Title: **Assessment Methodologies for Process Validation Stage 2 and Stage 3**

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Introduction:

With the implementation of ICH Q8, Q9, Q10, Q11 and draft Q12 guidelines, regulatory bodies mandate a data driven, science and risk based decision making process utilizing data from all three stages of the PV Lifecycle – Stage 1: Process Design, Stage 2: Process Qualification and Stage 3: Continued Process Verification. Stage 2 can utilize practical tools to determine number of batches required for a study. This best estimate is based on statistical confidence using observed intra-batch variability and estimated inter-batch variability of similar products/processes and product label claim. Pa (Probability of Acceptance) is an innovative statistical analysis tool applicable for multi-level acceptance criteria (example Content Uniformity, Dissolution) that is fit for pharmaceuticals.

Aims:

Stage 3A evaluation of substantial data gathered from Stage 2 and predetermined number of batches can be used to estimate Inherent Process Variability (IPV) and PaCS index, Stage 3B trend limits and Process Capability Quality dashboard (PCQd) for a product. Stage 3B is an effective quality risk management tool for mitigating risks to product quality; detecting trends and implementing preventative measures prior to failures

Methods:

Stage 3A is the **initial assessment post new product launch** that utilizes a substantial body of data for statistical evaluation to gain deeper product understanding, product robustness and variability.
Stage 3A assessment utilizes data from all PV Lifecycle Stages.
Stage 3A assessment is pivotal in understanding product variability.
Stage 3A evaluation is a valuable resource for product development and risk mitigation of similar products and processes.
Defining a Stage 3B monitoring plan is part of Stage 3A.
Stage 3A assessment demonstrates the organizations compliance in establishing an enhanced product control strategy and attaining a high level of product understanding and quality.
Stage 3A protocol may be initiated upon completion of Stage 2B.

Results:

The Inherent Process Variability, which represents unexplained process variation under current manufacturing conditions, may be expressed by the equation below.

$$\textbf{Inherent Process Variability} = \textbf{Overall Variability} - \textbf{Analytical Method Variability}$$

Once the IPV is calculated for a particular product it can be used to derive a PaCS index. The PaCS index is a derivative of a product's performance measured against a benchmark of similar process. PaCS index empowers management with site specific product performance oversight.

$$\text{PaCS} = IPV_P / IPV_B$$

where, IPV_B is the Benchmark and IPV_p is the Product Inherent Process Variability . A PaCS <1 indicates the process variability is low and a PaCS index > 1 indicates the process variability is high compared to the benchmark. In cases where PaCS > 1, further evaluation may be required. If IPV_p it indicates that there is an opportunity for reducing process variability of the current product through continuous improvement.

A corporate IPV_B can be established based on dosage form and process

Conclusions:
Stage 2 can utilize practical tools to determine number of batches required for a study. This best estimate is based on statistical confidence using observed intra-batch variability and estimated inter-batch variability of similar products/processes and product label claim. Pa (Probability of Acceptance) is an innovative statistical analysis tool applicable for multi-level acceptance criteria (example Content Uniformity, Dissolution) that is fit for pharmaceuticals. Stage 3A evaluation of substantial data gathered from Stage 2 and predetermined number of batches can be used to estimate Inherent Process Variability (IPV) and PaCS index, Stage 3B trend limits and Process Capability Quality dashboard (PCQd) for a product. These novel statistical assessments can be used to gain further understanding of new product launches prior to routine monitoring. Stage 3B is an effective quality risk management tool for mitigating risks to product quality; detecting trends and implementing preventative measures prior to failures.

Keywords:
Continuous Improvement, Metrics, Stage 3