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CONCEPT OF QUALITY BY DESIGN FOR PROCESS VALIDATION: A REVIEW

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Abstract: The new definition for process validation is a significant paradigm shift from the original concept, embracing the basic principles of scientific understanding put forth in ICH Q8 and Q9 as a foundation for controlling process variability. The challenge most organizations will have with this new guidance will be assuming responsibility for defining what is scientifically acceptable for characterizing the sources of process variability. This article will present a roadmap that is both practical and scientifically sound, for deploying a process validation program that is consistent with the new guidance. In our experience, the biggest challenge facing organizations attempting to bridge the classical paradigm of "*three batches and we're done,"* is in understanding how the new process validation stages work together to build the argument for process predictability.

Keywords: Process variability, Process validation, Process predictability, Three batches

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INTRODUCTION

The new process validation[1] uses the basic principles of scientific understanding put forth in ICHQ8—the foundation of Quality by Design (QbD)—to establish process understanding and link it to product reproducibility. So simply put, the new process validation guidance will make it much easier to justify moving toward QbD.

The challenge most organizations will have with this new guidance will be assuming responsibility for defining what is scientifically acceptable for characterizing the sources of process variability. This article will present in both practical and scientifically sound, for deploying a process validation program that is consistent with the new guidance.

Figure 1: Quality by Design Model

The new guidance divides process validation into three stages[2]:

- Stage 1 **Process Design[3]:** The commercial manufacturing process is defined during this stage.
- Stage 2 **Process Qualification:** The process design is evaluated to determine if the process is capable of reproducible commercial manufacturing or not.
- Stage 3: **Continued Process Verification:** Ongoing assurance is gained during routine production that the process remains in a state of control.

Figure 2: Process Validation Frame work

Product Design: (Stage - I)

Process predictability relies on understanding what is important to process predictability and product performance. Having an awareness of the formulation and product design rationale is essential to achieving that level of understanding. The formulation will provide an early look at to what processing steps may become critical downstream and hence become sources of dissimilarity in the process. The product design rationale will define how the formulation, raw materials and processing steps are related to achieving the desired product performance.

All projects begin with a summary of the target product performance qualities that are the foundation for the formulation activity. Interpreting the role of each component within the function of the dosage form should include material characterization activities that could influence processing such as particle size, solubility, melting point, bulk density, presence of polymorphs in the drug substance, loaded dose, etc. Ideally, a review of product design should also extend to knowing the basis for the in-vitro product release specifications and any in-process control measurements.

Process Design-Process Risk Assessment

A process risk assessment is a very effective way to connect the product design, process unit operation and final product performance critical quality attributes (CQAs). In this step a tiered risk assessment approach can be used to identify potential sources of variability before beginning process characterization studies.

The risk assessment can be divided into two parts.

1. Equating each process step against the defined CQAs is to identify which process steps would require confined process characterization studies.

2. Emphasis on the potential effects on the process parameters.

Any parameters identified as having a high potential impact on CQAs can be targeted for further study.

Process Characterization: Knowledge Space, Design Space, Control Space[4]

Looking at the basic principles of ICH Q8 guidelines, the guidance describes a tiered exercise in which process understanding and variability is systematically narrowed as the process definition moves from the knowledge space through the design space to the control space used for manufacturing. Characterization studies need to be balanced in their experimental design. This means that early **one-factor-at-a–time** (OFAT) studies can serve as supportive data for the design of these experiments but that characterization studies should be balanced or "orthogonal" when it comes to determining the contribution to process stability from critical input parameters. While the number of lots will increase during this phase, the smaller scale studies provide the opportunity for larger sampling plans and greater process characterization would be required for full-scale batches.

Characterization studies are based on several factors:

a) Sampling Plans

b) Sampling Technique

c) Method robustness

a) Sampling Plans

Designing a sampling plan that has the appropriate outcome to describe the process variability is important for building confidence as the process scales up and moves to validation. There is no appropriate approach for determining the sampling plan. The FDA does not legislate a

specific approach to establishing a sampling plan. Whatever approach has been selected, however, must have a clearly defined underlying principle behind it. Possible sources and approaches for developing a sampling plan include PQRI recommendations for powder processes, Acceptable Quality Level (AQL), Lot Tolerance Percent Defective (LTPD), or the Operating Characteristic (OC) curve. There is no right or wrong answer, but whatever sampling plan is developed must be defendable based upon the level of resolution necessary to see variation in the process.

b) Sampling Technique

Although the equipment may not reflect the sampling challenges at full scale, demonstrating that sampling and storage methodology does not introduce variability into the process it is a precursor step to performing characterization studies. A Gage Reliability and Reproducibility (GRR) study would be an effective way of demonstrating the sampling technique is robust.

c) Method Robustness

Typically, analytical and in-process methods are validated at this stage but it is important to ensure the accuracy and precision of the method itself. Making sure the measurement tool is capable of seeing the differences in the process performance which is being evaluated. It is necessary to know that you are characterizing process variability and not measuring noise.

Design Space Establishment

To identify the limitations and variables that drive process stability it is possible to focus only on the parameters that steer the process and the corresponding Key Process Output Variables (KPOV) which affect the product Critical to Quality (CTQs). The design space will deal with the boundary limits of the parameters that are critical to process stability. Identifying the Key Process Input Variables (KPIVs) of interest can be achieved using a combination of a balanced Design of Experiments (DOE) approach and statistical analysis, such as Analysis of Variance (ANOVA) to summarize the contribution of each variable to the variation seen in the data being analyzed.

Process Qualification: (Stage – II)

Before moving to this phase there are several critical precursors.

i. The facility and its supporting critical utilities must be in a state of control.

ii. The equipment must be qualified-meaning the IQ, OQ and PQ are all should be complete.

iii. The in-process and release methods used for testing must be validated, and their accuracy and precision well understood, in terms of the final control space being evaluated.

These steps are essential to ensure that the unknown variability we are evaluating is attributable to the process alone.

The new guidance introduces a new term **Process Performance Qualification**[5] (PPQ), in lieu of process validation for process demonstration. The PPQ is intended to consider all of the known variability from the manufacturing process and demonstrate that the process predictability is sufficient to ensure that the product performs as it claims to do. In this case, the big departure from past process validation approaches is that it is the cumulative understanding from **process design** and **process qualification** that drives the decision that the process is anticipated. The consistency applied in **process design** will dictate the level of characterization, sampling and testing required in **process qualification**. Dedicated focus in **process design** will result in reduce **process qualification** cost and timeline impact.

The process performance qualification exercise focuses on **demonstrating process control**. Data from platform formulations and unit operations can be used to manage the risk moving forward and establish the level of characterization required in the process performance qualification protocol. Consequently, the old rule of "three lots and we are done" goes out the window. For simple processes with a low risk of process excursion, e.g. high loaded dose, direct blend formulations, the process performance qualification may be three lots or less. For complex processes, e.g. low dose controlled release spray drying processes or mammalian cell processing, the number of demonstration lots will likely be higher. Old theories, supplied by FDA Guidance for such things as media fills for aseptic validation, will now require a risk-based statistical justification based upon lot size and risk tolerance. The process performance qualification will challenge the process control space. The **control space** represents the recommended manufacturing limits for the process. The **control limits** are typically established by moving away from the boundary limits of the design space, and selecting parameter limits in a process design space that will ensure process predictability away from the edge of failure for each Key Process Input Variables (KPIV).

There are no inviolable evaluation parameters for demonstrating a successful process performance qualification. Process Capability is a fundamental metric that can be used to compare process variability and process centering against allowable specifications. It can be used to justify Acceptable Quality Level (AQL) or Lot Tolerance Percent Defective (LTPD) sampling levels at the commercial level that could be a significantly on-going cost savings. If desired, this information will support any Process Analytical Technology (PAT) strategy the site may have for the process downstream.

A good practice at the end of the process performance qualification (PPQ) is to go back to the risk management evaluation and demonstrate that the process risk elements identified at the outset of process design have been mitigated. This data will be the basis of managing continued improvement on the process via the change control system.

Continued Process Verification: (Stage – III)

The goal of the third validation stage is continual assurance that the process remains in a state of control (the validated state) during commercial manufacturing. The FDA is looking for a monitoring program which helps in capable of detecting gradual or unplanned departures from the process as designed. Historically, we have used the product stability program, change control process and the Annual Product Review Process as vehicles for monitoring and assessing process stability. The challenge with this approach has always been the resolution of these systems making proactive intervention difficult to achieve when dealing with process drift. For this stage the agency is looking for a program that builds upon the process understanding acquired in process design and process qualification.

Continual process verification will require a monitoring program that balances sampling, testing costs. A matrix approach to sampling with a focus on looking at intra- and inter-batch variation of the Key Process Input Variables (KPIVs) and critical to quality (CTQs) for the process is one way to cost effectively monitor the commercial process stability. Employing Statistical Process Control, Moving Range Charts and XBar-R charts are also simple ways to evaluate if the process is wandering inappropriately. It is important to apply a data-gathering phase before establishing alerts and action limits, since the commercial process will considered the totality of variation from the raw material, process, and testing methods. This data should drive a statistical analysis of data against the process characterization and process validation lot performance. Understanding the intent behind each analysis is essential to coming to the right conclusion. Statistical software packages such as Minitab and JMP can make analysis simple and reproducible and introduce, as required, data evaluation criteria such as the Westinghouse rules which, when used to discriminate unusual data from true process variability, can determine if further action is required. As areas of further study are identified, the risk management tools should be revisited to ensure the impact of the process variation is evaluated consistently.

Quality Management System (QMS)

The largest paradigm shift within the new guidance is the Quality function. Moving away from a product centric QMS requires that Quality be intimately involved in the evaluation and decision-making criteria as the process moves through each stage. It will require a high level of study to make sure all supportive elements are in place. For example, ensuring critical

monitoring systems are calibrated will beg the question: "Is it single point or three point calibration?" Method capability will focus on accuracy and precision and interference points. Ensuring that controlling and measurement tools are capable will become the foundation for managing the QMS, rather than the QMS procedures and documentation audit trail. To facilitate both the knowledge management and QMS paradigm shifts, a milestone or stage gate approach to process validation is an effective way to ensure all key stakeholders and decision makers remain on board with the new process-centric philosophy. An example of one possible approach is shown in Figure 3.

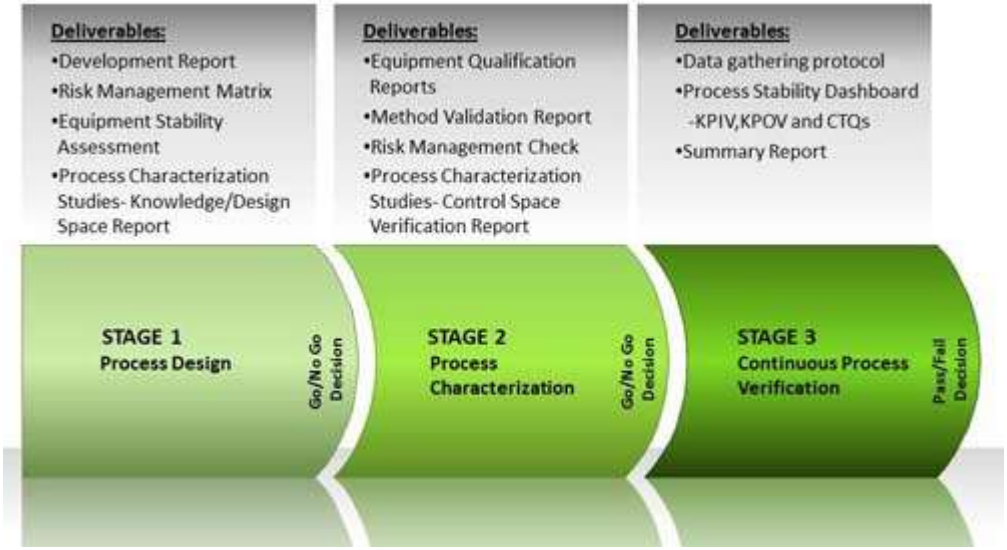

Figure 3: New Process Validation Stage Gate Approach

CONCLUSION

The new Process Validation guidance represents a dramatic shift from the 1987 FDA guidance issued to industry. While less prescriptive, it provides a sufficiently descriptive framework for industry to create a scientifically driven approach to demonstrating process predictability. There is no single answer to this guidance, and a structured plan, with clearly defined deliverables at each milestone. Which will ensure that the philosophical and technical components required to demonstrate process predictability will be applied in a uniform way across the organization. In addition, this homogenous approach to process validation will allow the organization to acquire the benefits of a more focused validation effort, potentially reducing the cost of process qualification, process performance qualification (PPQ) and resulting in products and processes which are both stable and predictable.

The application of the principles of ICH Q8 and will identify those parameters which are critical to process stability and product reproducibility. The new guidance will provide the impetus for

change if they are to successfully meet the new requirements for process and product reproducibility.

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