VAISALA / APPLICATION NOTE

The Care & Feeding of an Environmental Monitoring System: Getting to GxP Compliance & Staying There

Regulations require that monitoring equipment be used appropriately, validated, and calibrated according to the demands of your environment.

When you install a new continuous monitoring system in a controlled environment you have made an important investment towards reducing several kinds of risk that your company is vulnerable to. First, you have reduced the risk of ruined or adulterated product by installing a monitoring system with alarm capability. Second, you have reduced the risk of lost or missing data by way of devices and software designed with redundant memory storage. Any good continuous monitoring system is designed to meet the regulatory requirements that are part of the pharmaceutical and medical device industries. Moreover, a system that meets regulatory requirements must be easy to learn and use, or the functionality meant to ensure compliance may not be fully utilized. But, for the system to truly ensure compliance, it needs to be integrated into your firm's Quality System.

Not only must your software-based monitoring solution be integrated into your organization's Quality System, its compliance with regulations published by the European Medicines Agency and the U.S. Food and Drug Administration must also be maintained. This application note is a primer on how to maintain GxP compliance in your monitoring system over time.

The primary areas where your monitoring system must be properly integrated and supported by your Quality System are:

1. SOPs
2. Training
3. Validation
4. Change Control
5. Calibration

SOPs

Standard Operating Procedures are keystone documents in any Quality System. These step-by-step instructions help ensure that processes perform as required by your operational goals. In addition, it is an overarching expectation in the life sciences that written procedures for GMP processes are established, followed and maintained under revision control. In the following regulation excerpts we see the expectations clearly laid out, including the application (holding and distribution), the parameters (light, temperature etc.) and the importance of creating and controlling documented procedures:

21 CFR 211.142 states: *"Written Procedures… shall be established and followed. They shall include: 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."*[1]

21 CFR 820.40 states: *"Each manufacturer shall establish and maintain procedures to control all documents that are required…"*[2]

For the European Union, the EMA has published the document "ICH Topic 7, Note for Guidance on Good Manufacturing for Active Pharmaceutical Ingredients," which states under Computerized Systems: *"Written procedures should be available for the operation and maintenance of computerized systems."*[3]

To properly maintain your environmental monitoring system, you will rely on your SOPs for the operation and administration of both software and peripheral monitoring equipment. Ideally, there will already be dedicated SOPs within your Quality System governing other supporting activities such as Calibration, Training, Validation, and Change Control. If you don't have SOPS for these activities, you can address these support activities (as they apply to your monitoring software only) in your monitoring system SOPs. All SOPs must be treated as controlled documents and provided with controls for approvals and revisions.

Training

It is another primary regulatory expectation that personnel are trained in the written procedures they are expected to perform. This applies to all systems employed in maintaining Good Manufacturing Practice. This makes sense because it is, after all, people who will be responsible for all activities in your Quality Control System; your firm's compliance hinges on their knowledge of and adherence to established, documented procedures. Even in our world of automated processes, a human user is always going to either initiate, interact with, or oversee a process. To ensure that your personnel are adequate to the task, the following regulations from EMA and the FDA stipulate that responsibilities be assigned and training be undertaken as appropriate:

EMA: ICH Topic Q7 - Personnel Qualifications 3.10 *There should be an adequate number of personnel qualified by appropriate education, training and/or experience to perform and supervise the manufacture of intermediates and APIs.*

EMA: ICH Topic Q7 - Personnel Qualifications 3.11 *The responsibilities of all personnel engaged in the manufacture of intermediates and APIs should be specified in writing.*

EMA: ICH Topic Q7 - Personnel Qualifications 3.12 *Training should be regularly conducted by qualified individuals and should cover, at a minimum, the particular operations that the employee performs and GMP as it relates to the employee's functions. Records of training should be maintained. Training should be periodically assessed.* [4]

21 CFR 211 Subpart B - Organization and Personnel, states: *"Each person engaged in… holding drug products shall have the… training… to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs… including the… written procedures required by these regulations..."*[5]

21 CFR 820.25b states: *"Each manufacturer shall establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities. Training shall be documented."*[6]

Simply stated, every employee using an environmental monitoring system software must be trained according to the section(s) of the SOPs that apply to their job. Written records of the training should be maintained. Your organization must document who was trained, what the training consisted of, and who administered the training. The FDA provides a sample "Employee Training Record" as an exhibit in their "Postmarket Requirements (Medical Devices) article at "Device Advice: Comprehensive Regulatory Assistance."[7]

Validation

Processes that ensure quality in manufacturing are expected to be validated, especially when the process is automated, and this includes continuous monitoring systems designed for use in GxP environments. Basically, if a software is involved in a process that impacts the safety and purity of a drug or the efficacy of a device, it needs to be validated. To determine the scope of your validation efforts, a risk analysis saves both time and costs. Your monitoring software should be validated by its installation and operational qualification upon deployment. Changes in software versions, upgrades, updates, and patches or software upgrades will likely require re-validation. Your software manufacturer should be able to provide you with the necessary validation protocols to verify proper system operation following the installation of patches that are issued on your existing software.

To review key guidance from the FDA on process validation, there are three critical parts:

21 CFR 820.75 - Process Validation, states: *"Where the results of a process cannot be fully verified by subsequent inspection and test, the process shall be validated with a high degree of assurance and approved according to established procedures."*[8]

21 CFR 820.70 - Production and Process Controls, states: *"When computers or automated data processing systems are used as part of production or the quality system, the manufacturer shall validate computer software for its intended use according to an established protocol. All software changes shall be validated before approval and issuance. These validation activities and results shall be documented."*[9]

21 CFR 820.75(c) states: *"When changes or process deviations occur, the manufacturer shall review and evaluate the process and perform revalidation where appropriate. These activities shall be documented."*[10]

In regards to 820.75, validation must be performed either because you can't reasonably test and inspect to verify the success or failure of a product, so the process must be validated; or because, even though you can reasonably test a product to gauge its efficacy, it is more economical and just as reliable to validate the process. The key thing to remember about 21 CFR 820.75 is that it is the end result of a process that cannot be verified, which necessitates a validation of the process. In section 820.75 (c) it states that there must be processes in place to address deviations and the process(es) will be outlined and recorded in the appropriate documents. How you handle deviations depends on the structure of your Quality Management System; you may have a procedure dedicated to deviation reporting, or instructions for reporting deviations may be included within other procedures, such as those covering validation, OOS reporting, or CAPA.

Guidance for the EU, according to EMA's Note for GMP on APIs addresses validation under the section: "Computerized Systems":

EMA: ICH Topic Q7 - Computerized Systems 5.40 *GMP related computerized systems should be validated. The depth and scope of validation depends on the diversity, complexity and criticality of the computerized application.*

EMA: ICH Topic Q7 - Computerized Systems 5.41 *Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.*

EMA: ICH Topic Q7 - Computerized Systems 5.42 *Commercially available software that has been qualified does not require the same level of testing. If an existing system was not validated at time of installation, a retrospective validation could be conducted if appropriate documentation is available.* [11]

Validation Essentials:

- Validation protocols should be reviewed and approved prior to execution.
- The validation work is not complete until the executed protocol is reviewed and approved.
- Any future changes to the system must be evaluated to determine if they impact the validated state of the application.

Change Control

Any GMP process, automated or not, must be established with written procedures. When these procedures change, the FDA expects the change to be administered in a controlled fashion. This is generally known as "change control."

21 CFR 820.70 - Production and Process Controls, states: *"Each manufacturer shall establish and maintain procedures for changes to a specification, method, process, or procedure. Such changes shall be verified or where appropriate validated according to § 820.75, before implementation and these activities shall be documented. Changes shall be approved in accordance with § 820.40."* [12]

EMA: ICH Topic Q7 - Computerized Systems 5.47 *Changes to the computerized system should be made according to a change procedure and should be formally authorized, documented and tested. Records should be kept of all changes, including modifications and enhancements made to the hardware, software and any other critical component of the system. These records should demonstrate that the system is maintained in a validated state.*[13]

Any change to the system should be reviewed for impact prior to implementation. If necessary, additional validation testing may be required, depending on the nature of the changes.

It is a global regulatory expectation that devices in GxP environments be calibrated as often as the demands of the operating environment dictate.

Calibration

Monitoring systems, by nature, measure important environmental parameters such as temperature and humidity, using devices located in manufacturing, laboratory, and storage areas. There is an expectation from regulatory authorities that these devices provide accurate and reliable data. However, no sensor stays accurate forever. It is a basic expectation of the FDA that devices on your system be regularly calibrated to ensure accurate measurements and that records of the calibration events will be available for inspection. Depending on the sensor's original accuracy as well as the demands of your application's operating environment, calibration and functional testing of devices and metrological equipment is necessary, and mandated by EMA and the FDA:

21 CFR 211.68 – Automated, Mechanical, and Electronic Equipment, states: *"Automatic, mechanical, or electronic equipment... used in the manufacture, processing, packing, and holding of a drug product… shall be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. Written records of those calibration checks and inspections shall be maintained."*[14]

The European Medicines Agency guidance on GMPs for manufacturing, storing, handling, and processing active pharmaceutical ingredients addresses calibration at length. The type of instruments and equipment, standards, and documentation are outlined. Further, the EMA guidance also clearly stipulates that there be established criteria for calibration and when deviations occur, an investigation to determine the possible impact on quality must be conducted.

EMA: ICH Topic Q7 - Calibration 5.30 *Control, weighing, measuring, monitoring and test equipment that is critical for assuring the quality of intermediates or APIs should be calibrated according to written procedures and an established schedule.*

EMA: ICH Topic Q7 - Calibration 5.31 *Equipment calibrations should be performed using standards traceable to certified standards, if existing.*

EMA: ICH Topic Q7 - Calibration 5.32 *Records of these calibrations should be maintained.*

EMA: ICH Topic Q7 - Calibration 5.33 *The current calibration status of critical equipment should be known and verifiable.*

EMA: ICH Topic Q7 - Calibration 5.34 *Instruments that do not meet calibration criteria should not be used.*

EMA: ICH Topic Q7 - Calibration 5.35 *Deviations from approved standards of calibration on critical instruments should be investigated to determine if these could have had an impact on the quality of the intermediate(s) or API(s) manufactured using this equipment since the last successful calibration.* [15]

Conclusion

An automated monitoring system is now expected in any business participating in the life science industry. In this highly competitive and regulated sector, a continuous monitoring system designed specifically for critical and regulated environments will reduce the risks of adulterated product or incomplete records. However, a fully compliant system requires *maintenance* in order for compliance to be ongoing. This maintenance is easily achieved by applying the existing capabilities of your company's Quality System to the support of your monitoring system, as per the regulations noted in this application note. You will achieve the most payback in terms of regulatory compliance, by applying the bulk of your efforts to maintaining GxP compliance in these areas: SOPs, Training, Validation, Change Control, and Calibration.

Sources

[1] See Part 211.142 Current Good Manufacturing Practice for Finished Pharmaceuticals, Sub part H

[2] See Part 820.40, Quality System Regulation, Subpart D Document Controls

[3] See the European Medicines Agency's document: "ICH Topic Q7 Good Manufacturing Practice for Active Pharmaceutical Ingredients," Note for Guidance on Good Manufacturing Practice for Active Pharmaceutical Ingredients (November 2000)

[4] Ibid. Section 3.1 Personnel Qualifications

[5] See Title 21, Chapter 1, Subchapter C-- Drugs: General, Part 211 "Current Good Manufacturing Practice for Finished Pharmaceuticals" Subpart B—Organization and Personnel

[6] See Title 21, Chapter 1, Subchapter H—Medical Devices, Part 820 "Quality System Regulation" Subpart B—Quality System Requirements, Sec. 80.25 Personnel

[7] See Part 5: Personnel and Training, Medical Devices, Post Market Requirements Quality Systems Manual

[8] See Title 21, Subchapter H—Medical Devices, Part 820 "Quality System Regulation" Subpart G—Production and Process Controls, CFR 820.75

[9] Ibid. , 21 CFR 820.70

[10] See 21 CFR 820.70 Production and Process Controls 8 See Title 21, Subchapter H—Medical Devices, Part 820 "Quality System Regulation" Subpart G—Production and Process Control

[11] See the European Medicines Agency's document: "ICH Topic Q7 Good Manufacturing Practice for Active Pharmaceutical Ingredients," Note for Guidance on Good Manufacturing Practice for Active Pharmaceutical Ingredients (November 2000)

[12] See Title 21, Subchapter H—Medical Devices, Part 820 "Quality System Regulation" Subpart G—Production and Process Controls, Sec. 820.70 Production and Process Controls

[13] See EMA's ICH Topic Q7 Good Manufacturing Practice for Active Pharmaceutical Ingredients (2000)

[14] See Title 21, Subchapter C—Drugs General, Part 211, Subpart D—Equipment Sec. 211.68 Automatic, mechanical, and electronic equipment.

[15] See EMA's ICH Topic Q7 Good Manufacturing Practice for Active Pharmaceutical Ingredients (2000), Section 5.3 Calibration

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VAISALA / SUCCESS STORY

Global Nutrition Company Adopts Continuous Mapping Strategy to Strengthen Environmental Monitoring

Founded in 1980, Herbalife Ltd. is a global nutritional company that provides dietary supplements, vitamins, and personal care products in over 90 countries through a network of more than 3 million independent members. To ensure products are protected during manufacturing, packaging and storage, Herbalife maintains strict controls over environmental parameters with a risk-based approach. In its global distribution centers, quality testing labs, and manufacturing facilities, the company adheres to Current Good Manufacturing Practices (cGMP) and strives to meet or exceed all requirements that ensure the purity, safety and efficacy of Herbalife products from manufacture to final distribution.

To meet the highest standards, Herbalife Quality managers decided to perform several year-long thermal mapping studies to qualify storage environments according to regulatory guidance. The results of these studies would then be used to design the long-term monitoring systems for the warehouses. However, upon further examination, Herbalife's Quality team decided that if they were going to set up the mapping sensors, taking down half the measurement points after the studies were complete might be unnecessary. Instead, by leaving a higher number of sensors in place, as typically required in a mapping/validation study, facility managers would have access to more in depth data for detailed analysis and better decision making.

Gary Swanson, Senior Vice President of Quality for Herbalife International says, "We wondered if we wouldn't be better off maintaining the higher density of sensors for long-term monitoring and decided to leave all sensors in place. This essentially resulted in 'continuous mapping' of these environments. We have used this system for three years and found it very successful."

"Some key features that contributed to our final selection included the 10-year battery life of the data loggers, plus their ability to be validated. We also appreciated Vaisala's global service capabilities, especially their ability to provide site evaluation, installation, and validation execution services in many locations. It was important to us that the system could be deployed internationally and Vaisala was the only company we found that could support us throughout our other regions, ensuring proper training, support and system uptime."

Gary Swanson,
Senior Vice President of Quality
for Herbalife International

The continuous mapping setup provided information representative of year-round conditions while eliminating the time and cost of resources typically required for intermittent mapping studies.

Herbalife's storage and manufacturing areas range from 1,000 to 750,000 square feet and vary greatly in environmental attributes such as air conditioning, control systems, and climatic zones. Swanson notes that warehouses can have subtle fluctuations in temperature. Such problems often only become visible after analysis of data collected over a long time. Giving an example, Swanson says, "In Taiwan our continuous mapping method showed after six months that, although the warehouse had functional air conditioning, there were definitely a few excursions occurring. This information allowed us to intelligently reconfigure the warehouse HVAC system to create more even temperatures throughout." Another advantage of high sensor density is that if one sensor does fail or lose communication, personnel still have full visibility of warehouse conditions. This increases the sense of control and confidence in an alarm situation.

In early 2014, one of Herbalife's warehouses underwent a regulatory inspection. Over the days of the inspection, the Herbalife Quality team outlined the continuous mapping method. "We were in the middle of the inspection," says Swanson, "and the inspector requested some formal planning documents to provide detailed data on our rationale for continuous mapping. This required analysis that we couldn't execute during the inspection. But, Vaisala provided us with documents we were able to give to the inspector while he was still on site. In the end, the inspector reviewed and accepted the monitoring system's setup."

While evaluating monitoring system vendors, Herbalife tested multiple systems. Key requirements included: a system scalable to any size of warehouse, in any type of climate, and consistency in implementation and management. Over six months, Swanson and the Herbalife Quality and Facilities Management team evaluated several systems before selecting the Vaisala Continuous Monitoring System.

Challenge

- **Environmental** - Herbalife has warehouses in worldwide climatic zones 1, 2, 3, 4a and 4b: from hot tropical, hot dry, to cold. They require a system that can be stretched to the extremes of environmental conditions.
- **Historical Reporting** - To ensure compliance, Herbalife must have reporting capabilities that prove adherence to regulatory requirements. These reports must satisfy the global regulatory inspectors that visit Herbalife facilities throughout the year.
- **Guaranteed Product Quality** - The company needs to manage the overall product quality throughout the supply chain and adhere to current Good Manufacturing Practices (cGMP). Combined with Herbalife's own standards of Quality, this compliance guarantees that all Herbalife members and their customers receive the highest quality and safest products available.

Solution

- **High Performance Hardware** - The Vaisala Continuous Monitoring System (CMS) can use a wide array of high-performance sensors to monitor temperature, relative humidity, differential pressure, door switches, and more. With 10-year battery life and months of data redundancy in each sensor's memory, records are secure and gap-free.
- **Meet Quality Standards** - The Vaisala CMS ensures that Herbalife can meet or exceed rigorous regulatory standards. The system provides industry-best sensing accuracy and calibration is locally available from Vaisala's Regional Service Centers.
- **Multilingual** - The Vaisala CMS software viewLinc is available in English, German, French, Swedish, Chinese, Japanese, Spanish and Portuguese, with User Guides and Quick Starts.
- **FDA 21 CFR Part 11 Compliance** – The system includes triple data redundancy, Audit Trail, customizable graphing, and automated reporting options.

Benefits

- **Enterprise Solution** - Herbalife's goal of an enterprise-wide monitoring solution for global processing and storage facilities was met across almost 100 global distribution centers, quality testing labs, and manufacturing facilities.
- **System Support** - Vaisala provides 24/7 technical support. We offer Web-based self-service training tools along with expert guidance on the use and configuration of the CMS. An annual system analysis is available to review system performance and ensure that business objectives are being met.
- **Eliminate Product Loss** - The Vaisala CMS ensures that facilities personnel maintain full control of monitored areas, identify any problems quickly, and respond with corrective actions. The option of continuous mapping sensor configuration provides better data for long-term analysis.
- **Peace of Mind** - Vaisala's experienced validation and calibration experts are available online and by phone 365 days per year, as well as during inspections/audits to provide analysis, technical and calibration information, and formal reports to satisfy regulatory requirements.
- **Global Reach** - Vaisala has offices throughout the world. Visit www.vaisala.com/en/contact/offices/Pages/default.aspx

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