CONTINUED PROCESS VERIFICATION

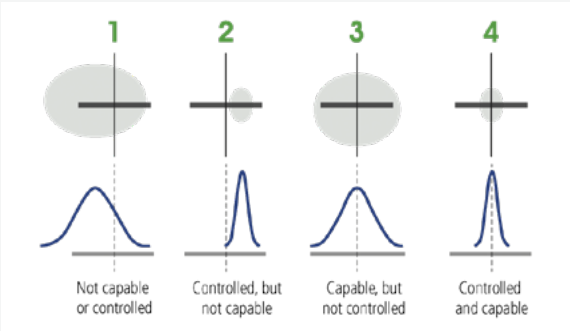
by Richard Kettlewell

In an earlier white paper, Continued/Ongoing Process Verification which can be found in NSF's resource library (**www.nsf.org/info/pblibrary**), Pete Gough introduced the regulatory expectations for Stage 3 of the process validation lifecycle. This article builds on that introduction and poses questions to pharmaceutical manufacturers as to how and why the concepts of Stage 3 could be built into pharmaceutical quality systems.

Arguably products and processes were always subject to development (process design), and since the advent of validation as a concept in the 1980s, we have always validated them – to a lesser or greater extent. So, Stages 1 and 2 of the lifecycle have always been around, as has Stage 3 – or at least the expectation for it and we have tested, reported, reviewed change and periodically reviewed product and process performance, haven't we?! The reality is that while we chose to believe that our annual or periodic review reports demonstrate the ongoing control and capability of processes, the brutal reality is that these reports are at best 12 months out of date, and any opportunity to leverage information about a batch manufactured 11 months ago evaporated as soon as the QC analyst recorded the batch as a pass!

The expectations have also been reinforced by the regulators:

- 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."*



Scenario 1: Further process understanding required to remove variability

Scenario 2: Process is well controlled with little variability, investigate how to re-center the process mean

Scenario 3: Process is controlled and well centered on its mean, investigate where sources of variability are occurring

Scenario 4: Process is well controlled, centered on its mean and highly capable

Figure 1.

Perhaps the consideration here should be how the industry can take more from the requirement to do Stage 3, and consider it not a retrospective look back at performance, but a forward-looking predictive and anticipatory view of how continuous improvements can be made to established processes.

The expectation from the regulators then is reasonably clear – Stage 3 needs to be data driven and provide ongoing confirmation that the product/process of interest remains controlled and capable (see Figure 1). The first requirement ***controlled*** can be taken as a direct reference to the control strategy being employed:

- How well do you understand what the patient/consumer needs (the quality target product profile, QTPP)
- What is important in the product (the critical quality attributes, CQAs) and
- What is important in the process that produces your product and its relationships to the CQAs (the critical process parameters, CPPs)?

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But the control strategy is more than just measuring CQAs and controlling CPPs; importantly to the regulators there are other sources of variability in the process, the so-called material attributes.

The second requirement ***capable*** could reasonably be taken as a direct request to calculate and monitor process capability, Ppk or Cpk, as indicators of how well a process is centered on its mean and, based on that, what capability the process has to produce consistently with minimal risk of producing defects.

The FDA is particularly interested in statistical evidence that the process remains controlled and capable, with sources of variability understood. For example:

Warning Letter 320-17-46 issued on Aug. 15, 2017 states *"Your firm does not have an adequate ongoing program for monitoring process control to ensure stable manufacturing operations and consistent drug quality." The response requested by FDA indicated that the manufacturer must "For each process, identify sources of variability in your raw materials and manufacturing process, and indicate the steps you have implemented to reduce variability or mitigate its potential effects on the quality of your products."*

The baseline for Stage 3 is clearly data and its timely analysis for underlying trends, shifts or excursions that could indicate that the process is in some way out of control or experiencing a variation either previously known or unknown. The value therefore is that Stage 3 offers the opportunity to react in a timely manner to prevent the potential loss of a batch or batches of product.

HOW OFTEN SHOULD THE DATA BE REVIEWED?

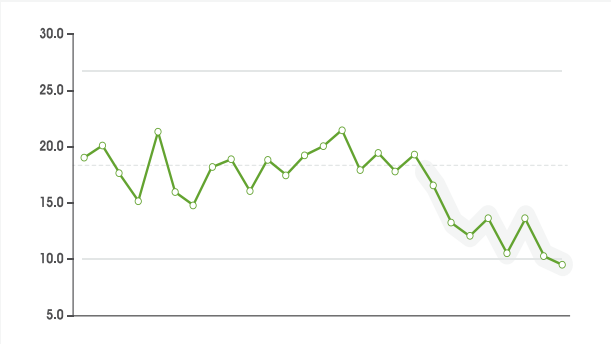
There is no single answer to this question, but the frequency of review should probably be commensurate with the rate of manufacture. If a product is only made once every three months, monthly review is not commensurate. Likewise, if a high-volume product is made twenty times a week, there is sufficient new information to support a weekly review.

WHO SHOULD UNDERTAKE THE REVIEW?

Again, no right or wrong answer, but it is important that ***someone*** does the review and that the business is aware of the output and motivated to take action when the product/process indicates it is in need of attention. Stage 3 provides the voice of the product – individual batches can only say ***pass*** or ***fail***, but when you listen to an ongoing sequence of batch data, the message can be very different (see Figure 2).

When considering the who, it could be useful to consider RACI:

R	**Responsible** – for providing data, reviewing data, reporting data
A	**Accountable** – for it happening
C	**Consulted** – when things look abnormal
I	**Informed** – all ok, not ok



In this sequence every batch passes spec, but the process is telling a different story.

Figure 2.

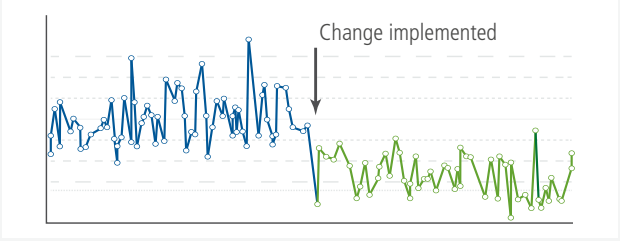
CAN DATA REVIEW BE USED IN A POSITIVE WAY TO ADD VALUE TO OTHER PHARMACEUTICAL QUALITY PROCESSES?

The short answer is yes. A well-conducted and documented data trending program has the potential to make the periodic validation review process easier, help justify requalification/revalidation frequency and provide significant input to the periodic product review process. Where automated tools are used to extract data from site systems to facilitate trending, it is feasibly a small step to automate a large section of periodic/annual product reports.

With regards to change control, it's a regulatory expectation for effectiveness checks as part of the overall

change management process. Data review can provide this post-implementation check and help illustrate that the desired change, (see Figure 3) or indeed no change, on process performance took place. How many validation exercises have been conducted in support of a supplier changing the site of manufacture for a particular excipient, when the impact on the product is expected to be absolutely zero?! Could it be feasible to write the validation exercise in a different way to leverage the Stage 1 knowledge and Stage 3 data trending to illustrate the expected change or lack of change?

The data review process can be used to help illustrate process understanding. FDA places significant emphasis on understanding the manufacturing process and factors that contribute to variability to ensure a robust process validation exercise. The knock-on effect from lack of process understanding is potentially an unexpected number of out-of-specification events for which root cause cannot be determined, or an unexpected number of lot rejections.



Positive demonstration of step change in process performance following introduction of change control

Figure 3.

WHICH ATTRIBUTES AND PARAMETERS SHOULD I TREND?

This comes down to product and process understanding, risk assessment and the question of available resources. The best answer is probably to trend everything, but clearly that is not practical in most cases. So, the answer is that risk assessment must be used so that those attributes and parameters that give indication of process change are most valuable for reviewing on a regular basis. For example, reviewing a set-point on a regular basis (e.g. adjust pH to 6.5) will most likely indicate a straight line on review and provide little information on the actual process. However, reviewing differential pressure across filter bags may correlate to the level of fines at discharge and ultimately impact product dissolution or compression performance. The value of Stage 1 manifests itself in Stage 3.

WHAT LIMITS SHOULD WE APPLY?

For an established product with a large body of data there is the opportunity to derive statistically-based warning limits, but for new products it is most likely that trending against specification limits is the sensible approach, until sufficient data has been collected to permit further assessment to be made (see Figure 4).

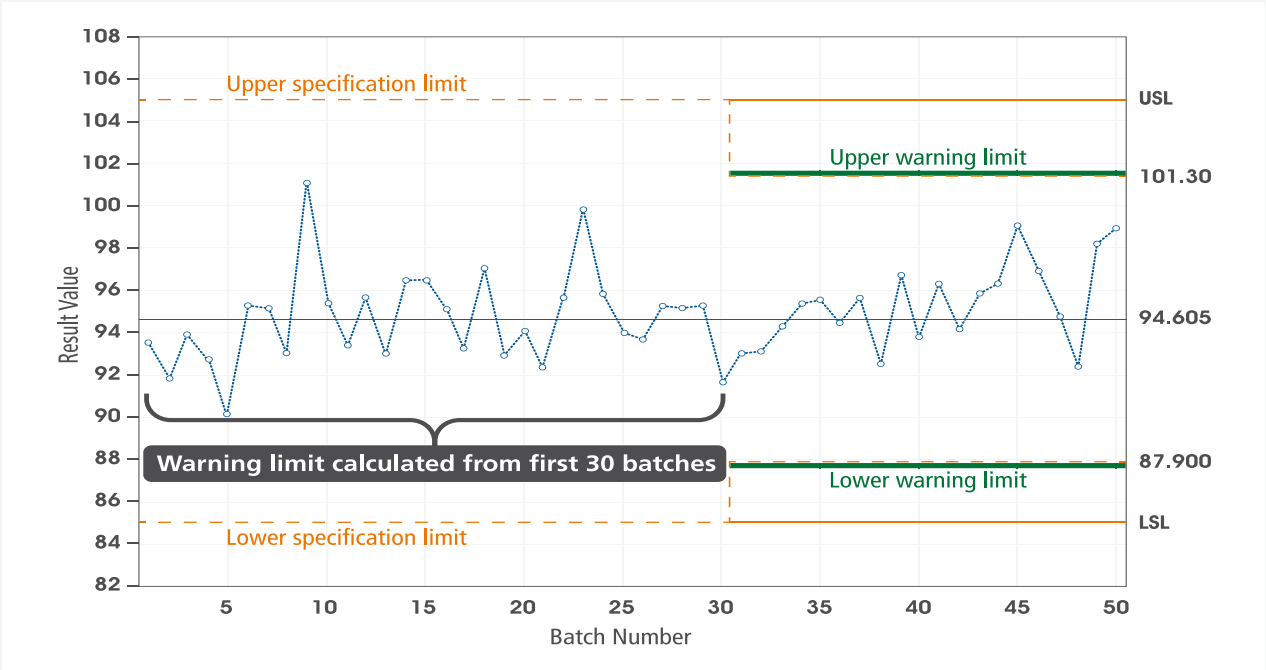


Figure 4.

ABOUT THE AUTHOR

Richard Kettlewell has over 30 years of experience in the pharmaceutical manufacturing sector. He has supported and inspected many sites of varied dosage forms worldwide.

Kettlewell has a master's degree in pharmaceutical sciences and joined the industry in 1986 at GlaxoSmithKline, where he spent 32 years in a number of QC, QA and technical roles. He spent time developing and implementing lifecycle approaches to process validation across the R&D and manufacturing organizations and supported a number of new products introductions for both API and secondary filing.

His areas of expertise include:

- Process validation Lifecycle – Stage one, two and three
- Validation strategy
- Commissioning and qualification
- Water systems
- Change control

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