Welcome to “Analysis and Control of Variation.”

We have seen many approaches to improving quality, compliance, and productivity during the past 30 years. However, from the approaches of Shewhart, Deming, and Juran to TQM, Kaizen, Kanban, and Six Sigma there is a golden thread that runs through all of these approaches: Understanding and reducing variation. It is axiomatic that if there is no variation, there will be no deviations and no out-of-specification results. Some degree of variation is unavoidable; we can nearly always reduce variation, but we can never eliminate it. Any successful approach to validating a process and then ensuring that it remains compliant must include elements that help us to reduce variation and then to continually monitor and control it.

This column is dedicated to revealing weaknesses in existing approaches to understanding, reducing, and controlling variation, and to recommend alternatives based on sound science that demonstrably work. Case studies will be used to illustrate both problems and successful methodologies. The objective of the column is to combine sound science with proven practical advice.

Reader comments, questions, and suggestions will help us fulfill our objective for this column. Suggestions for future discussion topics or questions to be addressed are welcome. Case studies illustrating the successful reduction or control of variation submitted by readers are also most welcome. Please send your comments and suggestions to column coordinator John McConnell at john@wysowl.com.au or journal coordinating editor Susan Haigney at shaigney@advanstar.com.

KEY POINTS DISCUSSED
The following key points are discussed in this article:

• The principles and practices for bringing a process into a controlled and capable state and then maintaining that condition over time are well developed
• A “go, no-go” attitude focusing on process specifications is a significant obstacle to improving quality, compliance, and productivity
• The pharmaceutical industry should minimize variation between batches
• Dr. W. Shewhart created the concept of statistical process control in the 1920s
• A quality manufacturing process has minimum, stable variation around the process optimum
• The US Food and Drug Administration has recommended identification and control of variation in manufacturing processes in the recent process validation guidance
• A process is under control when all outcomes fall at random about an unchanging mean and remain within the statistically calculated control limits pioneered by Shewhart
• The common practice of calculating process limits by using the rule of “mean ± 2 (or 3) σ” is likely to make even the most chaotic of data look stable when they are not
• Specifications are a necessary part of the business landscape, but to use them for process analysis and control or for process monitoring is wrong
• The Shewhart approach is well established and should be applied to pharmaceutical manufacturing processes.

INTRODUCTION
The importance of understanding, reducing, and controlling variation cannot be overstated. In too many places, the pharmaceutical industry has yet to apply approaches that are routinely successful in many other
industries. Recent regulatory documents and presentations addressing both pharmaceutical products and medical devices have been critical of the industry’s ability to reduce and control variation at inputs as well as in-process, and justifiably so. The principles and practices for bringing a process into a controlled and capable state and then maintaining that condition over time are well developed. However, the pharmaceutical industry has yet to widely adopt some of these principles and practices. It is our intent to pursue these issues in such a way that readers will be able to profit from the application of the principles and methods discussed in their daily work.

Central to this article is the observation that, in many cases, when the terms “variation” and “process control” are used, a significant proportion of people in the industry translate this to mean “compliant” or, “remains within specifications,” or “meets the required standards.” This “go, no-go” attitude towards quality and process control remains widespread, and this mindset is a significant obstacle to improving quality, compliance, and productivity.

A BRIEF HISTORY OF SPECIFICATIONS
During the craft era that led to the industrial revolution, craftsmen made all products. The craftsman usually made the entire product. Notions such as subcontractors, vendors, and outsourcing were hundreds of years away. The baker ground local wheat, collected and processed the essential ingredients, heated his oven with wood gathered by his family, and produced distinctive bread. Blacksmiths and armourers even made their own rivets and nails. Every product was one of a kind. Components were not interchangeable because every part was individually made to match other parts. Each sword had a scabbard specifically crafted to match it. In the days of muskets, the hammer from a broken musket could not be removed and fitted to another musket with a damaged hammer. If a component failed, another was made to order and hand finished to match the other components.

Early industrialists dreamed of the interchangeability of parts, and this dream created many rich opportunities. If components were interchangeable, a whole new concept of manufacturing would be created. It would allow parts to be produced in large volumes and then assembled to make a product by different people, sometimes in different countries. Production costs would be significantly reduced, as would maintenance costs. The cost of goods would fall, and the standard of living would soar.

These were sound dreams. The evidence that manufacturers overcame the major obstacle to mass production—variation—is everywhere. The benefits brought to humankind by this lack of variation defy measurement. Without mass production there would be no television or other electronic products such as computers, no refrigerators, no processed or packaged food, and no automobiles. There would be no public transport systems, no reticulation of clean water, and no sewage systems.

The application of this kind of thinking to medical devices is obvious. What about drugs and vaccines? Most drugs and vaccines are made in batches. The same principles of mass production apply, but in a slightly different way. A molecule is discovered or created and a production process is built. Inputs are blended, reacted, or grown and the desired molecule is created. Usually, this will be followed by several more steps to cleave, clese, bond, or otherwise modify the molecule until it becomes the final product. The drug or vaccine manufacturer tries to closely replicate the product, batch after batch. Here the interchangeability or repeatability of interest is between batches. This is still mass production, except that the manufacturer is concerned about driving down the variation between batches rather than between components in devices (1).

In laboratories, the variation of interest is found between analysts and between instruments. If a blind control sample provides repeatable results regardless of which analyst conducts the test or which instrument is used, true interchangeability has been realized (1).

In terms of advancing our material welfare and of lengthening our lifespan, the advent of mass production was an awesome triumph.

Nevertheless, many of the initial attempts to create interchangeable parts failed. Too often parts did not fit well during assembly, resulting in unacceptably high scrap and rework, along with raised costs.

The first breakthrough was to realize that exact repeatability was impossible. The second was the realization that it was not necessary. What was necessary was to ensure for the variability between components to be low enough to facilitate assembly into a workable product. The first practical approach developed to achieve this end was the creation of ‘go’ and ‘no-go’ gauges. Imagine the boring out of wheel hubs to accept axles. The hole bored must be big enough to allow the axle to be inserted, but not so big that the axle will flop around in the hub. In this case a bar of metal with one end machined to a slightly smaller diameter becomes the gauge. The small end must fit into the wheel hub, but the larger end must not.
Manufacturers soon converted their go, no-go gauges into tolerances or specifications.

This became the way manufacturers determined whether the parts made could be successfully assembled to make a sound product. The first definition of quality was born: All parts must remain within the specifications (i.e., in or out; go or no-go).

MORE RECENT DEVELOPMENTS

Despite the enormous advances made during the past 80 years, much of the pharmaceutical industry remains locked in this go, no-go mindset. In many areas the prevalent mindset states that providing the test result under examination remains within specifications not only does nothing more need to be said about that result, but also that nothing more should be said about it. This fundamental error leads to statistically significant signals that ought to warn of impending trouble being ignored. In turn, these overlooked or disregarded signals and disturbances eventually result in out-of-specification (OOS) results that should and could have been avoided (2). They also lead to an unnecessary increase in variation that, in accordance with Little's Law, damages not only quality, but also productivity. Any approach that blinds people to statistically valid signals and warnings is poor science.

In the 1920s Dr. W. Shewhart created the concept of statistical control, or stability. He was able to demonstrate that a process had no known capability until it was in statistical control. More than 70 years later we find many chemists, biologists, and engineers calculating process capability despite the fact that the data are demonstrably unstable. A number will be calculated, but in these circumstances it is likely to be meaningless (3,4).

In 1960, Dr. Taguchi won the Deming Medal for an approach we now call the Taguchi Loss Function. Essentially, Taguchi created new statistical tools that demonstrated that even when all outcomes meet specifications, loss is incurred (5). His methods supported Shewhart and Deming who had claimed that reducing variation was always a sound economic approach, even though all data were within specifications (6).

In the early 1980s an engineer from Motorola, Mr. Bill Smith, came to the same conclusions. Smith ultimately laid foundations for the concept of Six Sigma. Smith stated that all critical to quality (CTQ) characteristics should occupy no more than half the specification range. In more specific terms he stated that the nearest specification for any CTQ characteristic must be at least $6\sigma$ from the nearest specification (1).

From Shewhart and Deming to Taguchi and Smith; from TQM and Kaizen to Kanban and Six Sigma, there is a common theme that refuses to go away. Our job is to understand and conquer variation. Unfortunately, many in the pharmaceutical industry remain locked in an ancient mindset that says that providing outcomes meet specifications, all is well. This mindset can be demonstrated to be fallacious, and to be likely to increase deviations and OOS results. The most up-to-date definition of quality is: Minimum, stable variation around the process optimum.

THE CHANGING FDA THINKING

The US Food and Drug Administration increased the pressure on the pharmaceutical industry to better understand and reduce variation when it released its draft process validation guideline (7) that states the following, in part:

- Quality, safety, and efficacy are designed or built into the product
- Quality cannot be adequately assured merely by in-process and finished-product inspection or testing
- Each step of a manufacturing process is controlled to assure that the finished product meets all design characteristics and quality attributes including specifications.

Another section of this FDA guideline (7) states that manufacturers should do the following:

- Understand the sources of variation
- Detect the presence and degree of variation
- Understand the impact of variation on the process and ultimately on product attributes
- Control the variation in a manner commensurate with the risk it represents to the process and product.

Unfortunately, there is no shortage of scientists in the industry who believe that they meet these requirements, when they do not.

The FDA guideline further states (7), "After establishing and confirming the process, manufacturers must maintain the process in a state of control over the life of the process, even as materials, equipment, production environment, personnel, and manufacturing procedures change."

This begs the question, how should we define the statement “maintain the process in a state of control”? During the March 2009 Pittcon conference the opportunity was taken to ask many scientists working in the
pharmaceutical industry to provide a definition of this term. The majority responded by stating that a state of control existed if all results fell within specifications.

This is not correct. A state of control exists when all outcomes fall at random about an unchanging mean, and remain within the statistically calculated control limits pioneered by Shewhart.

It is worthy to note that the common practice of calculating the limits of a system by using the rule of “mean ± 2 (or 3) σ” is likely to make even the most chaotic of data look stable. This method of calculating limits assumes that the data are controlled or stable. When they are not, upsets which increase variation will cause limits calculated in such a way to widen and to make the data look stable, even when they are not.

Finally, the FDA guideline states (7), “We recommend that a statistician or person with adequate training in statistical process control techniques develop the data collection plan and statistical methods and procedures used in measuring and evaluating process stability and process capability. Procedures should describe how trending and calculations are to be performed. Procedures should guard against overreaction to individual events as well as against failure to detect process drift. Production data should be collected to evaluate process stability and capability. The quality unit should review this information. If done properly, these efforts can identify variability in the process and/or product; this information can be used to alert the manufacturer that the process should be improved.”

In this paragraph FDA states clearly what is required. The industry needs to use statistical process control (SPC) techniques to evaluate both process stability and process capability. This requires the use of Shewhart control charts to determine whether or not a process is in a controlled state; but why be so prescriptive?

**SHEWHART CONTROL CHARTS**

A significant part of the answer can be seen in the example in Figure 1 (2). Two charts for the same CTQ characteristic are displayed. The top chart shows results compared with specifications, and the lower chart uses limits calculated using Shewhart’s control charting techniques. The Moving Ranges chart is omitted from the Shewhart chart for simplicity and clarity.

In Figure 1, two results are reported OOS; one at batch 18 and one at batch 61. Because it is an isolated special cause event, it was correct to study batch 18 in an attempt to determine causality. To take the same action for batch 61 is a mistake. The Shewhart control chart shows a statistically significant upward shift in the mean at batch 41. That is a signal to which the scientists should react. Batch 61 reported as OOS not because anything changed during the
production of that batch. It is a random point in a system of data that shifted at batch 41, which is where the real root causes of the second OOS event will be found. Nevertheless, in most companies when similar circumstances exist we find scientists studying the failed batch, rather than the point in time where the process changed.

A similar problem can be found when scientists are still using the old “mean ± 2 (or 3) $\sigma$” approach to calculate limits, which is illustrated in Figure 2. Again, two charts are shown. Both charts show a CTQ characteristic in a chemical cleave process for a biologic. The top chart uses the “mean ± 3 $\sigma$” approach. The lower chart is a Shewhart control chart (again, the Moving Range chart is omitted).

Too many scientists conclude that the chart using the “mean ± 3 $\sigma$” approach shows no signals. If fact, there are seven signals in this data set, all of which are exposed in the Shewhart control chart. This is what the FDA guidelines are now demanding; that scientists can better tell the difference between random and non-random data; that they know when to take action, and when not to. According to the FDA guidelines, the situation in Figure 2 is unacceptable, even though all results to date remained within specifications. Because the Figure 2 process is not stable or controlled, it has no known capability. Sooner or later it will generate an OOS result; but why wait? If the managers and scientists working in this process did nothing more than to stabilize the process, they would all but guarantee its capability. No changes to current good manufacturing practices are required. In this case, all that is necessary to ensure good quality and productivity is to stabilize the process—to make it repeatable and predictable. Once the variation is reduced, then it will be easier to see the causal relationships and ultimately improve the process.

**Analytical Processes**

Any statistical approach can be no better than the data it uses. Imagine a production process that is in statistical control, but the analytical process used to measure it is unstable. This in turn will cause an investigation for causes of excessive variation in the production area—a hunt that is all wasted effort and that is doomed to fail because the problems are in the analytical area. This subject alone would fill several volumes, and it is earmarked as the subject for a future topic for this column. For now it will suffice to illustrate a similar analytical issue with the two charts in Figure 3. The top chart shows the laboratory controls with limits placed at mean ± $3\sigma$ and the lower chart shows the laboratory controls as a Shewhart control chart. The hunt for the trend factory people saw in the production data was never going to reveal root causes, because the trend was in the laboratory’s analytical processes.
CONCLUSIONS
In order to comply with the FDA guidelines, and to better guarantee quality and productivity, companies in the pharmaceutical industry have no choice other than to use SPC techniques to bring all their clinical trials, development, analytical, and production processes into a state of statistical control. The guidelines seem to leave little room for interpretation, and understandably so. Because an unstable process has no known capability, we cannot calculate the probability of either passing or failing specifications in a statistically valid way until the process under examination is known to be stable (4). Our consumers have a right to expect that the medicines they take come from controlled and predictable processes. Our stock holders have a right to expect that we will not throw away their investment with unnecessary variation and deviations. Our employees have a right to take pride and joy in their work. Production people have a right to expect that the analytical systems on which they are so dependent are stable. Bringing our processes into statistical control will help us to satisfy all these needs.

Specifications are a necessary part of the business landscape, but to use them for process analysis and control or for process monitoring is a recipe for trouble. The Shewhart approach is ideal for these purposes. It is a tried and true approach that has stood the test of time. All that remains is for the pharmaceutical industry to use it widely and wisely.

REFERENCES
3. W. A. Shewhart, Economic Control of Quality of Manufactured Product, Van Nostrand, 1931.

ARTICLE ACRONYM LISTING
CTQ Critical to Quality
FDA US Food and Drug Administration
OOS Out-Of-Specification
SPC Statistical Process Control