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.

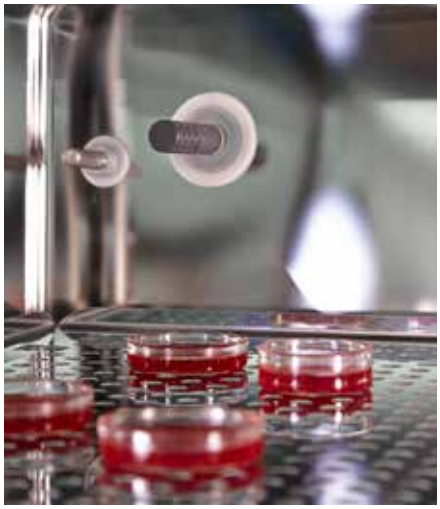
Change Control

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

VAISALA

For more information on validation applications, contact your local Vaisala representative at sales@vaisala.com.

Ref. B211278EN-A ©Vaisala 2013
This material is subject to copyright protection, with all copyrights retained by Vaisala and its individual partners. All rights reserved. Any logos and/or product names are trademarks of Vaisala or its individual partners. The reproduction, transfer, distribution or storage of information contained in this brochure in any form without the prior written consent of Vaisala is strictly prohibited. All specifications — technical included — are subject to change without notice.