reads and records hardware and firmware model, version, and serial number.
- Ensure the warehouse area and data logger locations are accurately described. A schematic or diagram helps ensure consistent sensor placement in subsequent mapping studies.
- Regular sample intervals have been determined. Intervals typically run between five and 15 minutes.
- Study 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 the data is trustworthy.
- Data loggers are functional and positioned in defined locations.

*Regulatory Note: GMPs require the use of calibrated equipment and calibration records. 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 Volume 4.*

## Step 7: Conduct a test and review data

You'll need to establish the reporting information you'll use to evaluate the test. When the test is complete, the software will read the secure files from the data loggers, show recorded data, perform calculations, and graph the results selected for a mapping study report. The test document will typically show the information in Figure 3:

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

Trend data from each sensor can be compiled in a single graph to provide an overview. Preset lines, such as acceptable minimum and maximum limits, can aid the analysis.

A graphical overview can help identify high-risk locations, especially where problems may occur sporadically. For example, a temperature spike may be linked to a time when loading doors were open.

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

*Regulatory Note: It's better to present a summary graph with a clear conclusion than a very detailed report that may generate additional questions.*

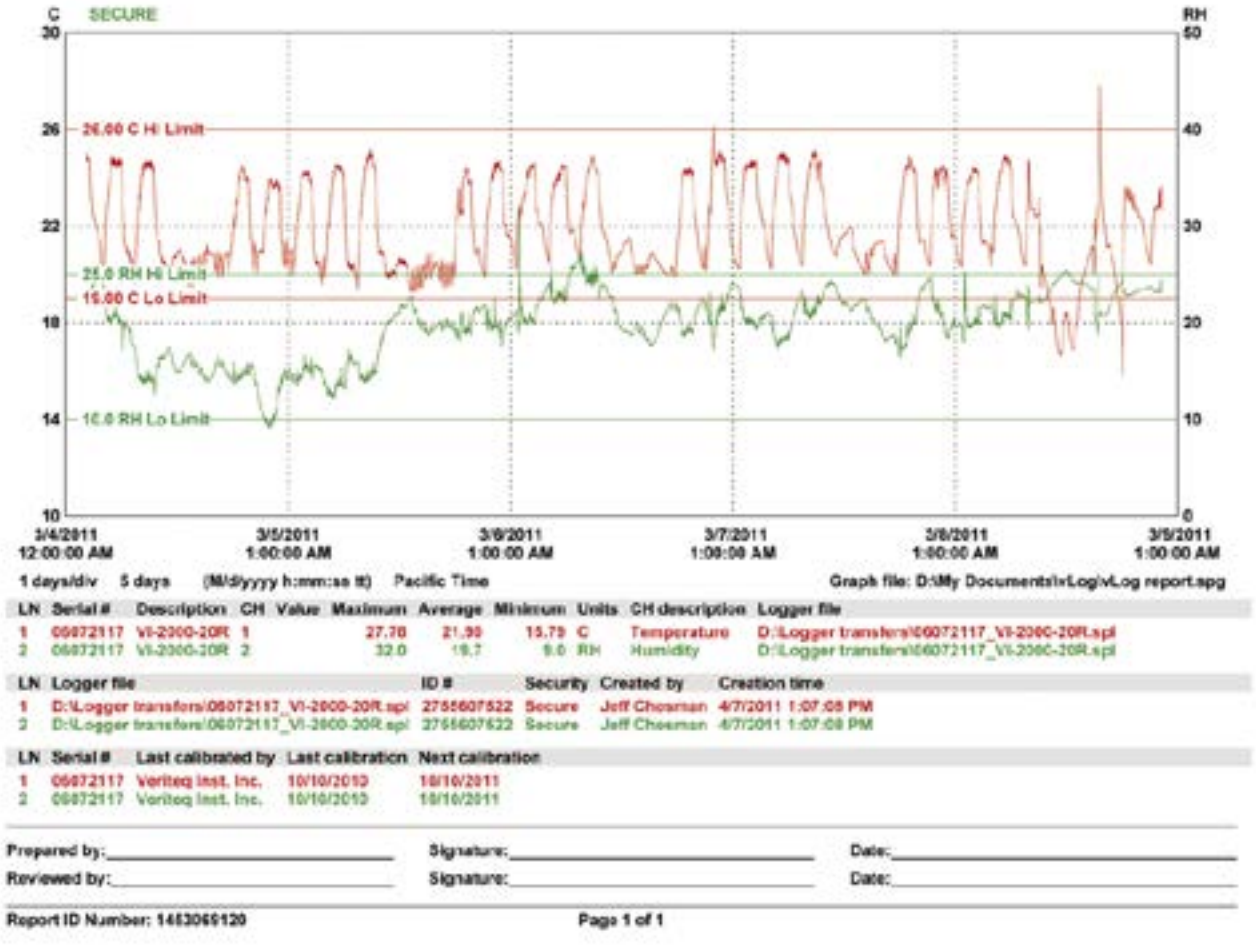



*Figure 3. The mapping report can show high and low limits to quickly visualize thresholds.*

## Step 8: Make modifications

Use the results from the initial test to identify locations where the product may be exposed to unacceptable conditions. 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 for raw materials or finished goods because HVAC controls are ineffective there. Name and describe these locations and modify the validation plan. Also, 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 the mapping study

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

### How long should mapping last?

As with your initial mapping test, there's no fast rule. Your rationale and protocol may support a single long study, or a series of shorter studies. 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.

### 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 master plan should anticipate variables that can change storage conditions after completion of a warehouse qualification. Warehouse construction, major HVAC changes, and similar modifications to the 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 mapping study 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 and easily retrieved 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 a successful warehouse mapping study include creating a validation plan and protocol, with 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 ensure you are mapping a controlled environment.

Document and schedule mapping studies to account for changes in the warehouse environment.

Keep records in a manner that they are secure and accessible.

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

## Regulations and guidance

Warehouse mapping regulations require documented evidence that an environment is in a state of control and suitable for the products stored there. Regulatory agencies and independent organizations also issue non-binding guidance documents that can provide greater detail than regulations in applying current regulations. However, even these guidance documents can lag behind technological advances. In a race to keep up, regulatory agencies and industry stakeholders worldwide revise their interpretations of GMPs, developing new guidance documents. So it's imperative to keep abreast of the changing standards.

## Links to resources

**International Conference on Harmonisation:**

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

**United States Pharmacopeia:**

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

**International Society of Pharmaceutical Engineering:**

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

**Parenteral Drug Association:**

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

**European Commission:**

- EC Guidelines on Good Distribution Practice of Medicinal Products for Human Use
- Eudralex Volume 4 Good Manufacturing Practices – Medicinal Products for Human and Veterinary Use, Annex 11: Computerized Systems

**Pharmaceutical Inspection Convention and Pharmaceutical Inspection Cooperation 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

**Health Canada**

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

**U.S. FDA:**

- 21 CFR Part 210 cGMP in Manufacturing, Processing, Packing, or Holding of Drugs
- 21 CFR Part 211 cGMPs for Finished Pharmaceuticals
- 21 CFR Part 820 Quality System Regulation
- 21 CFR Part 600 Biological Products
- 21 CFR Part 111 cGMPs in Manufacturing, Packaging, Labeling, or Holding Operations for Dietary Supplements
- 21 CFR Part 11 Electronic Records; Electronic Signatures
- Pharmaceutical CGMPs for the 21st Century – A Risk-Based Approach

**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

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