CONTINUED/ONGOING PROCESS VERIFICATION

by Pete Gough

The 2011 FDA Guidance on Process Validation and the recently issued revision of EU GMP Annex 15 require that manufacturers monitor performance of their processes throughout the commercial life of the product. The FDA calls stage 3 of its process validation "continued process verification," described as "An ongoing program to collect and analyze product and process data that relate to product quality…" The revised EU Annex 15 uses the ICH Q8 terminology of "continuous process verification" to describe the PAT approach to in-process monitoring during manufacture, and consequently calls the validation step analogous to stage 3 of the FDA guidance "ongoing process verification." While it is unfortunate that the language used by FDA and EMA is different, even confusing, the concepts are identical.

SOME DEFINITIONS:

- The FDA process validation guidance states that "The goal of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacture. A system or systems for detecting unplanned departures from the process as designed is essential to accomplish this goal."
- The revised EU GMP Annex 15 states "Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated."

WHAT DOES IT ALL MEAN?

- While the concept of continued/ongoing monitoring of a manufacturing process may be new to many in the pharmaceutical industry, it is virtually universal in other manufacturing sectors. It is sad that the science-led pharmaceutical industry has to be driven to do what is in its own best interest by regulatory guidance. Fortunately, thanks to others, the tools and techniques that are required are very well established and understood and are usually referred to as statistical process control (SPC) tools.
- Both FDA and EMA refer to the use of SPC tools. The FDA recommends "… 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." Similarly, the revised EMA guidance states that "Statistical tools should be used, where appropriate, to support any conclusions with regard to the variability and capability of a given process and ensure a state of control."

The three main SPC tools used for continued/ongoing process verification are control charts and process capability analysis to monitor release test parameters, and linear regression to monitor stability trends.

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THE CONCEPT – WHY BOTHER?

The concept behind continued/ongoing process verification as part of overall validation of a process is simple: You first establish a baseline of what is normal variability for a given process and then use the SPC tools to alert you to any significant departure from that baseline. A validated process should only have "common cause" variation (often colloquially called random variation) operating; it is then said to be in control. Departures from the baseline often occur when something changes introducing a "special cause."

Control charts provide an alert when a potential special cause enters a system. The related tool of process capability analysis compares the normal variability of a process to the specification limits to provide a measure of the probability of the process consistently meeting the specification. The tool that is employed to assess the rate of change of a specification parameter during a stability study is linear regression, as defined in ICH Q1E. For a process to be considered to be operating in a validated state it has to be in control and capable, and the stability profile should not be changing.

Today the calculations necessary to use these SPC tools are easily accomplished using one of the numerous software packages available. This also has the advantage of eliminating the all too frequent calculation errors that occurred when the calculations were performed manually.

CONCLUSIONS AND RECOMMENDATIONS

So continued/ongoing process verification is now a regulatory expectation, for both EU and US markets. Companies must have effective systems to capture the necessary data and perform the appropriate statistical analysis. Most companies who do this find that they generate valuable information that not only ensures that they comply with regulatory expectations but also allows them to improve their processes and reduce costs.

If you do not already have continued/ongoing process verification established as an integral part of the validation component of your quality system, then you need to take action now.

ABOUT THE AUTHOR

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