

GMP Monitoring— What, Why, Where, and How

Welcome to "Maintaining Validation."

This column addresses topics associated with maintaining the validated state of processes, equipment, facilities, utilities, and analytical methods (i.e., anything that has been validated or qualified and must be continually maintained in the validated state). We intend this column to be a useful resource for daily work applications.

This column was suggested by attendees at the 14th International Validation Week Meeting held in Philadelphia in October of 2008. The general topic of maintaining validation was a subject of great interest. An ongoing discussion addressing these questions and associated topics is warranted and will be useful to our readers.

Validation and compliance practitioners are well aware that the conformance lots of process validation, or the IQ/OQ/PQ of equipment, are at most "snapshots in time." These events serve to document standard performance when completed. However, they do not guarantee continued good performance. It is through monitoring, data evaluation, statistical analysis, change control, and other programs that ongoing good performance is maintained. These topics, including relevant examples, are addressed in "Maintaining Validation."

Reader comments, questions, and suggestions are needed to help us fulfill our objective for this column. Case studies submitted by readers are most welcome. We need your help to make "Maintaining Validation" a useful resource. Please send your comments and suggestions to journal coordinating editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS DISCUSSED

The following key points are discussed in this article:

- Monitoring is an important aspect of maintaining validation
- Monitoring includes information collection over time, reviewing and analyzing the information, and defining warning limits
- Monitoring is applicable to process parameters, raw material quality, utility performance, product characteristics, and other important considerations
- The 2008 US Food and Drug Administration draft guidance *Process Validation: General Principles and Practices* (1) identifies continued process verification, including monitoring, as an important aspect of maintaining validation
- Monitoring in the drug and medical device industries is a regulatory requirement
- Monitoring is also good engineering practice
- Critical points within the operation where problems are likely to occur should be monitored
- Monitoring requires calibrated instruments, regular intervals, data collection, data analysis, acceptable limits, and defined actions to be taken for excursions
- Selection of parameters to monitor may be based on product requirements, regulatory requirements, manufacturing experience, and other factors
- Monitoring is a key part of a total program to ensure an ongoing state of control.

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ABOUT THE AUTHOR

Gamal Amer, Ph.D., is principal at Premier Compliance Services, Inc., management consultants for compliance and manufacturing operations performance in the life sciences industry. He holds a Ph.D. in chemical engineering and has over 27 years of experience in the pharmaceutical and related industries. He can be reached by e-mail at vpainc@aol.com or amerg@premierc.net.

INTRODUCTION: WHAT IS MONITORING?

According to Wikipedia, "to monitor or monitoring generally means to be aware of the state of a system." Webster suggests that monitor (v.) "is to watch or check on a person or a thing" (implying data collection and review), while monitor (n.) "is one who warns of faults or informs of duty or could be something that reminds or warns" (implying anticipation and control). Based on these definitions, monitoring entails the following three distinct activities:

- Collecting information over time
- Reviewing and analyzing the information collected, thus continually being aware of the current state
- Defining reminders and warning.

It is important to recognize that collecting data and filing it without review and analysis is considered gathering and not monitoring. Monitoring implies gathering data over a long period of time at pre-established intervals, or when certain events occur. This enables the understanding of what is going on, anticipation and correction of problems, and enhanced control of the operation.

From a good manufacturing practice (GMP) point of view, monitoring implies collection of information about the performance of a system related to GMP manufacturing. Such system/variable could be a raw material, intermediate, utility system, frequency of deviations, conditions within the manufacturing facility, product characteristics, or personnel related issues. The information collected is then reviewed and analyzed to determine whether or not the system being monitored is in a state of control. Should the data suggest a potential problem based on pre-determined values, investigation can then be initiated.

The 2008 FDA draft guidance *Process Validation: General Principles and Practices* (1) identifies three stages in the lifecycle approach to process validation. The third of these, continued process verification, captures the essence of validation: Maintaining the validated state throughout ongoing performance of the manufacturing process. This is the same objective for all things validated or qualified—maintaining their intended operational state throughout their lifetime of use.

WHY MONITOR?

Monitoring in the drug and medical device industries is a specified regulatory requirement. The following is a partial list of such regulatory and guidance requirements:

- **21 CFR 211.42-10(iv).** "Buildings and Facilities." Design and Construction Features (2). A system for monitoring environmental conditions.
- **211.110 (a).** "Sampling and Testing of In-Process Materials and Drug Products" (3). "Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product."
- **211.122 (h).** "Packaging and Labeling Control" (4). "Materials examination and usage criteria. Printing devices ...shall be monitored to assure that all imprinting conforms to the print specified in the batch production record."
- **21 CFR 820.70 (a).** "Production and Process Controls" (5). General. "Each manufacturer shall develop, conduct, control, and monitor production processes to ensure that a device conforms to its specifications."
- **820.70 (2).** "Production and Process Controls" (6). "Monitoring and control of process parameters and component and device characteristics during production."
- **820.75 (b).** "Process Validation" (7). "Each manufacturer shall establish and maintain procedures for monitoring and control of process parameters for validated processes to ensure that the specified requirements continue to be met."
- **820.75 (b2).** "Process Validation" (8). "For validated processes, the monitoring and control methods and data, the date performed, and, where appropriate, the individual(s) performing the process or the major equipment used shall be documented."
- **ICH Q7, Good manufacturing Practice Guide for Active Pharmaceutical Ingredients** (9). This document discusses various monitoring topics in several sections. For example, section 2.50 states that regular quality reviews should be conducted to verify the consistency of the process. Items cited include critical in-process control and test results, batch failures, critical deviations, non-conformances, and investigations; process changes, analytical method changes, stability data, returns, complaints, and recalls; and corrective actions. Other specific sections discussing monitoring include Sections 4.2 Utilities, 4.3 Water, 8.3 In-Process Sampling and Controls, 11.5, Stability Monitoring of APIs, 12.7 Cleaning Validation, and 14.4 Recovery of Materials and Solvents.

- **ICH Q8, *Pharmaceutical Development*** (10). ICH Q8 focuses on development of the commercial product. However, the need for ongoing monitoring is recognized as follows: "The manufacturing process development programme or process improvement programme should identify any critical process parameters that should be monitored or controlled (e.g., granulation end point) to ensure that the product is of the desired quality." Also, "Collection of process monitoring data during the development of the manufacturing process can provide useful information to enhance process understanding." ICH Q8 suggests that continuous process verification (where applicable) could be an alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.
- **ICH Q9, *Quality Risk Management*** (11). ICH Q9 recognizes monitoring as part of various risk management activities. Techniques used include failure mode and effects analysis (FMEA), failure mode, effects, and criticality analysis, (FMECA), hazard analysis and critical control points (HACCP), and hazard operability analysis (HAZOP). Risk management should be used to select, evaluate, and interpret trend results, and to interpret monitoring data. Quality risk management should also be used in validation to determine the extent for follow-up activities such as sampling, monitoring, and revalidation.

The need to monitor is not only dictated by the regulation but also by good engineering practices. Monitoring is used to do the following:

- Fulfill the promise of continuous improvement in that collection and analysis of operating data improves the understanding of the underlying technology and supports continuous improvement
- Ensure systems and operation (process, facility, and personnel) are always in a state of control, compliant with GMP, and in a validated state
- Develop baseline information to establish operating capabilities
- Identify problems before they occur
- Maintain the validated state and demonstrate consistency. Seasonal variation may be observed.

WHAT TO MONITOR IN A GMP ENVIRONMENT

All parameters known or suspected to affect the quality, efficacy, or safety of the product should be monitored. These include the following examples:

- Critical process parameters (CPP)
- Product critical quality attributes (CQA)
- Process performance
- Process deviations
- API attributes such as impurity profile
- Intermediates quality
- Water system performance used to support the manufacturing operation
- Environmental conditions of the facility surrounding the process
- Facility and equipment cleaning effectiveness
- Performance of procedures and personnel
- Critical utility output (e.g., water for injection water quality, compressed air characteristics)
- Microbial monitoring and endotoxin monitoring within the facility, utility, and cleaned equipment
- Performance of suppliers vis-à-vis the quality of the material, component, service, etc. being supplied
- Laboratory analytical results and the performance of analytical techniques
- Analytical equipment performance
- Equipment maintenance
- Microbial loads in product, manufacturing space, utilities, etc.

In short, monitoring should cover the entire operation and should collect appropriate data and be implemented at the appropriate frequency. For example, in the case of environmental monitoring, the norm is to collect temperature, relative humidity, particulate count, microbial levels, and relative pressurization between spaces. The frequencies of collecting such data depends on the type of area being monitored and is defined by compendial entries, regulatory guidance, and/or operating experience.

WHERE TO MONITOR

Monitoring is always performed at the critical points within the operation. Points where problems are known to occur or likely to occur and at the end of any critical steps are also logical spots to monitor. In manufacturing processes, one would also monitor the product and the conditions at the point where the product is at its highest vulnerability. When monitoring a water system, data should be collected at critical steps in the process and at the critical use points. In environmental monitoring, microbial and particulate data are collected at surfaces where human or machine activities occur, and at the doors, where the direction

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Table: Environmental sampling frequencies for aseptic manufacturing facilities.

Area Classification	Sampling Frequency
Class 100	Each shift*
Support to Class 100 (Class 10,000)	Each shift*
Other support areas (Class 100,000)	Twice/week
Potential product/container contact	Twice/week
Non-product contact are (Class 100,000 or less)	Once/week

*FDA guidance on sterile processing suggests daily monitoring (13).

of airflow is of critical importance to prevent cross contamination. Processes and associated activities should carefully evaluate using risk analysis principles to determine appropriate monitoring requirements.

HOW TO MONITOR

Monitoring requires the following:

- Calibrated instruments suitable to collect the required information
- Established, regular, intervals for collecting and recording data
- Either a paper or electronic repository for the data to be collected
- Established graphical and/or statistical techniques to facilitate data evaluation
- Data analysis to detect and identify trends or issues to avoid problems
- Establishing action levels where corrective actions and preventive actions (CAPA) may be taken
- Defining the types of actions to be taken if issues or trends are identified.

A monitoring program consists of the following actions:

- Sample the desired parameter at the designated intervals. The intervals are decided by the criticality of the parameter and by the expected fluctuation within the value of the parameter.
- Correlate the value of the parameter to time, normally done in the form of a control chart
- Define alert and action levels and what you would do if they are reached. Normally the action levels are defined based on the design values of the parameter, while the alert levels are based on the values at which you expect to operate.

- Define investigative actions (e.g., CAPA) to be conducted if issues arise
- Communicate results of investigations and devise methodology to circumvent potential problems.

Sampling frequencies for monitoring can be defined by the natural cycle of the operation, by compendial recommendations, by the anticipated frequency of changes for the parameter being monitored, or based on experience.

For example, environmental sampling frequencies for aseptic manufacturing facilities are defined by the United States Pharmacopeia (USP) (12) and FDA guidance on aseptic processing (13) in the Table.

ESTABLISHING THE PARAMETERS TO MONITOR

Establishing which parameters to monitor is not a trivial matter. The parameters to monitor must be the correct parameters which, if they deviate, would cause product characteristics to suffer. An example would be monitoring delivery time of a device component from the supplier. It may be that the supplier delivers components on time, but delivers defective components. So although, based on the monitoring of delivery time, it would appear that no problem exists, one can plainly see that the resulting product would have a defective component. The manufacturing organization would have problems with the product despite the fact that the purchasing organization is meeting its objectives. Thus the parameters to monitor must support the product quality and be consistent across all departments.

Some of the basis for choosing the parameters to monitor include the following:

- Product requirements, such as temperature sensitivity, purity of the product or intermediates, process yield or the yield of certain critical steps
- Regulatory requirements, such as the requirement of low microbial content for sterile areas and products
- Compendial, engineering, ISO and federal standards, such as operating conditions of a blender based on the engineering design criteria, or ion content in purified water based on USP-published criteria
- Literature and industry experience abounds with examples of what other manufacturers monitor and why. It also details the frequencies and suggests how to deal with trends and issues as they arise.

SUMMARY

Monitoring an operation is a GMP requirement. It serves to identify problems before they happen. It allows the manufacturer to take necessary steps to ensure the process is in a state of control. The data collected helps establish a baseline for the operation. Seasonal variation on the validated system may be demonstrated. Continuous monitoring allows for ongoing verification and ensures that systems remain in a validated state. Choosing the variables to monitor, establishing the frequency of monitoring, developing the analytical and statistical approach to visualize the monitored parameter, and defining the alert and action levels as well as the approach to respond are the bases of a successful monitoring program.

REFERENCES

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ARTICLE ACRONYM LISTING

CAPA	Corrective Action and Preventive Action
CPP	Critical Process Parameters
CQA	Critical Quality Attributes
GMP	Good Manufacturing Practices
FDA	US Food and Drug Administration
FMEA	Failure Mode Effects Analysis
FMECA	Failure Mode, Effects, and Criticality Analysis
HACCP	Hazard Analysis and Critical Control Points
HAZOP	Hazard Operability Analysis
USP	United States Pharmacopeia