Effective Quality Control in Management of Processes

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“Global Regulatory Viewpoint” addresses various regulatory and compliance topics including newly published regulations from a global perspective. The content in this column is useful to those who deal with pharmaceutical development, expectations for CMC sections of regulatory dossiers, and guidances for manufacturing, validation, and current good manufacturing practices.

Reader comments, questions, and discussion topic suggestions are requested to help us fulfill our objective for this column. To submit manuscripts for publication in this column, please contact the coordinating editor at shaigney@advanstar.com.

KEY POINTS DISCUSSED

• The purpose of quality control evaluation is to determine, with a high statistical confidence, whether or not the process mean or variability have changed
• All processes should be designed to produce a desired target value
• The choice of equipment, materials, methods, and training defines the predictable range of process variability
• Process variability is cumulative
• Quality controls must be simple and easily understood
• Quality control data are used by the front line to make real time decisions
• Quality control data have limited predictive power
• Quality control points must be placed at logical process check points to facilitate a “go” or “no-go” decision by an operator.

INTRODUCTION

Quality control should be a simple practice. However, quality control is often very difficult to implement properly because in-process controls are considered as an afterthought—only after the process is designed, installed, and first run. Effective quality control must be factored into the process design as each of the process component resources (e.g., man, machine, method, material, and environment) is configured to meet a business purpose. Please note that the term “man” generically represents a human resource of the process.

This article discusses effective quality control from an experienced hands-on perspective. Many US Food and Drug Administration presentations (1,2,3) and management literature (4,5,6) describe the theoretical outcomes and mathematical considerations that underlie process management in general and quality controls in particular. The reader is encouraged to review these references at the end of this article to gain additional understanding of the theory and application of effective quality control and process management. However, hands-on experience is essential to assure that proper quality controls are selected and applied effectively.

EFFECTIVE QUALITY CONTROL EQUALS EFFECTIVE PROCESS MANAGEMENT

Every process consists of a minimum of five business resource elements: Man, machine, method, material, and environment. Man is the human resource element that is deployed to run the process. Machine is the equipment used to convert input raw materials into intermediate or finished goods outputs. Methods are the techniques that assess the various stages of

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the input material conversion. Materials consist of unfinished component materials brought together to be converted by the process into an output. Finally, the environment consists of the conditions under which the input materials are converted to the output materials. All processes, either service or manufacturing, contain these elements to accomplish the objective of the process.

Quality controls are placed at the points within the process where the real time performance is assessed against the design's intended performance. The outcome of the quality control examination is a decision to either:

- Allow the process to continue—test results are acceptable
- Stop the process—test results are unacceptable
- Problem solve (adjust) the aberrant situation.

The goal is to progress a conforming workflow towards completion. The in-process specification is the gauge against which the quality control (QC) test data are evaluated for both centering and variability. The application and integration of effective QC within a process is not learned from a book, but rather from actual on-the-shop-floor, hands-on experience. To this point, the following seven considerations are fundamental to establishing an effective quality control program.

**QC Results Must Be Judged Against The Process Design Criteria**

Acceptance of quality control data must be based on a comparison against the process design criteria rather than general compendia limits and ranges stipulated in monographs. It is important to note that quality data should not exceed existing official compendia limits as this would be a violation of law. This is a critical point. Meeting a specification range while missing the design target should be treated as a "process failure."

Every process must include capable, validated tests and statistically justified sampling plans for verifying the intended target mean of the process. The allowable variation of the process will be the sum of intrinsic imprecision of the equipment, purity of the materials, and technological basis of the methods selected. Compendia standards represent good science; however, most compendia standards are too broad to support process excellence that is achievable by today's technology platforms such as high-performance liquid chromatography (HPLC) and precision scales and balances.

Why would rote acceptance of compendia standards lower outgoing quality? Because the wide compendia specification range allows acceptance of off-target process results where the mean lies within the compendia range, a defacto legal limit of release. Consequently, the off-target test sample does not prompt a root cause investigation because of insensitivity of the metric. The outcome is increased variability of process results and an accompanying reduced quality of the product.

**QC Tests Must Be The Correct Control Type**

The quality control test plan must align to the data type that is to be generated at the specific control point of the process. There are two basic data types: Variable data and attribute data.

Variable data provide quantitative information about the process and are generated by test instruments or process controls. Variable data describe precise relationships and are traceable to a reference standard. Variable data are generated either by a well-defined method or by an instrument that has directly traceable standards, such as with an analytical balance. Examples of variable data include weight of tablets, assay of tablets, and temperature of a fluid-bed drier. Variable data facilitate process control by quantifying the process output with easily understandable and well-calibrated number sets.

The second type of quality control data management technique involves what may be termed relative data or attribute data. Attribute data are qualitative and may be subjective. Attribute data may have no absolute reference standard perse but provides highly relevant information about subtle changes of input materials or finished product outputs. Often attribute data are highly sensitive to variability beyond the analytical abilities of variable data. Examples of relative data include visual descriptions of product color, excipient textures, and crystal appearance. Management of relative data is best accomplished through control charts of attributes (e.g., c, p, or n-p charts). Relative data provide critical information about the overall consistency of the process.

The key purpose of these data is to identify variability between lots. Both data types are necessary for effective quality control and should be considered for critical process parameters. Further, the management and interpretation of data management should be consistent with proven quality practice (7).
QC Tests Should Assess Both Centering And Range
Collecting quality control data has two general objectives. The first objective is to evaluate the mean of the sample against the intended process target. A test of the process target would involve a composite sample over a defined period of time. Testing this sample is meant to assist the machine operator in deciding whether or not the process mean has shifted or drifted from the intended target mean. These statistically derived data provide for decisive action to adjust the mean if the data supports such action. Restating this point from a different perspective, machine adjustments should only be made when there is high degree of statistical evidence that the mean has changed. An example of such statistical evidence would be seven samples in a row, monotonically increasing or decreasing. If the machine operator concludes the process mean has changed and decides to adjust the target, they would be correct approximately 999 times out of 1000.

The second purpose of quality control data is to evaluate the variability of the individual values that comprise the mean. In a similar manner, the range of the data could be evaluated for statistical consistency. The root cause of a range change may be different than the root cause of the mean target change, but the two in concert signal the equipment operator of a pending problem of product consistency.

Assessments of the process centering and process range are termed X-bar (average) and R (range) charts. The X-bar and R charts are probably the best known of data management techniques of statistical process control.

QC Tests Must Measure One Discrete Outcome Of A Process Element
The goals of effective quality control plans are to identify and resolve problems that are foreign to the process design. Any resulting action to meet these goals must be supported with a high degree of statistical certainty and must be data and design driven. For quality control data points to be meaningful, the test must evaluate only one potential source of process variability. A process action may involve several sequential manufacturing steps, but taken as a whole, there should be one unique quality control test data set to establish one unique root cause. Therefore, placement of the quality control test point according to the process design factors (i.e., man, machine, method, material, environment) is very important.

The following example clarifies the point: An analytical value generated by a laboratory HPLC was determined to be out of specification (OOS) for a content uniformity test. The OOS investigation did not reveal an immediate root cause from the most suspect quality control point: the sample preparation. However, every lab analysis consists of at least two control points—the sample preparation and the instrument performance. In this case, the analyst had failed to inspect the sample containers (machine performance) even prior to evaluating the test data. By failing to review the quality control data from the HPLC instrument, the problem now had two potential root causes, but only one set of data, the content uniformity test chromatogram. Without the instrument QC evaluations, it would not be possible to distinguish between the two root causes. Fortunately, the sample tray had not been discarded and inspection of the vials revealed a damaged sample vial matched the OOS test result. Therefore, the most likely root cause resulted from the instrument malfunction during sample removal. Had the sample tray been discarded without identifying the sample vial problem, the OOS would have had an indeterminate root cause. This example shows the importance of QC evaluation for each discrete point for effective process management.

QC Sampling Must Be Rational For The Process
Much of the effectiveness of the QC plan lies in the design of the sampling plan. Sampling must be representative of the control objective and be of adequate size to detect either a change in the mean or a change in variability. Process sampling is the first chance to fix a product problem. Often insufficient time is spent developing adequate sample plans specific to the manufacturer’s process. Commonly accepted compendia plans, such as 10 tablets for content uniformity (stage 1) or 6 tablets for dissolution (stage 1), may be selected out of convenience or cost considerations but do not support the goal of process excellence. These sample sizes may be adequate relative to the specifications published in compendia, but may be completely inadequate to manage the mean or variation of the particular process.

There is one general rule about samples and the ability of the QC system to detect a problem. Most processes create defects at well-defined points that are not random in nature (i.e., start-up and shut-down) when the equipment is not in a steady state condition.
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The concept that quality control samples are supposed to be random and have a statistically equal probability of being selected has more to do with mathematical probability theory and proper calculation of a confidence interval than effective process control practice. There is only one system that is truly random, and that is in a fluid like system.

Looking at the process in a common-sense manner, a machine is not designed to intentionally produce random defects when it is running normally. Industry spends countless dollars to validate normal operating characteristics of high quality machines. However, industry does not spend as much time in assuring that quality control procedures adequately isolate and remove materials during abnormal operating conditions.

The following example illustrates this point: Printed folding cartons (i.e., secondary packaging) were found to pass the incoming quality tests. Lot sizes of cartons were large and the sample size was equally large. Yet during product packaging, cartons were sometimes found to be glued shut and could not open or unglued so they “fell apart” during high-speed operation. The result was damaged equipment and poor supplier relations. The root cause was eventually determined to occur during machine secondary start-up times following mid-morning breaks and lunch breaks. The machine was not cleared during shut down for break and the glue dried on the in-process cartons. The quality control sample, being a random plan, did not include start up beyond the first start in the beginning of the manufacturing shift. The point is that random sampling alone is often insufficient to manage the quality of a discrete process when non-random events are present.

**QC Decision Must Be Simple**

QC samples and evaluation are intended for the manufacturing operator who is faced with a decision at time of sample analysis. The operator’s choice is to continue the process or hold the process based upon sample evidence. Stated differently, the QC sample presents the questions “Has the mean changed—Yes or No?” and “Has the variability changed—Yes or No?” Decisions should be simple without a set of complex rules that reflect all possibilities that are theoretically possible but are generally outside of the process design range. The operator should resolve simple to moderately difficult problems based upon training and experience. Complex investigations exposed during quality control sampling should be handled by an independent group as a larger system issue may be present.

**QC Tests Must Consider Both The Current State As Well As The Past**

Finally, process evaluation decisions reflect the current state of sample data as well as the historic performance of the process. The point is that samples must control both the within-lot variability as well as the between-lot variability. Robust QC plans should include within-lot quality control approaches, such as X-bar and R samples and between-lot controls such as run charts and attribute charts of non-variable data. Robust process management truly requires both to complement the quality program.

**IMPACT ON PROCESS VALIDATION**

Effective quality controls improve the consistency of the process output as the process design and the process performance are aligned. Additionally, the firm will save significant time and money that is often associated with over or under adjusting of the process during operation. Further, when a problem does arise, it can be confined and resolved in a much more timely manner.

The greatest impact to the validation effort is continuing success of the process long after validation is completed. Validation should be an affirmation of the validity of the quality control system as much as it is verification that the equipment and equipment controls are working properly over defined ranges. It is important for validation practitioners to know and understand the interrelationship of the test controls to the confirmation of the process design targets: Center point and the expected variability around the point. Successfully validating an improperly managed process will be a meaningless validation. Failing to validate an improperly managed process is equally disastrous.

**CONCLUSIONS**

All processes share a common foundation of resources and purpose. The goal of process management and the embedded quality control testing is to produce products that are consistent to process design targets. In order to achieve optimum results from the process, it is important to consider how the process design will be managed and controlled. In-process quality control check points should be tailored to the specific process and should generate data to allow an employee to assess actual process performance against the intended process performance targets and act upon identified gaps between the actual state and the desired state. Actions should be made with significant statistical evidence. Process excellence is not much more complicated than this.
REFERENCES

ADDITIONAL RESOURCES
Additional texts to direct and supplement “hands-on” experience found helpful in understanding process management for the purpose of effective quality control include:


ARTICLE ACRONYM LISTING
HPLC High-Performance Liquid Chromatography
OOS Out of Specification
QC Quality Control