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Pharma Process Validation: Initial Conclusions Are Often Deceptive

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As a pharmaceutical consultant, I have had the fortunate and unfortunate experiences of observing pharmaceutical process validation outcomes. In this article, I will provide insights into two recent process validation problems that could have been avoided with an enhanced developmental approach and a greater understanding of the impact of critical material attributes and the critical process parameters. Both processes were considered successfully validated and were ramped up to commercial production requirements, at which point the processes became problematic. One process issue revolved around equipment equivalency, while the second process exhibited materials and dosage strength variabilities. Each situation required unique, time-consuming, and costly interventions to achieve a process that was truly capable and in control.

1. Case Study: Equipment Issues

The first product was made by a continuous manufacturing process in several different strengths. The company uses the same manufacturing technology for other pharmaceutical products and all the processes have been and continue to be successfully validated. The company required additional manufacturing capacity and installed a new manufacturing line using the same equipment, models, specifications, and criteria that are used in the other validated manufacturing lines. The new line was qualified, and the product and process were “successfully” validated in the new area. Within two weeks of manufacturing of launch quantities, the new line began having many more process interruptions than the other lines. The interruptions were leading to testing and release constraints. The operational issues varied from pump feed rates to excessive yield losses. Product quality was not compromised since the defective material was easily separated from the acceptable material, but the yield loss demonstrated a lack of process capability and control.

What happened to cause the process to become unstable (not rugged or robust)? First and foremost, the equipment, especially the flow pumps, was not equivalent, even though the same equipment specifications from the same manufacturer were mandated and demonstrated. Secondly, the expansion of the line required additional operational personnel and there were not enough qualified operators to run all the existing and new manufacturing lines. The process was shown to be highly operator- and equipment-dependent. How could these issues have been avoided?

The equipment should have been broken in for a longer period and under normal operating conditions (routine personnel and across multiple shifts). Operations personnel know how to keep an operating line running by sight, sound, and feel, so having qualified operators becomes critical to keeping the equipment within desired operating ranges/parameters. My suggestion is to execute numerous (10+) batches in a continuous operational environment (multiple shifts over seven successive days) using a mixture of highly qualified operators and lesser qualified operators. Ensure the equipment and materials are the same grade that will be used for routine production. Understand where the problematic areas and equipment are, and take precautions to minimize materials, equipment, and personnel variability. Do not assume that “like for like” equipment will perform equivalently, even with the same product.

2. Case Study: Materials & Dosage Strength Variabilities

The second example is a manufacturing process that uses multiple subprocesses (three granulations and blending) that are subsequently combined into a master blend prior to compression into a chewable tablet. Two of the materials used in the process are natural products, and compositional changes from these materials (qualitative and quantitative) are expected. The validation batches were manufactured using a single lot of the natural materials and mostly targeted the lower strengths of the dosage forms.

Developmental data had shown that the higher-strength dosage forms were more problematic during manufacturing, especially during the compression process. The manufacturer was lulled into a false sense of security by successfully making multiple successive batches using a matrix approach. Process capability analysis of the first seven validation batches compared to the process capability of the next 60 batches exhibited a dramatic reversal (PpK 1.67 [capable] for the validation batches versus PpK 0.33 [not capable] for the next 60+ batches).

A detailed investigation determined the two natural materials had the largest impact on capability performance and that varying levels of fats and protein from the natural materials performed differently during the different compression forces in the compression cycle. The investigation also revealed that the compression cycle impact on tablet quality was not proportional across strengths. Higher

compression forces on the higher-strength tablets had a magnified deleterious effect on tablet CQAs. Those differences exhibited variability in the CQAs within a batch (beginning, middle, and end), between batches, and between strengths. The CQAs were meeting specifications but required additional testing (S2, L2) to demonstrate acceptable product quality attributes. Significant variability between shifts was observed, indicating a technique-dependent process. The variability of the components in the natural materials had been observed and shown to be problematic in the manufacture of other dosage forms and should have been anticipated as a probable issue for this process.

My advice to avoid the revelation that "we have a validated process but not a capable one" is:

1. Understand what the data from the development activities is telling you and assess any trends from the development/transfer batches.
2. Do not rely on previously accepted concepts, such as that the lower strengths are the most challenging for control and capability, that three lots of critical materials (especially natural materials) are sufficient to demonstrate process capability and control, or that all strengths will behave the same during the manufacturing process.
3. Use advanced statistical models and multivariate analysis to understand the sources of variability and what controls are required to minimize the impact of those variabilities to keep the process in control.
4. Ensure all equipment has been qualified for its intended use and ranges and has been "broken in."
5. Use operators across all shifts expected to manufacture the dosage form.

In summary, if it can be demonstrated through scientific and statistical evidence that you have control and consistency of the critical materials and the different manufacturing processes, then you should have the confidence to initiate normal production activities. Best practices are to maintain a running statistical analysis to demonstrate continuous process verification and keep track of and investigate the source and cause of any trends or shifts in the data.

About The Author:

Michael Rutledge is a managing consultant at Tunnell Consulting. He has more than 35 years of experience in the life sciences industry, encompassing biologics, new drugs, generics, and devices. He has significant expertise in all technical and scientific functions (analytical, formulations, and processes) associated with the development and manufacturing of numerous dosage forms, delivery systems, and sterile environments. He has participated in most activities associated with approval of drug products in the U.S., Canada, and Europe. He can be reached at michael.rutledge@tunnellconsulting.com.

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