



Reexamining the "Set It and Forget It" Approach

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Process variations inevitably result in change, and change may mean new regulatory hoops. Statistical quality control is a cost-effective and efficient method for coping with change while still remaining compliant with 21 CFR Part 58.

Laboratory analysts operating under GLP regulations (21 CFR Part 58) often feel that it is unwise, if not impossible, to make changes to an established method (EM). Although the inability to change a method after it is validated may not appear to be a great hindrance, it clearly is when you consider the practical effect this limitation has in the laboratory. Many panicked calls to chromatography vendors have resulted from this limitation. Typically, the panicked analyst describes to the vendor a problem in the laboratory and the vendor recommends changing either the column used or the mobile phase conditions. Either change violates the policy prohibiting postvalidation changes, but under duress, the analyst must make a change. Usually, the analyst will change the column brand because the method being used specifies the use of a specific brand "or equivalent," which allows the column to be changed while technically staying within the realm of acceptable QC parameters.

After trying several "equivalent" columns and finding one that meets the method's system suitability criteria, the analyst typically stays with the new column hoping that it solves the problem encountered. If the analyst cannot find a brand of column that solves the problem, the method may be sent back to R&D, stalling the process.

EXAMINING THE DIFFICULTY

Under circumstances like these, the QC analyst has to make a choice regarding a problematic chromatography method: Either send it back to R&D and wait for a response, or try to correct it without technically deviating from the method "as written."

Because the method allows the use of equivalent columns, the QC analyst tries different columns until one is found that "works," or after trying different columns without success, sends the method back to R&D and waits.

This practice creates a dysfunctional dynamic. When I worked in chromatography sales, I fielded calls from analysts requesting liquid chromatography media packed into hardware with odd dimensions. When informed that the requested media was no longer available, some analysts requested equivalent packing in the same oddball dimensions. The assumption implicit in the requests is that a change of brand is a lesser sin than altering the column dimensions stated in the method.

Embracing change. A change in the dimensions of a liquid chromatography column, however, usually has little effect on the separation, as long as the flow rate is scaled accordingly, and the detection method still works well with the new flow rate (1). Furthermore, the selectivity differences that a method undergoes when the mobile phase

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is modified are more predictable than those when the column is changed from one brand to another (2,3). To make matters worse, few methods give guidelines for determining column equivalence (4,5). Typical QC analysts try to correct method problems by changing things in what appears to be the most disruptive order: First change the column to an equivalent brand, then modify the mobile phase, and finally change the column's dimensions.

Laboratory workers know occasions arise when a change must be made to an existing methodology. It doesn't matter how rigorous the original method developers were; no methodology can continue unaltered forever. Variance exists in all processes, including analytical methods, and to behave as if it doesn't is to stick one's head in the proverbial sand. Advocates of statistical quality control have an effective method for coping with variance.

STATISTICAL QUALITY CONTROL

Schools of thought differ on how to apply statistics to quality control. However, all are derived from the same body of work published during the last 80 years by "quality pioneers" such as Walter Shewhart, W. Edwards Deming, Joseph Juran, and Phillip Crosby (6-9). American industry began to use statistical quality control in the 1970's when Japanese automotive and electronic companies captured U.S. market share by capital-

Managing Variance

W. Edwards Deming developed a statistical quality model that includes the following concepts. These concepts are quite intuitive and have been repeatedly validated in manufacturing environments (6-9).

- Variance exists in all processes.
- A product's ability to consistently meet quality criteria is a reflection of the variance that exists in the manufacturing process.
- Final product inspection does not make up for quality lapses caused by a faulty process.
- Eliminating manufacturing process inconsistencies brings the process "in control" statistically.
- Once a process is "in control," it can be systematically improved to better meet expectations.
- The economic benefits of reducing variance in the manufacturing process almost always outweigh the costs of doing so.

izing on the quality management techniques espoused by those authors (6).

Deming is the most prominent of the quality pioneers. His statistical quality model is based on a few, relatively simple concepts listed in the "Managing Variance" sidebar.

Quality defined. Confusion exists about the definition of quality. Conventional thinking defines quality as an arbitrary aspect of goodness inherent in a product. That thinking suggests that increasing a product's quality — or level of goodness — costs money and should be avoided if the customer can be satisfied with less. In contrast, statistical quality thinking defines quality as a product's ability to consistently meet specific criteria. According to statistical quality thinking, any increase in product consistency usually pays for itself.

BUILDING YOUR QUALITY MODEL

To give an example of how the different definitions of quality play out in manufacturing, con-

sider the following hypothetical example. Let's say that final inspection noticed small dings in the bodies of widgets coming off the assembly line. A **conventional management approach** would include the following.

- Blame the production staff for the discovered defect, and proceed to give the staff a lecture or workshops on the value of quality and of having a good work ethic.
- Estimate the cost of assigning an additional inspection test for widget dings and of reworking the dings found in widget bodies.
- Compare the estimated cost of these changes to the estimated cost in lost sales and returns if the ding problem is ignored.
- Based on that cost comparison, either correct the problem with additional inspecting and reworking or simply ignore the problem.

In contrast, a **statistical quality approach** to the same problem would include the following.

- Carefully document the occurrence of dings, along with the environmental and personnel conditions under which the dings occur.
- Analyze that data and hypothesize on the different causes for the dings, then test each

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hypothesis to isolate the problem's root cause.

- Once the problem is isolated, formulate a solution and test it on a small scale to see if the solution corrects the problem.
- When a solution to the problem has been found, modify the standard operating procedures (SOPs) and established methods to reflect the new "profound knowledge," and thus improve the manufacturing process.

As these examples show, the statistical quality approach does not require the additional cost of inspecting and reworking required in the conventional approach, which is why quality pioneer Phillip Crosby asserts that "quality is free." According to Crosby, the elimination of root causes is always an economic benefit to a company. Therefore companies should set a goal of "absolutely zero defects." "Zero defects" is the same goal that GLP/GMP companies have. However, instead of ignoring process variations, as many companies do, statistical quality technicians study variance and ultimately seek to reduce it.

By using the techniques of statistical quality control, one analyst at a major biotechnology company was able to institute changes to a validated method that resulted in a threefold decrease in sample analysis time. When the changes were later reviewed by FDA, they were allowed to stand, in part because of the clarity and validity of the statistical approach (10).

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