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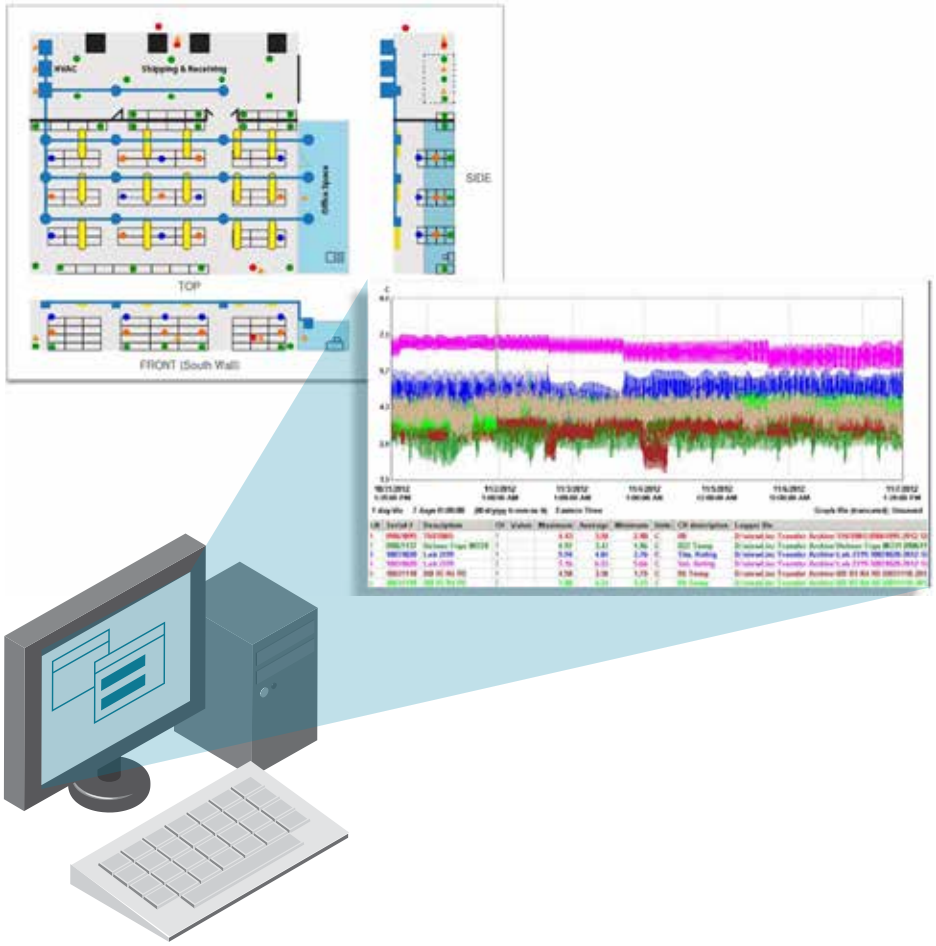
Validation/Mapping Applications

Troubleshooting Tips and Best Practices



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Paul Daniel, Senior Regulatory Compliance Expert at Vaisala, has 16 years of validation experience in the pharmaceutical , biotechnology and medical device industries. He has worked on a wide range of qualification projects, including process, cleaning, shipping, laboratory equipment, packaging, network, and software validation. As one of Vaisala's subject matter experts, Paul offers extensive practical advice in applying the good manufacturing practices and principles of the FDA's 21 CFR Parts 11, 210, 211, and 820, as well as authoring and executing validation protocols for pharmaceutical manufacturing and software validation with a risk-based approach drawn from GAMP guidelines. Daniel has a bachelor's degree in biology (with honors) from the University of California, Berkeley.

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Jon Aldous is the Product Manager for Vaisala's Life Science environmental monitoring system offering. His background is in electronics and electrical science and he holds a bachelor of Engineering. He lectured at the University of the West of England teaching digital and mechanical engineering and was involved with the development of poly-silicon micro structures for use within thermopiles and intelligent data acquisition sensors. After immigrating to the US, he worked for 12 years with Kaye Instruments as Product Manager developing that company's thermal validation systems. He later joined Veriteq Instruments, which was acquired by Vaisala in 2010. The acquisition has enabled Aldous to expand his role into both software and hardware product management for life science applications.

5 Frequently Asked Questions about Temperature and Humidity Validation/Mapping

The FDA mandates the validation of environmental conditions that can affect the strength, identity, safety, quality, and purity of pharmaceuticals, medical devices, or biologics. To meet these requirements for temperature or humidity, we perform a mapping validation, usually as part of an installation qualification and operational qualification of the environment, be it: incubator, fridge/freezer, stability chamber, cold room, or warehouse.

Most people who contemplate doing a mapping validation for the first time look for answers to these five questions:

1. What limits should I use as an acceptable range for my study?
2. What type of sensor(s) should I use?
3. How many sensors do I need, and where should I place them?
4. What kind of calibration do my sensors require?
5. What is the appropriate duration for a mapping study?

What limits should I use as an acceptable range for my study?

This depends on what you are storing. You should be able to use the results of your stability studies, or the recommended storage conditions from the manufacturer of the product you are storing. You can use tighter limits if you wish, but it will be hard to justify using limits that are wider.

What kind of sensors should I use?

Your sensors should measure the parameter of concern, e.g., temperature and/or humidity. Sensors should be accurate. According to current industry standards, an error of ±0.2° C is good for temperature, and ±3 per cent is good for relative humidity. If you use devices that require software, you will need to show that the software has been validated and is compliant to 21 CFR Part 11.

How many sensors do I need?

The International Society for Pharmaceutical Engineering (ISPE) provided some guidance in its document, “ISPE Good Practice Guide: Cold Chain Management” published May 2011. For spaces less than 2 m^3 in volume, 9 sensors are recommended. For spaces between 2 m^3 and 20 m^3 in volume, 15 sensors are recommended. An additional sensor should be placed adjacent to the display, control, and monitoring probe(s), if applicable. If you are mapping spaces with volumes larger than 20 m^3, there is no easy guideline. You must assess the space and determine likely sources of variation in temperature and humidity, such as HVAC systems, doors, and windows. An approach to larger spaces is to limit the sensor placement to the spaces where product is actually stored. However, if you map only the racks and shelves, the area will require procedural controls to ensure that product is stored only in the areas that were mapped.

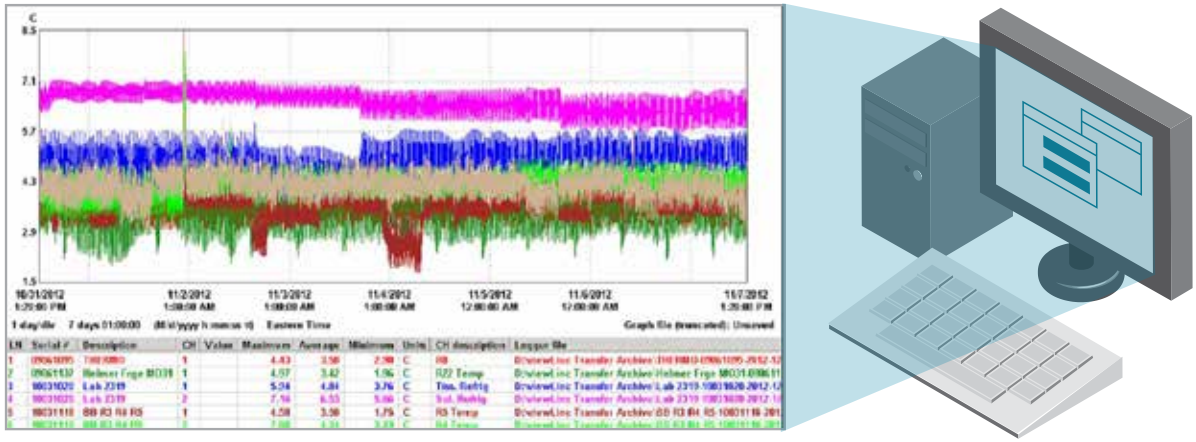
What kind of calibration do my sensors require?

Sensors must be shown to be in calibration prior to the study, and the calibration must be verified following the study. Traceability to NIST or another National Standards agency is expected. If you have purchased or rented sensors, you can likely depend on the vendor to supply initial calibration services.

What is the appropriate duration for a mapping study?

Your study should be long enough to provide confidence that you have accurately captured the environmental dynamics of the space being mapped. Forty-eight hours is sufficient for most small spaces under 2 m^3 and 5 to 7 days is common for warehouses. However, the larger the space, and the more actively it is used during the study, the longer the expected duration of mapping. For a warehouse in use 5 days a week, a study duration of 1 week may be appropriate. Consider seasonal changes as well for large spaces, performing your mapping studies during the hottest and coldest times of the year.

For all of these questions, it's important that you develop a clear rationale for your choices and document them in your validation protocol. Your rationale should be scientifically based, appropriate to your facility and product, and suitable for the intended use of the space being mapped.



5 Scientifically Sound Steps to Determining How to Monitor Temperature in your GxP Space

In controlled environments, managing risk means developing evidence of appropriate conditions. The evidence must satisfy your quality standards and those of your auditors/inspectors. Most importantly, this evidence must prove that products are processed and stored according to their specifications.

A mapping validation is used on a newly operational space in order to determine whether the space will meet the needs of a product. To illustrate how to determine the best way to monitor such a space, let's look at a hypothetical situation where your mapping study has identified the high-risk areas in the area you want to monitor, let's say, a cold room. Assuming that you know where the hot and cold spots are, let's also assume that the entire space, including the hot and cold spots, stayed within specifications during your study. Once the space is qualified, we use the study results to figure out how to monitor it effectively.

STEP 1: Hot/Cold Spots

The simplest and most obvious first step is to locate the hottest and coldest locations in the room. Once that is accomplished, place a monitoring sensor at both locations. This is technically a "statistical analysis" because we are looking for maximums and minimums. This can be expensive because there are two locations and can also sometimes be logistically challenging when the hot/cold spot is in an inconvenient, or a difficult control location.

STEP 2: Find an Exemplar

Next, choose a spot that is **most** representative of the entire space. For example, say your cold room specifications are 2 – 8° C. By analyzing the data, you establish that your representative spot is at 6.5° C when the hot spot hits 8° C. Likewise, you determine that the representative spot is at 3° C when the cold spot hits 2° C. So you create alarm limits for the representative location at 3 and 6.5° C. The downside here is that the most representative location might not be in a location where the temperature is easy to control. Additionally, facility personnel might keep trying to correct your alarm limits of 3 – 6.5° C back to the 2 – 8° C they think the unit is supposed to control at. This depends on the level of quality sophistication at your site, the amount of GMP training provided to facilities employees, as well as the level of control you have over your monitoring system.

STEP 3: Position the Sensors

Often people do the same analysis as Step 2, but apply it to a monitoring probe located at the same location as the control probe, or some other standard location, such as just inside the door. Usually though, probes are placed beside the door and monitor at the straight specification limits (2 – 8° C in this case). This may seem strange because no analysis is done to adjust for the temperature variation in the space. However, the virtue of this approach is simplicity. For some groups, the advantages of simplicity outweigh the disadvantages.

STEP 4: Account for Error

Take into account the accuracy errors in your monitoring and mapping devices. The combined error could be up to, or even over 1° C, depending on the sensors you used for monitoring and mapping. That just makes it all more complex.

STEP 5: Troubleshoot Problem Areas

One easy way to approach the whole situation is to make the warm spot off limits. If you have space to spare, just cage it off and then find the next warmest spot. This should reduce alarms caused by hot spots. Alternately, you can evaluate the data based on what you actually store in the space. This works best if you always store the same product in the space. For example, if your product is always a paperboard box of 25 5 cc vials of "Product X", you could do a study on product temperature to justify raising the high alarm level to (for example) 10° C, by showing that product temperature remains below 8° C in those situations. Or perhaps you leave the alarm level at 8° C, but justify a delay on the alarm based on your data. In any case, the best way to manage problem areas is always to have air temperature within limits.

Once you've taken the steps to establish baseline data, used your study to learn about your environment, positioned your sensors according to your findings, determined (and documented) sensor accuracy, you have accumulated evidence to justify your monitoring methods, including sensor placement, product placement, sampling rates and possibly, adjustments to your heating/cooling systems. This evidence is what is required to prove that an in-depth process was undertaken to determine a monitoring method which meets or exceeds GxP standards.

Mapping Validation Sensor Placement

The Whole Warehouse and Nothing but the Warehouse

When mapping an area, the size of the area affects the complexity of sensor placement because greater volume can increase the impact of variables such as air flow, material types, shelving configuration, and HVAC considerations. Scale is critical, especially in terms of height because heat rises. We try to use every inch of space, but every foot can affect the environment and it's our job to understand the environment. As an example, imagine a warehouse where the sensors are placed at a height of 6 m (at the top of the rack), but products are stored up to 8 m (2 m high on the top rack). This was the case at a customer's warehouse where they have rationalized their sensor placement as follows:

The purpose of the placement of the data loggers is to approximate the geometric corners and middle locations of the warehouse areas. The top location heights were to be in the general area of the top plane, they were not meant to be the extreme top plane. The temperature variation will not be much in a space of 5-10 feet, considering the whole of the warehouse area was mapped and shown to be within limits.

Validation Sensor Placement

Was this appropriate?

The objective of a mapping study is to capture the conditions in the entire storage area. Best practice is to place sensors at the limit of the usable space. This is an easy concept to apply in a small space like a refrigerator or an incubator. But even then, the principle is the same: If we map a 1 m^3 refrigerator, with the corner sensors 10 cm from the adjacent sides, are we obligated to never place my sensors out of these bounds? Consider that, in practice, we can never prevent users from placing product outside the mapped space of a refrigerator (between that 10 cm and the walls of the chamber). And we can all probably agree that the 10 cm doesn't make much of a difference.

However, in a large space such as a warehouse, the challenge is precisely the opposite. We will usually need to store things on top of the uppermost racks, but there is no easy way to get sensors there safely, especially in an active warehouse. The only way to confirm 100% that the product storage locations on the top racks are within the temperature specifications is to get sensors up there.

There are a few factors to consider, and like all things metrological, it really depends on the variables of the environment. There are four critical factors that should inform your warehouse mapping methods.

1. **Standard Practice:**
   Standard practice is to place the sensors up as high as possible on the racks. In most instances, this means there is product storage above the sensors. This is where the realities of our environments conflict with the perfect world we'd like to see in our studies.

2. **Special Circumstances**
   There are few instances where you can place sensors above the actual storage area by placing the sensors on the ends of poles. This kind of effort is reasonable when the environment has a feature that might affect conditions at the top of the storage space, which can include seasonal factors, ducts, air flow etc. However, more often the difference is insignificant, except a few cases where the sensors were placed near HVAC vents.

3. **Product Specifications**
   Whether just at or above product placement level, once we have the conditions at the top plane, there's a decision to be made: If conditions are well within specifications, this indicates product is safely stored in the space. If conditions are very near the limits of your product specifications, it is worth investigating. But then the issue, and therefore the solution, is not one of sensor placement in a mapping study, it's one of the control system(s) needing adjustment.

4. **Inspectors and Audits**
   If an auditor found a problem with sensor placement in your studies, it's unlikely to be a crucial observation. The fact is that by having performed mapping studies, you are showing considerable commitment to best practices in GMP. Unfortunately, despite it being a GMP requirement, many companies struggle to validate properly, if at all. At worst, the auditor will ask you to place the sensors higher on your next scheduled validation. It's unlikely that a revalidation would be requested.

View the webinar: http://cc.readytalk.com/play?id=5dyuy3

Sensor Placement Troubleshooting

Sensor Response Times & Mapping In-air or In-media

There are two questions in mapping validation that we often encounter in incubation or stability environments. The first question is: How do we compare data for an Intelligent RTD probe and a data logger that are in the same position when they show different response times? The second: If an incubator is fully loaded with vials of media, should we be mapping temperature distribution in the chamber, or in the vials?

Sensor Response Times

The thing about sensors is this: they all have different response times. So the question can be asked about a data logger itself, relative to the air it is mapping. Of course, we need to make sure that our data logger is responsive. But, how responsive is responsive enough? Our recommendation is: Don't worry about the different temperature response times of the data logger and the IRTD/monitoring probe. If both sensors are monitoring air temperature, they will both likely have faster response times than the product being stored.

By monitoring air (representing worst case conditions) a safety factor is built into the analysis that effectively cancels out the concern of the different response times of different sensors. However, this answer only applies if both sensors are in air.

Chamber Load and Process Specificity

What does "Fully Loaded" mean? Generally, an incubator should only be loaded to 50-60% of its actual possible physical volume. Otherwise there will not be enough space to allow for air flow and the resulting cooling/heating processes. This is based on French Standard: NFx15-140: "Measurement of Air Moisture – Climatic and Thermostatic Chambers – Characterization and Verification." (The newest version is: FD X 15-140 of May 2013: "Measurement of air moisture - Climatic and thermostatic chambers - Characterisation and verification". Unfortunately, as of January 2014, this is only available for purchase in French. The older version of the standard NF X 15-140 of October 2002 is available for purchase in English. Email adv@afnor.org for more information.)

In addition, consider whether the process is actually storage. The concept of using air as a representative of the worst case only applies if the process is storage. If the media you are placing into the incubator is not already within a few degrees of the incubator set-point, or is not intended to be stored in the incubator for some period of time, then the process is actually a directional temperature change (heating or cooling) of the media, and **not** storage. In this case, the air temperature is not a measure of the worst-case challenge. Media temperature would then be representative of the worst-case challenge.

So, if it is truly a storage process at a uniform temperature, and your incubator is not overloaded, the best choice is to measure air temperature. But if the process is a directional temperature change, then measure media temperature with some air temperature locations for reference.

Chamber Design and Convection

Finally, consider that the loading capacity of any temperature chamber depends on the design and the convection mechanism used to transfer the heat in the chamber. Instead of taking the 50-60% loading space recommended by NFx15-140, you may study the temperature distribution with an empty chamber and afterwards with a loaded chamber.

In this case the sensors are measuring air temperature in the same places as in temperature distribution with empty chamber. This establishes acceptance criteria for "Fully Loaded" the same criteria as for empty chamber, i.e.: average temperature in the chamber less than 1° C from set-point temperature and less than 1° C between any sensor and the average temperature at any one reading after stabilization.

View the webinar: Validation Protocols http://cc.readytalk.com/play?id=2l3jxp

The Validation Master Plan

Checklist and Regulation Summary

While there is no formal requirement for a Validation Master Plan by national enforcement and governmental agencies such as the FDA and EMA, it's a standard practice in the industry. Most regulatory bodies that perform inspections will expect a set of planning documents, and most pharmaceutical, biological, and medical device firms work under a high-level Validation Master Plan.

However, a review of the Code of Federal Regulations does not yield a single mention of a "Validation Master Plan." Instead it is mentioned in many peripheral documents. Moreover, if you scan Warning Letters and Notice of Observations (483s) on the FDA's electronic reading room, you will find several mentions of a Validation Master Plan, which reveals that this document is an expectation of the FDA's enforcement arm, and often requested during an inspection.

Here's an example from a Warning Letter dated March 15, 2013 - from the FDA's Office of Global Regulatory Operations and Policy Electronic Reading Room:

> *'"Process Validation" SOP4.2.1 was revised to Rev. V to include requirements for a **Master Validation Plan**. A Master Validation Plan for process validation of [x] machines has been completed and an Installation Qualification (IQ) protocol for [x] machines has been released.'*

Pharmaceutical, biotechnology and medical device companies are faced with several similar challenges, and often find similar solutions. This is the basis of industry best practice and the basis of GMP. Solutions to similar challenges create collective industry standards against which we are all measured and the "Validation Master Plan" is now a commonly used document.

Validation planning documents must briefly describe the processes and equipment that require validation, along with persons responsible and methods to be used. As far as expectations go, most inspectors want a summary document showing that you have suitable practices in place to ensure that you have identified the processes/equipment that require validation, including in what order and by what priority.

The Pharmaceutical Inspection Co-operation Scheme has published a document called: "Recommendations on the Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation/Cleaning Validation." Although the recommendations are neither mandatory nor enforceable, they can be considered "appropriate." This document, in combination with the PIC/s's "Good Practices for Computerised Systems in Regulated 'GxP' Environments" briefly outlines a Validation Master plan, comprising the following:

- *A list of all validation activities: prospective, concurrent, and retrospective*
- *A list or copies of any parallel Validation Plans*
- *References to existing documents such as Policy Documents, SOP's and Validation Protocols/Reports*
- *A list of facility management who have agreed upon the master plan*
- *A statement of the firm's validation policy*
- *General description of the scope of the operations of the firm detailing the facilities, processes and products*
- *The time and location of validation activities (ideally prioritized)*
- *A list of personnel responsible for the VMP, SOPs and protocols*
- *A list relevant validation reports and documents*
- *A list of personnel (roles) who provide approval*
- *Description of any tracking systems used for reference and review*
- *Validation training program plans: either the plans as appendices or references to the plans as separate documents*

For your reference, here is a list of some other important validation documents for Pharmaceutical manufacturing:

- *ICH Quality Guidelines (QbD: ICH Q8, Q9, and Q10)*
- *FDA Guidance; Process Validation: General Principles and Practices (2011 Jan, Revision I)*
- *EMA Draft Guideline on Process Validation (March 29, 2012)*
- *Final Version of Annex 15 to the EU Guide to Qualification and Validation*

How to Validate your CMS software according to GAMP

When selecting an enterprise system for monitoring GMP storage areas, there are three concerns that inform your choice:

1. The parameters you need to measure
2. Your existing IT infrastructure
3. The validation strategy you will use in qualifying the system's performance

In this article we will focus on the third: validation.

The ISPE created a convenient framework in their guide "GAMP: Good Automated Manufacturing Practice." The GAMP guidelines separate monitoring systems into three categories:

- *Off-the Shelf (GAMP Category 3)*
- *Configured (GAMP Category 4)*
- *Custom (GAMP Category 5)*

To evaluate a monitoring system according to the level of effort involved in system validation, we assess the effort with a rating system on a scale of 1 to 25. On that scale, nothing has less than a 5; this is to recognize the fact that all validation requires effort. Even the simplest system installed in a GxP environment is going to require validation that includes, at a minimum, the following documents:

- *User Requirements*
- *Functional Specification*
- *Validation Protocol*
- *Traceability Matrix*

Using the GAMP categories, this table shows the difficulty of validating each type of system:

Category 3	**Off-the-shelf**	**Validation is easy**	**5/25 difficulty**
Category 4	**Configurable**	**Validation is moderately difficult**	**10/25 difficulty**
Category 5	**Custom**	**Validation is time-consuming & labour intensive**	**25/25 difficulty**

Pros & Cons of Monitoring System Types

Choosing a monitoring system is more complex than just comparing levels of expected validation effort. While an Off-the-Shelf system may be relatively simple to validate, it will come with the compromise that the system will likely not be very flexible and only have limited capabilities. Similarly, a Custom-built system requires significant effort to validate, but yields a higher level of capability. Many prefer the middle-ground choice of the Configurable System, which provides the comfortable compromise of a moderate validation effort coupled with the flexibility of a configurable system.

Evaluating validation effort is only one element of choosing the correct system. If your organization has limited validation experience, capability, or resources, you should include ease of validation in your User Requirements document according to the rating scale outlined above. This will guide you to systems with appropriate level of validation, or to vendors that offer validation services. Organizations in this group will likely select Off-the-Shelf or Configurable systems. Organizations with experienced and capable validation personnel are more likely to opt for greater system flexibility and greater validation effort, and select Configurable or Customized systems.

Where to Start: Honest Evaluation

Regardless of the type of system you choose, every validation effort should start with a clear, comprehensive User Requirements document to define your business needs. Make sure you include an honest evaluation of your validation needs in this document, as it will serve as a kind of check list for ensuring you select the right system. This is the single most important step in ensuring that your system will suit your needs, and that validation of the system will be within your ability.

View the Webinar: "How to Validate your Monitoring System" http://cc.readytalk.com/play?id=gge63m

Resources & Further Reading*

"ISPE Good Practice Guide: Cold Chain Management"

- *http://www.ispe.org/ispe-good-practice-guides/cold-chain-management*

"Recommendations on the Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation/Cleaning Validation" The Pharmaceutical Inspection Co-operation Scheme

- *http://www.picscheme.org/publication.php?id=8*

ICH Quality Guidelines (QbD: ICH Q8, Q9, and Q10)

- *http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html*

"Process Validation: General Principles and Practices" (2011 Jan, Revision I)

- *http://www.fda.gov/downloads/Drugs/.../Guidances/UCM070336.pdf*

"EMA Draft Guideline on Process Validation" (Draft, March 29, 2012)

- *http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/04/WC500125399.pdf*

PDA Technical Report No. 58: Risk Management for Temperature Controlled Distribution (2012)

- *https://store.pda.org/ProductCatalog/Product.aspx?ID=1772*

"Final Version of Annex 15 to the EU Guide to Qualification and Validation"

- *http://ec.europa.eu/health/files/eudralex/vol-4/pdfs-en/v4an15_en.pdf*

"ISPE – GAMP Good Automated Manufacturing Practice Resources"

- *http://www.ispe.org/good-automated-manufacturing-practice-gamp-resources*

ISPE Good Practice Guide: Cold Chain Management (2011)

- *https://www.ispe.org/ispe-good-practice-guides/cold-chain-management*

USP 36 Chapter <1079> Good Storage and Distribution Practices for Drug Products (2013)

- *http://www.pharmacopeia.cn/v29240/usp29nf24s0_c1079.html*

**These Web pages were confirmed as available January 9, 2014.*

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