

# FDA 2011 Process Validation Guidance: Process Validation Revisited

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This article is based on a technical training seminar presented to United States Food and Drug Administration policy advisors, management, and field staff in Silver Spring, Maryland, in May 2012. It summarizes the regulatory drivers that led to the publication of FDA's 2011 Process Validation Guidance for industry. In particular, the article emphasizes that process validation is a meaningful scientific endeavor that strives to ensure process control and product quality rather than a discrete and isolated activity. The article proceeds to describe practical steps that product manufacturers can take when applying the Guidance to both legacy and new product manufacturing situations. The article introduces the concept of "validation trilogies" as a proposed method of aligning the three inter-related stages of process validation (process design, process qualification, and continued process verification) with the key concept of product lifecycle. The article concludes with an exhortation to industry to capitalize on this updated view of process validation as a means to carry out sound, science-based process improvements and an integrated approach to product quality.

## AGENCY CONTEXT

### Background

In January 2011, FDA announced the availability of a final guidance for industry entitled *Process Validation: General Principles and Practices* (the 2011 Guid-

ance). The 2011 Guidance revises and replaces FDA's Guidance for industry entitled *Guideline on General Principles of Process Validation*, issued in May 1987 (the 1987 Guideline).

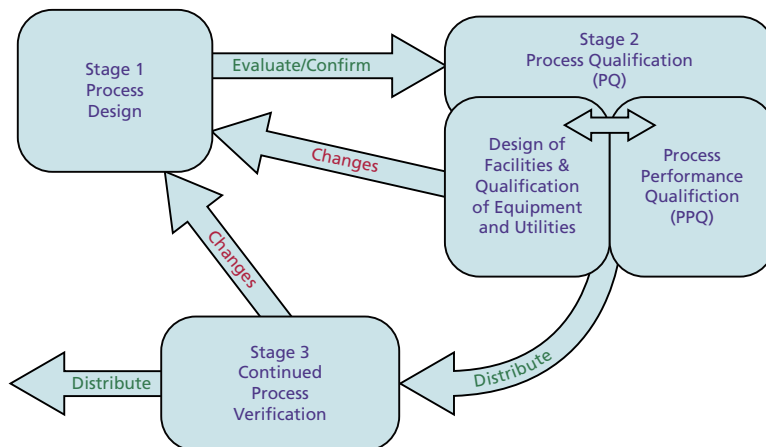
The 2011 Guidance defines process validation as "the collection and evaluation of data, from the process design stage through commercial production which establishes scientific evidence that a process is capable of consistently delivering quality product." The 2011 Guidance promotes a "lifecycle" approach to process validation that includes scientifically sound design practices, robust qualification, and process verification. In particular, the 2011 Guidance describes process validation activities in three stages:

- In Stage 1, process design, the commercial process is defined based on knowledge gained through development and scale-up activities.
- In Stage 2, process qualification, the process design is evaluated and assessed to determine if the process is capable of reproducible commercial manufacturing.
- In Stage 3, continued process verification, ongoing assurance is gained during routine production that the process remains in a state of control.

In addition to discussing activities typical of each stage of process validation, the 2011 Guidance provides recommendations regarding appropriate documentation and analytical methods to be used during process validation. Figure 1 illustrates how the three stages of process validation relate to one another and

**Figure 1:**

Stages of process validation. Used with permission of Grace E. McNally.



to the actions taken during and after each stage.

### Regulatory Drivers and Expectations

Nearly a quarter of a century elapsed between the time FDA first issued the 1987 Guideline and the publication of the 2011 Guidance. The 2011 Guidance is entirely consistent with the basic principles of process validation articulated in the 1987 Guideline—and indeed, with principles imbedded in the current good manufacturing practice (cGMP) regulations in *21 Code of Federal Regulations (CFR)* Parts 210 and 211 as published and described in the 1976 preamble to those regulations. Nonetheless, more than 25 years worth of experience and regulatory oversight, along with the cGMPs for the 21st Century Initiative (1), prompted FDA to revisit the principles and concepts in an effort to update and clarify FDA’s thinking on process validation.

Among other motivating factors, FDA sought to emphasize process design and maintenance of process control during commercialization. By aligning process validation activities with a lifecycle approach, the 2011 Guidance communicates that process validation is an ongoing program rather than a discrete and isolated activity. Under the 2011 Guidance, process validation is presented as a series of activities that manufacturers carry out over the lifecycle of the

product and process. This view of process validation underscores the importance of detecting, understanding, and controlling sources of variability over time in order to consistently produce safe, effective drugs that meet all quality attributes. In turn, the emphasis on understanding and controlling process variability leads to a clarification that FDA expects manufacturers to employ objective measures and appropriate statistical tools and analysis.

Again, none of these concepts are new to process validation. Rather, the 2011 Guidance reinforces central themes of the cGMP regulations that drive successful process validation and the production of quality products over time. The 2011 Guidance underscores the link between process validation and existing regulations such as the following:

- § 211.100(a) requires “written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess...” Manufacturers are required to design a process, including operations and controls that yield a product meeting these attributes.
- § 211.110(a), sampling and testing of in-process materials and drug products, requires that manufacturers establish control procedures “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.” From a process validation perspective, even well-designed processes must include in-process control procedures to assure final product quality. Furthermore, § 211.110(b) requires that in-process specifications be “derived from previous acceptable process average and process variability estimates where possible and determined by the application of suitable statistical procedures where appropriate.” Manufacturers must continually analyze process performance and control batch-to-batch variability using appropriate statistical techniques.

- Sampling methodology becomes a key factor in carrying out process validation insofar as it concerns monitoring and evaluating variability, especially in process qualification (Stage 2) and continued process verification (Stage 3). cGMP regulations specify that samples must:
  - Represent the batch under analysis (§ 211.160(b)(3)).
  - Meet specifications and statistical quality control criteria as condition of approval and release (§ 211.165(d)).
  - The batch must meet its predetermined specifications (§ 211.165(a)).

Finally, § 211.180(e) requires that information and data about product quality and manufacturing experience be evaluated at least annually to determine the need for changes in specifications or manufacturing or control procedures. Regular review and analysis of product quality and process performance data to monitor trends is, by definition, an essential feature of continued process verification.

## MISCONCEPTIONS ABOUT PROCESS VALIDATION

### Validation Protocols and the “Rule of Three”

In addition to revisiting important long-standing principles of process validation by linking them to regulatory requirements, the 2011 Guidance dispels

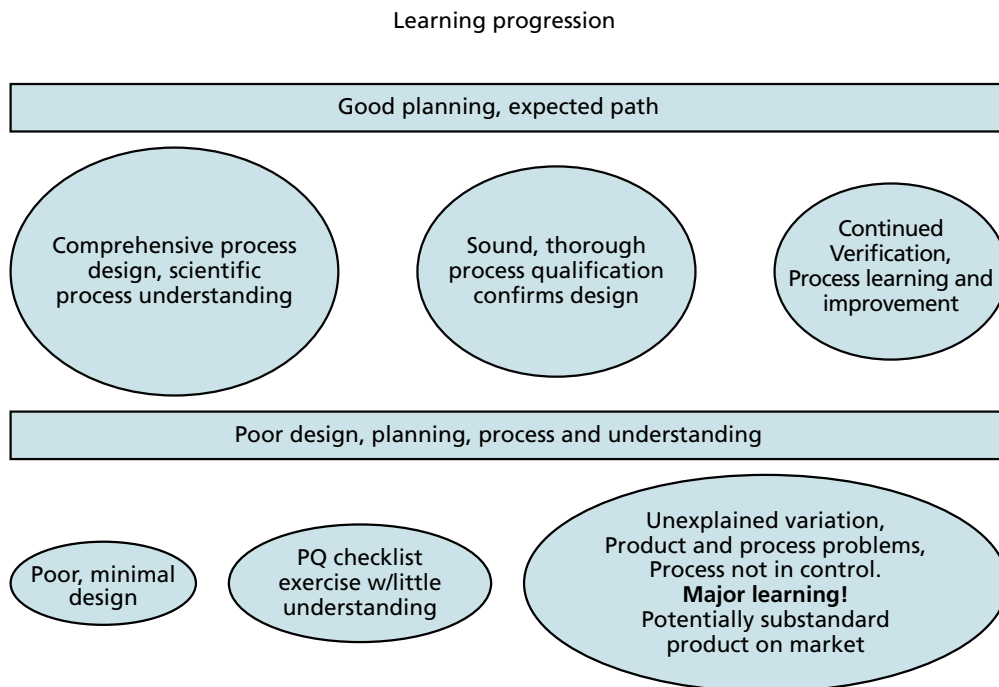
common misconceptions about process validation. One of the most widely-discussed has been the rebuff of process validation’s (perceived) three-batch requirement. Prior to the issuance of the 2011 Guidance, “...it was widely accepted throughout industry, and, indeed, implied or stated in some FDA guidance documents, that process validation was a static, three-batch demonstration event. (2)”. With the advent of the 2011 Guidance and its emphasis on design, lifecycle, and control of variability, the “rule of three” has been effectively rejected. Although some may harp at the idea that there is no longer a magic number, FDA’s position remains that there never was a three-run requirement in the first place. Despite the pervasive practice of three-batch validation, note that even the 1987 Guideline used the following language to describe the validation protocol:

“It is important that the manufacturer prepare a written validation protocol which specifies the procedures (and tests) to be conducted and the data to be collected. The purpose for which data are collected must be clear, and data must reflect facts and be collected carefully and accurately. *The protocol should specify a sufficient number of replicate process runs to demonstrate reproducibility and provide an accurate measure of variability among successive runs.*”

The 2011 Guidance is deliberately less prescriptive than the 1987 Guideline. Under the 2011 Guidance, the process performance qualification protocol need not specify the number of batches to be performed. Instead, the 2011 Guidance describes how manufacturers should develop a protocol that builds upon process design knowledge to identify criteria and process performance indicators that allow for science and risk-based decision-making about the manufacturing process. Does the process consistently produce quality products? Is it in a state of control? The 2011 Guidance emphasizes documenting and evaluating evidence that answers these questions rather than satisfying a three-batch checklist. The notion that manufacturers must make deliberate, rational decisions about whether their specific processes are validated and their products ready for commercial release is hardly new. As

**Figure 2:**

Process validation learning progression (2). Used with the permission of Grace E. McNally.



the 2011 Guidance states, “[f]ocusing exclusively on qualification efforts without also understanding the manufacturing process and associated variations may not lead to adequate assurance of quality.” Accordingly, the 2011 Guidance recommends an approach to process validation that is tailored to and based upon up-front learning and knowledge about the product and process rather than simply getting to the goal of three acceptable batches (see Figure 2, below).

### “Criticality”–Revisiting Attributes and Parameters

Another important change in the language adopted by the 2011 Guidance is the notion that criticality is a continuum rather than a binary (“yes or no”) state. The 2011 Guidance does not designate specific attributes and parameters as “critical.” Instead, the 2011 Guidance stresses the need to exercise control over attributes and parameters commensurate with their risks to process variability and

output. Because the 2011 Guidance is based on the premise that process validation must be tied to product and process lifecycle rather than a static event, different attributes and parameters may have different roles in the process. These may pose greater or lesser risks to product quality over time, and manufacturers are expected to reevaluate the level of risk assigned to attributes and parameters as new information becomes available and respond accordingly. Again, this expectation implies that process validation is an on-going practice rather than a single event. Viewing process validation in this light facilitates process improvements that can in turn improve product quality.

### Use of Statistics in Process Validation

An additional item of note in the 2011 Guidance is its emphasis on the use of statistics. As with other elements of the 2011 Guidance, FDA’s choice to underscore the importance of using statistical analysis

in process validation is hardly a new idea. Indeed, the cGMPs discussed above indicate that the use of statistical tools and analyses is a required part of compliance with the cGMPs for drug manufacturing. The 2011 Guidance reminds manufacturers of this requirement and reaffirms the role that statistics can and should play in all three stages of process validation. Again, FDA is not prescriptive about this issue. The 2011 Guidance references a number of acceptable industry standards but clarifies that manufacturers must make deliberate decisions about which statistical tools and analyses are appropriate for their products and processes. Choosing suitable statistical tools depends on factors such as the size of the data set, and the selection of variables, attributes, and parameters being used to make inferences about process performance (process capability and process stability) and product quality.

### ENFORCEMENT STRATEGY AND STATUS

As illustrated above, process validation has always been and continues to be an enforceable cGMP requirement. Moreover, the 2011 Guidance, like all FDA guidance documents, represents the current thinking on the topic and does not create or confer any legal rights or obligations. Nothing about the 2011 Guidance changes FDA's enforcement policy with respect to process validation in a strict sense. Rather, the expectation is that the 2011 Guidance provides greater clarity regarding FDA's expectations and the types of activities that firms should conduct during each of the stages of process validation.

A review of inspectional observations and warning letter citations since the publication of the 2011 Guidance indicates that FDA has continued to cite firms for process validation deviations across a wide range of product and facility types. Among the most-frequently cited regulations are 21 CFR § 211.100(a) and § 211.110(a)-(b). The former is typically invoked when product quality issues and failures can be linked to stage 1 errors (poor process design). For example, warning letters have cited 21 CFR § 211.100(a) for "inadequate" process validation efforts that relied on incomplete validation reports, such as reports that failed to include and evaluate all

deviations observed during process validation. This cGMP regulation has also been cited in situations where firms released product despite revalidation efforts that failed to demonstrate process robustness. In some cases, firms have responded to inspectional observations with claims that they had "controls" in place to control for process variability, but ensuing warning letters cited 21 CFR § 211.100(a) on the grounds that such controls for variability had not been deliberately and prospectively assessed in process validation studies. In such cases, firms relying on the recommendations in the 2011 Guidance might have fared better if they returned to the stage 1 "drawing board" upon discovering significant problems during process qualification, rather than reaching premature conclusions about process capability and performance and distributing product to the market (see Figure 1).

In the context of process validation, another commonly-referenced regulation is 21 CFR § 211.110, often in connection with missteps observed during stages 2 and 3. For example, many firms utilize standard operating procedures (SOPs) in routine commercial production that permit batch release outside of established in-process specifications. Consider the continued process verification (stage 3) implications of a SOP allowing for drug product batches to be released despite some level of failures of in-process testing. There is nothing inherently wrong with such SOPs, but in the context of process validation and depending on the facts of the case, such SOPs could lead to a violative situation. Under 21 CFR § 211.110(a), manufacturers must establish control procedures that monitor the output and validate the performance of manufacturing processes that may cause variability in the characteristics of in-process material and the drug product. Even if the SOP discussed above conditioned batch release on the proviso that no more than a certain number of units failed to meet specification, then a pre-determined level of in-process specification failures would also need to trigger follow-up investigation(s) to determine the root cause of process failures as part of the firm's process control and monitoring program for cGMP compliance.

From a process validation standpoint, the inability to quickly detect unreliable batch operations and correct deviations has a clear impact on product quality.

Finally, the link between process validation and in-process specifications is also apparent in citations and observations related to 21 CFR § 211.110(b). For example, § 211.110(b) might be cited when firms blindly refer to or rely on statistical methods and tools, (e.g., using process capability index ( $C_{pk}$ ) values without previously demonstrating statistical control, understanding the distribution of underlying data, etc.), to suggest that a process is in control in spite of observed specification failures or variability. This type of post-hoc rationalization is tantamount to “testing into compliance,” and it is not adequate under the regulations. Using statistics alone is insufficient; such tools must be applied appropriately in order to provide valuable and meaningful inferences about the state of control for a given process and the quality attributes of the products within and between batches. The 2011 Guidance affirms the regulatory requirement that firms make deliberate decisions about use of statistics in light of their own products and processes, and that controls and variability should be assessed through completion of successful process validation studies.

As industry becomes more familiar with the 2011 Guidance and with FDA’s recommendations for executing and demonstrating process validation, firms should be better able to show that they understand how process inputs and parameters impact the safety, efficacy, and quality of drug products. Successful process validation is a matter of carrying out comprehensive design work, executing qualification efforts that employ meaningful performance criteria and extend beyond rote checklist exercises, and implementing process monitoring programs that offer useful information about whether or not the process remains in control (see Figure 2). Manufacturers that can document these important steps and the knowledge gained from them in a systematic way will find themselves not only better

equipped to address FDA’s questions about process validation activities, but, more importantly, better able to utilize their own data and process understanding to improve quality over the lifecycles of their products.

## INDUSTRY IMPLEMENTATION

This section proposes a practical view on how manufacturers might carry out some of the 2011 Guidance’s recommendations.

### Getting Started

Unit operations (or process steps) constitute the central spine of both the manufacturing and validation process, and are emphasized accordingly within the Guidance. This is good news for manufacturers, and provides the first step in a systematic response. Using a limited number of unit operations as building blocks, complex manufacturing processes can be designed, qualified, and verified across each of the three stages of process validation. These building blocks (c. 20-25 per process) represent the foundation layer of the platform-driven strategy articulated here.

Figure 3 is a simple but effective example of how this can be implemented in practice. There is nothing fundamentally new here, except for the fact that the Guidance introduces some alternative terminology, and that the proposed framework is depicted pictorially.

The approach can be summarized as follows:

- The purpose of a unit operation is to deliver or protect some aspect(s) of the target product profile (also known as attributes at risk).
- The identification and management of significant variables constitutes the control strategy for the unit operation.
- Significant variables can entail equipment monitoring (EM), material analysis (MA), or quality control (QC) testing.
- Process analytical technology (PAT) is treated as a means to an end, rather than a variable per se, within the framework. PAT does not replace required in-process testing and finished product release testing, although it can provide real-time data for use in such cGMP tests.

**Figure 3:**

Process validation framework.

Unit Op _____			ATTRIBUTE @ RISK				
			Identity	Strength	Quality	Purity	Potency
SIGNIFICANT VARIABLE	EM	EM-1				X	
		EM-2		X			
		EM-3					
		EM-4				X	
	MA	MA-1			X		
		MA-2	X				
		MA-3					
		MA-4					X
	QC	QC-1		X		X	
		QC-2			X		
		QC-3	X			X	
		QC-4			X		

PAT

- The compilation of control strategy commitments can be prospective or retrospective (new versus legacy products), and be based on a combination of manufacturing experience, technical literature, quality by design, risk analysis, etc.

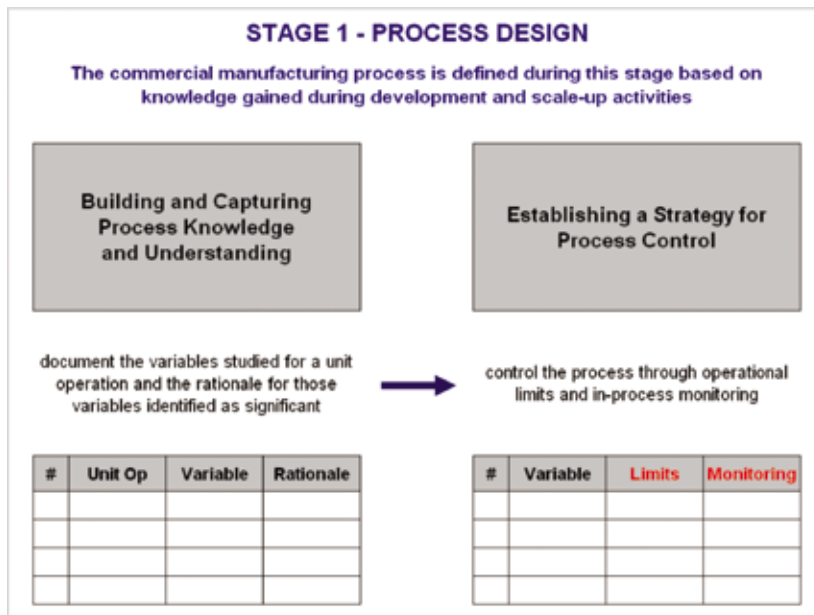
Diagrams such as Figure 3 above can be readily customized based on specific requirements of particular products. Identity/strength/quality/etc. are more accurately defined as “super-attributes,” in most cases referencing a number of sub-attributes, also known as critical quality attributes (chemical, physical, microbiological). These items can be explicitly named and further quantified within the cells of the matrix. Support processes are also amenable to a similar level of analysis. Equipment monitoring equates to what are traditionally known as critical process parameters within the industry. Material analysis (for in-process materials) equates to what are traditionally known as in-process controls. Note that incoming materials must also be in a state of control; the default industry response to this item is based on a combination of supplier audits, quality agreements with suppliers, certificates of analysis, raw material testing, and related monitoring programs.

### Stage 1–Process Design

Stage 1 involves the itemization of significant variables and their rationales for each of the process’s unit operations, followed by the definition of operating limits and related monitoring requirements/techniques for each variable. As previously indicated, associating variables with unit operations can be a largely generic activity, whereas the definition of operating limits and methods of monitoring is more context specific. As can be seen from Figure 4, stage 1 has its own internal lifecycle, with the names of the significant variables normally being known in advance of the associated operating limits. What the diagram depicts, and what the Guidance invokes, is the beginning of a structured and interconnected chain of validation evidence.

The extent to which rationales should be provided is a vexed issue. Cogency and consistency work best, the objective being to demonstrate and justify the linkage between significant variables and quality attributes, (i.e., this variable protects or jeopardizes this attribute, the rationale being underpinned by risk assessment). The linkages can be derived empirically, and do not necessarily imply full-blown quality by design. Note also that from the point of view of a standardized response, pharmaceutical manufacture

**Figure 4:**  
Stage 1—Process Design.



is comprised of a relatively small number of variable types (10s rather than 100s), many of which are shared across unit operations and processes—not to mention organizations.

### Stage 2—Process Qualification

Stage 2 is a seamless extension of stage 1, and involves the definition and execution of a testing strategy on behalf of the variables itemized and quantified in stage 1. As with stage 1, stage 2 also has its own internal lifecycle, approximating to the acceptance criteria, protocol preparation, protocol execution, and report aspects of traditional validation. What the 2011 Guidance is emphasizing here, to the dismay of diehards, is that a testing strategy is only as good as the corresponding sampling and analysis commitment, and that assertions to the effect that “this process is validated” only carry weight if all of its significant variables are in a state of control. This is conveyed schematically in Figure 5.

Many organizations are of the view that GMP compliance will continue to require three ubiq-

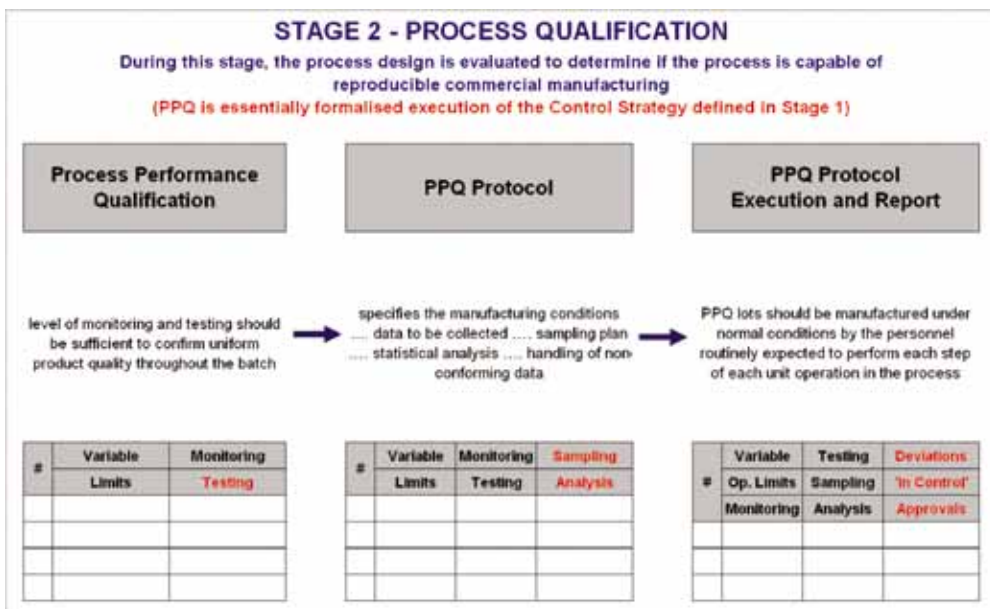
uitous validation batches, particularly during the transition phase. In such situations, carrying out the recommendations envisioned by the 2011 Guidance is based on the proviso that the validation report makes a commitment to an ongoing monitoring and review program. On that basis, processes can be provisionally declared to be “in control” relative to the level of evidence available when the declaration was made. This is a key aspect of the 2011 Guidance; validation is an unequivocal function of time and the inferences permissible based on the available data.

In regard to satisfying the “in control” expectation, what this means in practice is that control charts can be initiated for all significant variables during stage 2, and this continues until a sufficient number of batches have been manufactured to enable a declaration to be made to the effect that “this process is currently capable—for these variables.” This is easier said than done when dealing with low volume products and statistically insignificant datasets. In such cases, statistical inferences should not



**Figure 5:**

Stage 2—Process Qualification.



be contrived, but the spirit of the 2011 Guidance can still be satisfied and defensible conclusions drawn, to the effect that “these variables are within their operational limits—and therefore in a state of control, at this time.”

Fitness for purpose of facilities and equipment is an obvious prerequisite of process qualification. The 2011 Guidance actually incorporates this as a stage 2 activity, but it has been excluded from Figure 5 above for the sake of simplicity. The key point here is that systems and components must (as was always the case) be suitable for their intended use and perform properly. Taking metrology as an example, the “intended use” stipulation merely means that instruments have been specified, calibrated, and maintained relative to their process duty, namely the measurement/control of significant variables with defined tolerances. This also squares the circle in regard to instrument “criticality,” such instruments being those that measure or control significant variables. Note that the 2011 Guidance is non-committal in regard to qualification tech-

nique, allowing manufacturers deliberate scope in this area.

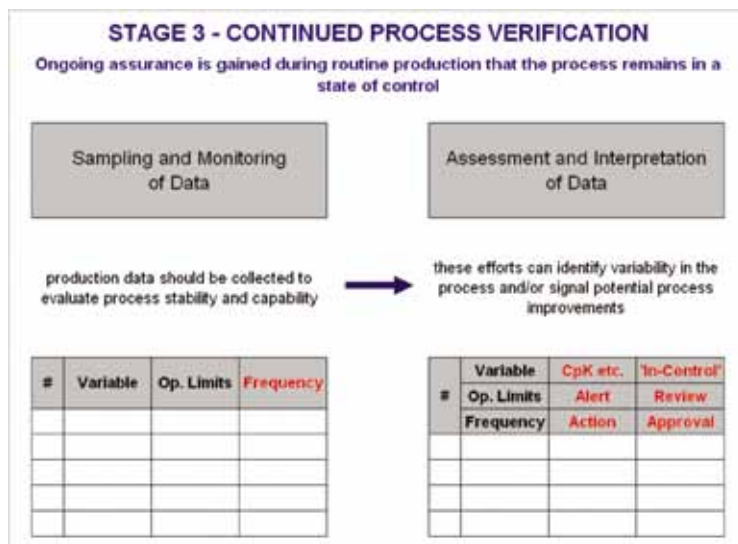
### Stage 3—Continued Process Verification

Stage 3, while conceptually straightforward, is proving to be problematical for a number of manufacturers. This is due in part to the perception that the requirement for process monitoring is totally new. The 2011 Guidance merely formalizes what was always an implicit expectation. Significant variables quantified at stage 1 and qualified at stage 2 should be subject of continued process verification (CPV) during routine manufacturing at stage 3. The expectation is summarized schematically in Figure 6.

A logical strategy in regard to stage 3 implementation takes the following course. As part of the “handshake” between stage 2 and stage 3, continue monitoring all significant variables until sufficient data has been acquired to enable process capability to be declared, the default monitoring frequency here being “every batch.” Take remedial action for any rogue variables in parallel with the monitoring

**Figure 6:**

Stage 3—Continued Process Verification.



effort. Assess the data on completion, and confirm that all variables are “in control”. For each unit operation, select one or two leading variables, (i.e., those that are predictive of process performance or process distress). Focus the ongoing stage 3 monitoring program on these variables, along with any “intensive care” variables that may also be in play. Continue to capture process performance for the remaining variables via the batch record or its attachments. Once sufficient data have been acquired, assign alert/action limits for leading variables. Using manual or automated data acquisition procedures, monitor these variables for stability (i.e., absence of drift) as well as capability (i.e., within operating limits) as close to real time as is practical. Recalculate alert/action levels once sufficient data become available, not simply on a quarterly or annual basis. Synchronize the above efforts with the facility’s alarm management, event logging, and dashboard systems, these items being considered as facilitators of stage 3.

This is another key aspect of the 2011 Guidance; the review process is dynamic and data-driven rather than static and document-based. That is not to say that validation has suddenly become docu-

ment free, but rather that the documented evidence of compliance with process validation regulatory requirements is migrating to a data-centric representation, whether this be captured in hard copy or electronic format.

When implementing stage 3, manufacturers should consider the semantic difference between the terms “continued” and “continuous”. The 2011 Guidance deliberately speaks to continued process verification, which some organizations have misinterpreted to mean continuous, with mandatory enablement via PAT. The expectation is decidedly *not* that in-process or release testing required under the cGMP regulations be replaced by PAT approaches. Rather, the expectation is for ongoing, (i.e., inter and intra-batch, monitoring, and review).

Process owners are encouraged to compile inter-batch data registers for their significant variables, these forming the basis of CPV control charting and process monitoring programs. Process owners should also reflect on the term “significant” when designing their CPV programs. With “significant” comes “significance,” the implication being that material attributes, process parameters, and in-

**Figure 7;**

Process validation trilogy.

STAGE 1 - PROCESS DESIGN	
<b>Building and Capturing Process Knowledge and Understanding</b> <u>significant variable &amp; rationale</u>	<b>Establishing a Strategy for Process Control</b> <u>&amp; operating limits &amp; monitoring</u>
STAGE 2 - PROCESS QUALIFICATION	
<b>Design of a Facility and Qualification of Utilities and Equipment</b> <u>&amp; fitness for purpose</u>	<b>Process Performance Qualification</b> <u>&amp; testing</u>
<b>PPQ Protocol Preparation</b> <u>&amp; sampling &amp; analysis</u>	<b>PPQ Protocol Execution and Report</b> <u>&amp; 'in-control' &amp; approvals</u>
STAGE 3 - CONTINUED PROCESS VERIFICATION	
<b>Sampling and Monitoring of Data</b> <u>&amp; frequency &amp; alerts &amp; actions</u>	<b>Assessment and Interpretation of Data</b> <u>&amp; capability &amp; stability &amp; review</u>

process controls are no longer monitored in isolation, but visibly correlated against the associated product attributes that they are intended to deliver or protect. There is ample opportunity for imaginative and ergonomic control chart design and revision here.

Manufacturers should not be intimidated by the degree of statistical know-how that compliance with the relevant process validation cGMP regulations and recommended stage 3 activities may seem to imply. As a benchmark, early warning track and trigger systems have been in place within the clinical setting for many years, with relatively little by way of statistical sophistication (e.g., “contact doctor for early intervention if patient triggers one red or two amber scores at any one time”). For all their simplicity, such systems really do pack a punch, capturing multiple variables, including risk categories, alert levels, and response mechanisms within a single chart. CPV 101 can follow a similarly frugal course, with specialist support from in-house or contracted statistical resource being provided as required.

### PROCESS VALIDATION TRILOGIES—PER SIGNIFICANT VARIABLE

From a manufacturer’s point of view, implementing a new guidance typically involves fine-tuning or modifying existing policies and procedures. Depending on the level of validation maturity within the organization, such an approach may not always be sufficient or appropriate. The traditional approach to compliance is based on an established lifecycle, with the phases of validation occupying pole position within the model. Because these phases are disconnected in time, manufacturing systems and processes, and their significant variables, reappear in a diversity of plans, protocols, and reports, often inconsistently and incompletely across their lifecycles.

From a knowledge management perspective, such fragmentation is counterintuitive and not conducive to process understanding or economy of compliance. The emergence of the 2011 Guidance provides industry with an opportunity to reassess the suitability of existing methods to satisfy the requirements of a risk-based approach. For example, the simple manoeuvre of flipping the X and Y “axes” of the cur-

rent model (such that X = significant variable and Y = validation phase) results in all of the expectations of the 2011 Guidance being immediately facilitated (see Figure 7).

As a result of this inversion, significant variables become the dominant item within the lifecycle, with the phases of validation providing the requisite books of evidence (also known as trilogies) on a subordinate basis. The fact that the three chapters of a variable's biography are written sequentially rather than simultaneously—or in reverse order for legacy products—is a technicality. And again, there is nothing radically new here, the proposal being in total accord with a V-model approach.

The challenge/opportunity for industry is to cultivate a mindset that is prepared to revisit those aspects of validation practice that are proving to be inadequate or unfit for current purpose. Manufacturers have little trouble in assembling libraries of documentation for the many thousands of technical items within their care. It should not be too arduous to compile a more compact and informed narrative that provides accurate line-of-sight for significant variables across their lifecycles. Whether such an initiative constitutes incremental or step change is for readers to consider.

## CONCLUSIONS

FDA's 2011 Guidance on Process Validation sets out a framework that is entirely consistent with longstanding principles and existing regulatory requirements. By aligning process validation activities and expectations with the lifecycle concept, the 2011 Guidance offers a perspective that underscores the importance of risk and science-based decision making from the outset of product design, through process qualification, and into continued process verification. The 2011 Guidance illustrates that using objective measures to detect, understand, and control sources of variation can ultimately improve product quality and safety over time. Industry for its

part is encouraged to avail of the opportunities for streamlined compliance that the new Guidance invites. Manufacturers with a thorough understanding of their processes and platforms, supported by an interconnected and systematic approach to the information lifecycle, have nothing to fear from the arrival of the Guidance. Defining and cross-correlating significant variables in the first place, and monitoring/improving their performance across time in the second, is a highly logical and valued-adding activity that should be shared by process owners and quality units in order to reduce negative quality outcomes and improve process performance.

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2. FDA, "SUPAC-IR Questions and Answers about SUPAC-IR Guidance," 1997, available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm124826.htm>. (See, e.g., "SUPAC-IR Questions and Answers about SUPAC-IR Guidance," describing the "first three production batches" as "validation batches;" *Guide to Inspections of Oral Solid Dosage Forms Pre/Post-Approval Issues for Development and Validation*, 1994, available at <http://www.fda.gov/ICECI/Inspections/InspectionGuides/ucm074928.htm>, indicating that "at least three batches are needed to demonstrate consistency."). **GXP**

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