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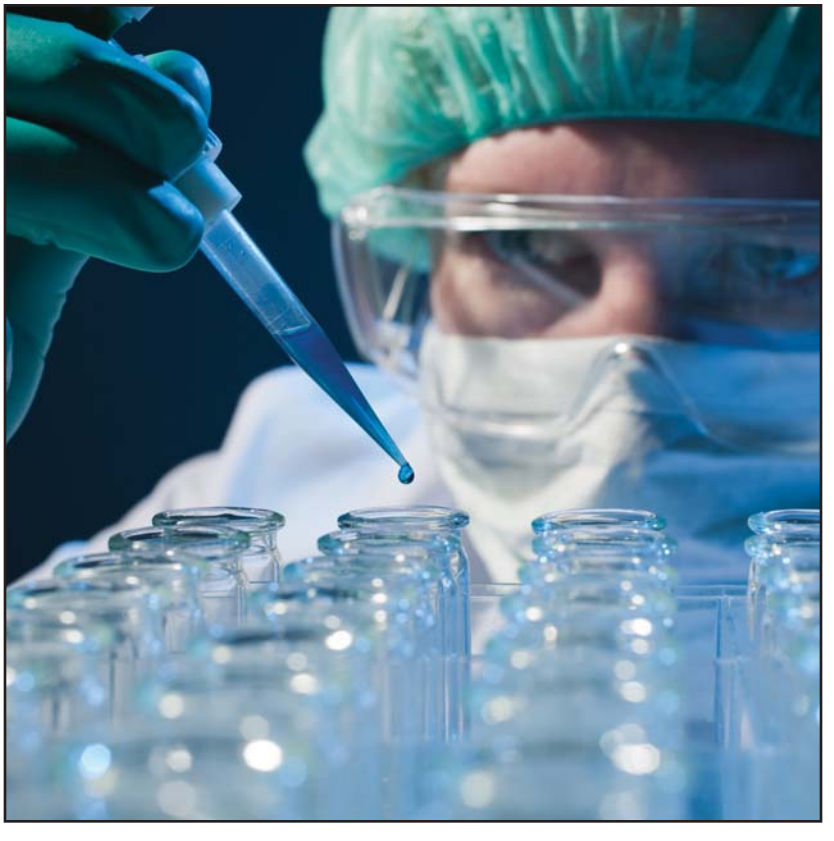
Regulatory Review and Analysis of Independent Monitoring Systems

Independent Monitoring Reduces Risk and Cost in Pharmaceutical Manufacturing and Storage Facilities



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Vaisala Oyj
P.O. Box 26
FI-00421 Helsinki
Finland

Phone (int.): +358 9 8949 1
Fax: +358 9 8949 2227

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Independent Monitoring Reduces Risk and Cost in Pharmaceutical Manufacturing and Storage Facilities

Executive Summary: Advances in technology have increased real-time communication and put more functionality on fewer devices – a door left open to a freezer with temperature-sensitive products in a Bejing laboratory can send notification of an impending quality problem to the mobile phone of a quality manager in Singapore.

While consolidation of technology helps to better understand our environment and improves response to mechanical and human failure, it is good practice to keep some functionality separate in the manufacturing of regulated medicines in Good Manufacturing Practice (GMP) facilities, specifically those systems that monitor critical environments and those that control the environments. Types of monitoring systems include chart recorders, standalone or networked data logger systems. Types of control systems include SCADA, DCS, BMS, PLC, and HVAC.

International GMP guidelines set standards for independent systems for production, storage, and distribution of medicines. Government agencies are revising their GMPs to use common language and align with these international standards. The new GMP for pharmaceutical products from China's State Food and Drug Administration (SFDA), effective March 1, 2011, is a recent example.

This paper examines the importance of independent systems for monitoring and for control from a regulatory perspective, guides to managing risk to product quality and the consequences of noncompliance.

Quality Defined

First, it is important to understand regulators' language of quality in pharmaceutical manufacturing and distribution. All regulatory authorities in developed countries cooperate with the Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (jointly referred to as PIC/S), making PIC/S the most universal source for GMP and quality standards for makers of medicinal products. PIC/S defines quality assurance and quality control as distinct but related functions:

> *"Good Manufacturing Practice is that part of Quality Assurance which ensures that Medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use... Good Manufacturing Practice is concerned with both production and quality control."*

PIC/S sets basic requirements that manufacturing processes are defined, reviewed and "shown to be capable of consistently manufacturing medicinal products of the required quality and specifications."

Critical steps and significant changes of manufacturing processes must be validated, operators trained; and records made during manufacture which "demonstrate that all procedures and instructions were followed and that the quantity and quality of the product was as expected."

In addition having all manufacturing processes and procedures—and their results—documented for compliance, PIC/S standards require that:

- *Significant deviations are to be fully recorded and investigated*
- *Records for batch traceability for manufacture and distribution are retained and accessible*
- *Product distribution minimizes risk to quality*
- *Recall system is available*
- *Complaints about marketed products are examined*
- *Causes of quality defects investigated*
- *Appropriate measures are taken to prevent recurrence*[2]

Similar descriptions of a quality framework are described in the GMPs of the U.S. Food and Drug Administration (FDA), European Commission (EC), International Committee on Harmonisation (ICH), and the World Health Organization (WHO) as guidelines progress towards international harmonization.

Definitions of quality practices may vary between companies, but a quality system needs checks and balances to fulfill GMP requirements.

GMP Guidance on Independent Systems

Guidelines and recent citations from various GMPs provide insight to regulatory thinking on the concepts of separate and independent. Common guidelines for independent systems begin with separation of responsibility for key personnel:

> *"The heads of Production and Quality Control must be independent from each other." – PIC/S Guide to Good Manufacturing Practice for Medicinal Products*[3]

> *"The independence of quality control from production is considered fundamental." – WHO GMP for Pharmaceutical Preparations*[4]

> *"There should be a quality unit(s) that is independent of production and that fulfills both quality assurance (QA) and quality control (QC) responsibilities." – ICH Q7 GM*[5]

These guidelines are designed to help eliminate conflict of interest between meeting production output goals and product quality requirements.

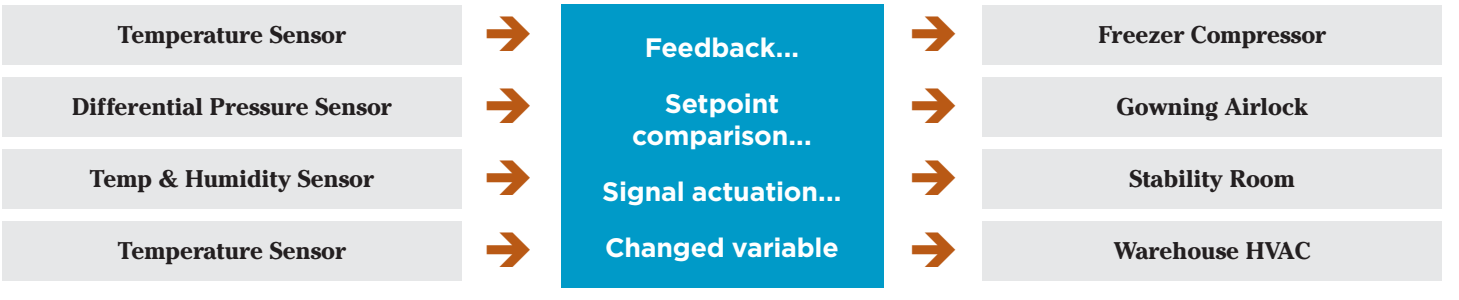
Moving from separation of responsibility, PIC/S continues to address data:

> *"Data may be recorded by electronic data processing systems, photographic or other reliable means, but detailed procedures relating to the system in use should be available and the accuracy of the records should be checked."*[6]

A control system such as a PLC uses a closed feedback loop to reach decisions and take action. However, a sensor that has drifted from specification can still provide positive feedback to the PLC that may result in an undesired control adjustment. The problem is compounded if the PLC's main processor fails. Completed batches could appear to be within specifications, only to be rejected later by laboratory validation tests—a cost that could be avoided with independent monitoring.

Compliance with PIC/S GMP on checking the accuracy of recorded data is difficult without separate monitoring equipment. Independent systems generate their own documentation, serving as a check against the control functions. Combining control functions with monitoring may also increase the complexity and cost to re-validate the system after corrective action.

Figure 1. If sensors, electronic processors, actuators or other components fail, a traditional control system may not generate sufficient data to fully document and understand a problem to take corrective action or meet compliance reviews. Documenting critical areas with redundant monitoring lowers the risk and cost of non-compliance.



Control system with central points of electronics failure.

Similar to checking the accuracy of records during production, the PIC/S addresses storage areas:

> *"Storage areas should be designed or adapted to ensure good storage conditions. In particular, they should be clean and dry and maintained within acceptable temperature limits. Where special storage conditions are required (e.g. temperature, humidity) these should be provided, checked and monitored."*[7]

Warehouse HVAC systems are designed to maintain specified environmental conditions, however, stable conditions are affected by seasonal climate changes, irregular air flow, product stacking, rack configurations, floor-to-ceiling temperature gradients, and daily exposure from loading-door operation. Independent monitoring can serve as a quick check that warehouse conditions are being held within specification as well as for independent records for audit purposes.

A Case for Independent Systems

There are many examples and interpretations of the implications to risk and cost of not using a monitoring system that is independent of controls. Following are samples from areas of continuous monitoring, alarms, sterilization, and stability testing.

The FDA cited the following deficiency in an FDA Warning Letter to a drug repackage firm:

> *"Failure to ensure that drug products are stored under appropriate conditions of temperature and humidity so that the identity, strength, quality and purity of the drug products are not affected, in that(1) your firm has not determined that the temperature/humidity equipment used to monitor the storage area is adequate to monitor the entire area; [FDA 21 CFR 211.46(b)] …2) the monitor is not equipped with an alarm to alert your firm to environmental control failures;..." [FDA 21 CFR 211.142(b)].*

In this case an independent monitoring system that continuously monitored warehouse conditions would have met these requirements. Continuous monitoring systems are also specifically designed to notify personnel when there is a problem, especially when no one is at the facility.

PIC/S guides for sterilization are clear on the reasons for and expectations of independent systems, stating:

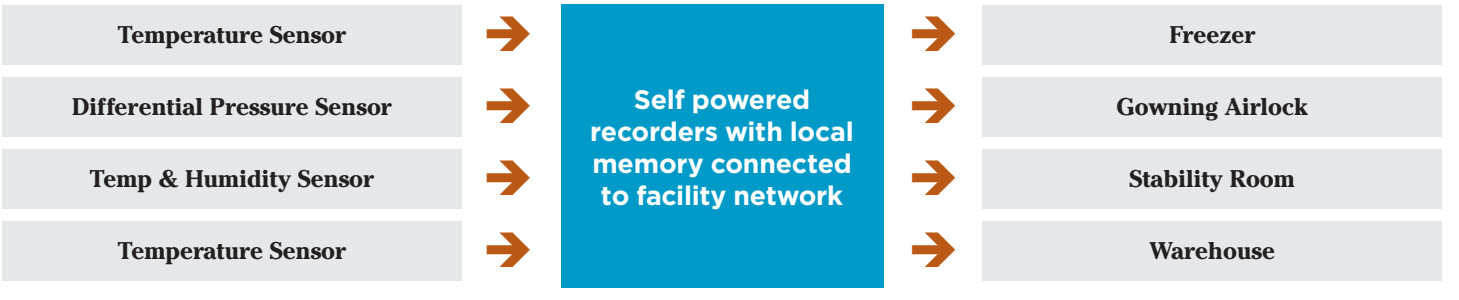
> *"Each heat sterilization cycle should be recorded on a time/temperature chart with a sufficiently large scale or by other appropriate equipment with suitable accuracy and precision. The position of the temperature probes used for controlling and/or recording should have been determined during the validation, and where applicable also checked against a second independent temperature probe located at the same position… Control instrumentation should normally be independent of monitoring instrumentation and recording charts"*[8]

Stability testing is another area that requires maintaining recorded data. For instance, the FDA states:

> *"Complete records shall be maintained of all stability testing performed in accordance with 21 CFR 211.194(e)".*

An FDA Warning Letter to one drug manufacturer cited that "Operating parameters were maintained with the relevant xxx. However, electronic raw data was not saved." A monitoring system compliant with FDA 21 CFR Part 11 or EC Annex 11 would have recorded the data and saved it to a primary and backup location. A PLC designed for control would not perform these functions, posing a higher risk to regulatory inspection failures.

Figure 2. A continuous monitoring system running in parallel with the control system creates a redundant capability that can prevent data loss, incomplete records, product loss, and regulatory deficiencies.



Independent monitoring - no influence from control system.

WHO GMP on Critical Monitoring

Obtaining a real-time record of data and events is an essential element for correcting immediate problems, understanding root causes of error and designing corrective actions. The WHO GMP clearly designates monitoring as a separate function on critical control points:

> *"Monitoring is the scheduled measurement or observation of a critical control points (CCP) relative to its critical limits. Monitoring should be recorded. The monitoring procedures used must be able to detect loss of control at the CCP, and this information should ideally be available in time to make adjustments to ensure control of the process and prevent violations of the critical limits."*[9]

If the control system is monitoring itself—and using its own measurements to adjust parameters— a problem with the controls may not be detected in time to take corrective action. Independent monitoring checks measurements from the control system.

Finally, the WHO describes the monitoring of critical control points as an important tool for identifying common failures and implementing suitable control measures:

> *"1. Component failures. Causes of such failures include bad design, pressure, corrosive media, high temperatures, mechanical failure of pumps, blowers and stirrers, failure of control systems, such as sensors, failure of welds and flanges, and failure of safety systems (e.g. valves).*
> *2. Deviations from normal operating conditions. Deviations from normal operating conditions include failures in the monitoring of crucial process parameters (e.g. pressure, temperature), failures in utilities such as steam, cooling, electricity and compressed air, failures in shut-down and start-up procedures, and formation of by-products, residues and impurities.*
> *3. Human and organizational errors. A wide variety of errors can be made by operating personnel. Common errors include operator error, pressing wrong buttons, disconnecting alarms, mix-ups of materials, communication errors, and incorrect maintenance and repairs."*[10]

The longer it takes to detect a deviation, the higher the risk to product quality and cost. Reliance on a control system that monitors its own critical parameters may not improve detection time. Cost-effective solutions can provide the redundancy to identify problems in real time to help reduce waste, improve yield and meet quality goals.

Conclusion

The systems that monitor critical environments and those that control regulated processes should be distinct and independent. A control system that monitors itself is vulnerable to risk and unnecessary cost of both product loss and regulatory noncompliance. Control systems are not designed to document problems, identify faults or maintain a complete data record. An independent monitoring system can document that the environment was kept within limits despite a failure in the control system, perhaps avoiding product destruction.

To maintain quality at optimal production efficiencies, quality assurance (QA) needs independent data to meet its responsibilities to investigate and resolve critical deviations promptly. By comparing results from a redundant monitoring system to trends created by the control system, single points of failure can be identified more quickly. QA must also produce those records for inspectors on demand. Automated monitoring capabilities that operate independent from the controls of PLCs, HVAC and distributed systems provide cost-effective measures to secure needed records essential to proof of quality and response to regulatory audits.

The GMPs of the WHO, PIC/S, ICH and the FDA emphasize the need for critical systems to be checked by independent methods. The 2010 revised edition of China's SFDA GMP is now consistent with the WHO GMP for pharmaceutical products. Standards include personnel with different responsibilities for production and quality, separate areas to prevent product contamination, and independent instrumentation dedicated to their primary functions.

It is recommended that pharmaceutical production facilities conduct a risk-benefit analysis to compare the risk and costs of a control system without independent monitoring to the risks and costs with independent, continuous monitoring. Key considerations should include:

- Production downtime if a critical environment deviates from specifications
- Product damage or missed shipments if a critical environment deviates from specifications
- Cost to process a deviation including resources to document, investigate, correct, validate, review and approve

Regulations have changed from treating all areas of a GMP facility equally to focusing on areas especially prone to risks to product quality and patient safety. The objective is to help life science companies be more effective in maintaining quality and lowering the cost of compliance. While documentation may no longer be necessary in some areas a GMP facility, high-risk areas may warrant a need for more investment in systems and procedures to ensure regulatory compliance and control life-cycle costs.

Endnotes

1 SFDA Good Manufacturing Practice for Pharmaceutical Products (2010 revised edition) issued http://eng.sfda.gov.cn/cmsweb/webportal/W43879541/A64031585.html

2 "Guide to Good Manufacturing Practice for Medicinal Products Part I", GMP Section 1.2. PIC/S, Sept 2009

3 "Guide to Good Manufacturing Practice for Medicinal Products Part I," Key Personnel, Section 2.3. PIC/S, Sept 2009: Geneva, Switzerland

4 "WHO Expert Committee on Specifications for Pharmaceutical Preparations" Section 17.2. WHO technical report series; 908, 2001: Geneva, Switzerland

5 "Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients Q7," Section 2.13. ICH Harmonised Tripartite Guideline, 10 Nov 2000.

6 "Guide to Good Manufacturing Practice for Medicinal Products Part I," Documentation, Section 4.9. PIC/S, Sept 2009: Geneva, Switzerland

7 "Guide to Good Manufacturing Practice for Medicinal Products Part I," Storage Areas, Section 3.19. PIC/S, Sept 2009: Geneva, Switzerland

8 "Guide to Good Manufacturing Practice for Medicinal Products Annexes," Sterilisation By Heat, Section 90 & 94. PIC/S, Sept 2009: Geneva, Switzerland

9 "WHO Expert Committee on Specifications for Pharmaceutical Preparations" Section 7.9. WHO technical report series; 908, 2001: Geneva, Switzerland

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Resources

Inspections, Compliance, Enforcement, and Criminal Investigations
U.S. FDA Code of Federal Regulations Title 21
U.S.FDA 21 CFR Part 210 Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs, Volume 4, Revised as of April 1, 2010
U.S. Pharmacopeia, USP General Chapter <1079> Good Storage and Shipping Practices

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