PAT: Déjà vu All Over Again?[1]

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The current Good Manufacturing Practice regulations were published in the Federal Register on September 29, 1978. Section 211.110(a) of those regulations contains several concepts that have substantially changed our industry since they were approved. I am particularly impressed by one specific sentence:

"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."

I enjoy pointing out to people that the words "validate" and "variability" occur in the same sentence. Not to be putting words in the mouths of those who wrote this section, but it always seemed to me that the authors were telling us to find, control, manage and, if possible, reduce variation as part of our validation studies.

I am supported in that idea by a journal article entitled, "The FDA Viewpoint," written in 1985 by Ed Fry (Fry, 1985) who was then Director, Division of Drug Compliance, CDER Office of Compliance, U.S. FDA. In that paper, speaking for the FDA, he made several profound and important statements about validation and its connection to variability:

Experiments are conducted (that is, validation runs) to assure that factors that would cause variability, are under control and will result in an output that meets the specifications within the limits of the ranges that you had previously established.... The regulations require validation of those processes responsible for causing variabilities in characteristics of in-process materials or finished products....However, the regulation implies that not everything that takes place in a pharmaceutical manufacturing plant causes variability. Therefore, some things don't need to be validated. We never intended to require that everything [that] takes place in a manufacturing operation is subject to a validation study.

Are we coming full circle back to the original intention of the GMPs with process analytical technology? Is there a feeling of déjà vu in reading the PAT. Guidance? In that guidance, we find many references to statistics and variability:

- *What sources of variability are critical? (p. 5 of the guidance)*
- *How does the process manage variability? (p. 5)*
- *Facilitating continuous processing to improve efficiency and manage variability. (p. 5)*
- *A process is generally considered well understood when (1) all critical sources of variability are identified and explained; (2) variability is managed by the process; and, (3) product quality attributes can be accurately and reliably predicted over the design space. (p. 6)*
- *A flexible process may be designed to manage variability of the materials being processed. (p. 9)*

Variation is the Enemy

Variation (i.e. change or differences) is one of the great concept of statistics. In our personal lives, variety is the spice of life. We want and seek change in our foods, music and entertainment. But, in many areas, variation is the enemy and must be dealt with directly. In business processes, such as accounts payable or purchasing, variability is the source of errors, lost time and lost business. In clinical and preclinical studies, variation obscures and complicates the search for important medical effects. In quality and manufacturing, excessive variation often results in out-of-specification results, out-of-trend results, SOP deviations, data outliers, rejected and recalled lots, Form 483 observations, warning letters, massive fines, consent decrees and loss of business. Variation is the enemy of Safety, Strength, Quality, Identity and Purity, or SSQuIP. If we decrease variability we increase our ability to achieve our goals at less cost.

We, as individuals and as an industry, need to work every day to reduce variation and variability in our selves, our methods, materials, measurements, machines, processes, products and the environment. Each of us must ask ourselves and each other the question: "Where is the variability coming from and what have I, or we, done to manage it, minimize it, control it and, if possible, eliminate it?"

Statistics and statistical thinking (Torbeck, 2001) are the tools needed to address this unwanted variation. It is a natural progression to go from process design to statistical thinking, because:

Where there is process, there is measurement.

Where there is measurement, there is data.

Where there is data, there is variability.

Where there is variability, there is statistics.

Where there is statistics, there is statistical thinking.

Statistical thinking can be summarized with these ten concepts:

1. Work occurs in systems of processes and subprocesses of interconnected and interrelated steps. Processes have Suppliers that provide Inputs into the Process activity. The end result is the Output that then goes to the Customer (SIPOC). This model provides an overview that is useful for broadly defining the process.
2. Processes can be mapped, flowcharted, studied ➤

systematically, understood, and improved. However, optimizing each step separately may result in a sub-optimum process.

3. Work is done by teams of people with differing backgrounds, education, expertise, skills, needs, and expectations all working for a common goal.
4. Process outputs vary due to both special or systematic causes and common or random causes.
5. Cause-and-effect relationships are the bedrock of science. These relationships can be found, quantitated, studied, understood and exploited to control special cause variability.
6. Excessive variability is the enemy of the cGMP's, validation, SSQuIP (safety, strength, quality, identity, purity), productivity, cycle time, efficiency and profits.
7. Variability can be measured using the standard deviation and thus quantitated, studied, and understood.
8. Statistics is the science of variation and uncertainty.
9. Excessive variability in processes can be reduced.
10. Organizations succeed and survive by continuous improvement using teams to reduce variation and to bring processes into engineering and statistical control.

Sources of Variation

A major advance in modern statistical thinking is that variability can not only be measured, it can be reduced through specific actions. Variation in our product and business processes is often thought of as coming from either a single source or from multiple sources.

The single source (called a special cause) of variation is addressed in the pharmaceutical industry by deviation investigation, root cause analysis, corrective action and where possible, preventive action or CAPA. We, as an industry, have more or less achieved this activity, but many CAPA's and investigations do not realize a real solution or find the root cause because of a lack of true process understanding. Ironically, there has been a historic disincentive to finding problems because of the fear of indicting a validated process.

In contrast, common causes are the result of a summation of many small sources of variations. This has not been well addressed in theory or in practice. Root cause analysis doesn't work for common cause variation since the results can be attributed to multiple small sources of variability all adding together. Textbooks tend to call this "inherent" variation, implying there is nothing that can be done to reduce it.

> ***If you can't describe what you are doing as a process, you don't know what you're doing.***
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> **—W. Edwards Deming**

Root Cause vs. Common Cause

In its CGMPs for the 21st Century report, FDA defines "root cause" as the singular source of a deviation/process failure and "common cause" variability as inherent variability stemming from a number of sources: excipients, equipment, measurement systems, etc.

Controlling Common Cause Variation

However, I think there are specific actions that can reduce these sources of common cause variation. It does require, however, the concerted effort of many people working together, and thus becomes a management issue of implementation and culture change.

There are five variations on the theme of consistency that, when taken together, can have a real impact on the reduction of common cause variation.

1) Operational Definitions: Unlike a short dictionary definition, an operational definition can be several paragraphs or several pages long. Note that SOPs are a form of operational definitions. But, we can further reduce variation by applying the concept to situations in which it is not clear how things are to be performed. Activities considered to be "common practice" are usually done differently by different people.

For example, what does it mean to "sample the tank" or "soak until soft and pliable"? Consistent definitions and consistent actions will yield more consistent results and less variation.

2) Achieve the Target: Many characteristics or variables have specification criteria. The usual cultural attitude is, "If we can get within the limits of the criteria or specification, then we have met the goal." I propose, instead, that we all work to achieve the target every time, often the center of the limits, not just fall within the limits.

For example it is common to have a specification like 25 to 35 minutes. I suggest that it should be written as 30 (25, 35) minutes, thus forcing the reader to see the target first. Admittedly, if only one person does this once or twice, no progress is made. But if hundreds of employees adopt a personal goal of everyday always striving to achieve the target every time, we will begin to see variation reduce.

3) Flexible Consistency: Sounding contradictory, this idea is another way to minimize common cause variation. Often in our work, there is more than one acceptable way to perform an activity. People doing these activities should agree, as a group, to doing it one way, and then they all do it that way all the time without exception. If, at a later time, it is proposed that ➤

there is a better way, all of the people should change all at one time to the new way of doing the work.

For example, a test method has many activities that are not detailed in the method documentation. The analysts that use that method should agree on doing these activities the same way every time to minimize the method variability. Again, one incidence is negligible, but implementing the concept hundreds of times will reduce variation.

4) Hold Constant Controllable Factors: This is almost too obvious to mention, but controllable factors such as time, temperature, pressure and speed should not vary if they can be controlled and held constant. Don't let so-called "noncritical" factors vary if they can be held constant. Every little bit helps.

5) Mistake Proofing: We need to design our processes to make it impossible or nearly impossible to make a mistake. Examples include putting mechanical "stops" on equipment so that it is not possible to make a bad part.

One biotech company color coded two bioreactors blue and green and then used light blue and light green paperwork so that misplaced paper forms were obviously out of place. Another classic t example is that of a truck frame assembly process where a nut had to be torqued to a given level. At that station of assembly there were three operators. The person who was free had responsibility for tightening the nut with a torque wrench. Inevitably, the operators would mistakenly think the other person had torqued the nut. To prevent this confusion, the torque wrench was placed in a small bucket of white paint. If the nut had been tightened, the operators would see it clearly—white paint on the nut. If it had not been tightened, everyone on the assembly line would have a visual signal reminding them that it needed to be done. Expanding this concept a hundred fold can have dramatic results on variation. In business processes, for example, forms design can have a dramatic impact on reducing mistakes in recording information and data.

Conclusion

In summary, this paper proposes that the FDA has been asking the pharmaceutical industry for close to 30 years to reduce special and common cause variability as a key element of process validation. Now that same theme is an integral part of Process Analytical Technology and Quality by Design, QbD.

Notes:

1. Apologies to Yogi Berra

References:

CGMPs, *Federal Register* 43, September 29, 1978, page 45076

Fry, E., "The FDA's Viewpoint," *Drug and Cosmetic Industry,* Vol. 137, No. 1, July 1985

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U.S. FDA, *Guidance for Industry: PAT — A Framework for Innovative Pharmaceutical Development, Manufacturing, and Quality Assurance, 2004*

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Five Approaches to Limiting Common Cause Variability

This paper has recommended five specific approaches be used to reduce common cause variation and achieve to consistency. It is recognized that these approaches are easy to articulate and difficult to implement. They require a culture change. They require consistent support and reinforcement by management at all levels everyday in all aspects of business. While not easy, the rewards are real and financially substantial.

1. Operational Definitions
2. Achieve the Target
3. Flexible Consistency
4. Hold Constant Controllable Factors
5. Mistake Proofing