Title: **Assessment Method for Newly Launched Pharmaceutical Products**

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Introduction:

Stage 3A assessment is pivotal for new products in understanding **product robustness** and managing variability. Stage 3A assessment encompasses all Process Validation Life-cycle Stages (Stage 1: Process Design, Stage 2: Process Performance Qualification and Stage 3: Continued Process Verification).

Aims:

Based on a substantial body of data, Stage 3A assessment enhances the control strategy developed in Stage 1, 2 and predicts the performance of future Stage 3B commercial batches

Methods:

This paper describes a novel methodology and use of statistical tools to determine the Inherent Process Variability, evaluate material attributes, process parameter impact on in-process quality attributes, quality attributes affecting the patient, evaluation to reconfirm the design spaced estimations based on the multivariate DoE studies during Stage 1 Process Design still holds true, predictive modeling to confirm correlation between Stage 3A in-vitro results and clinical responses, determine continuous improvement opportunities and establishing critical quality attributes to be trended in Stage 3B with recommended alert limits.

Results:

Critical material attribute trends for different batches of raw materials used in the manufacturing of Stage 3A CPV batches are assessed. Primarily the attributes such as API particle size, assay, related compounds are considered. The results for the raw material critical quality attributes obtained from the manufacturer are compared with that reported In house. Further, the CMA's that impact the finished product quality attributes such as dissolution, content uniformity and assay can be assessed. Uni-variate and multivariate trends of in-process quality attributes at each of the manufacturing stage and finished product quality attributes are evaluated among all the batches. Impact of the process parameters on the in-process and finished product quality attributes for each stage is analyzed to identify the factors that may be attributed to variation in the CQA within and between batches. Stability data from the Stage 2 PPQ batches are trended along with Stage 1 and Stage 3A batches. In Vitro-In Vivo Correlation (IVIVC) is derived between Bio Clinical Trial Plasma Concentration-Time results and Stage 3A Batch Dissolution profiles to evaluate the consistency of patient impact by dissolution performance throughout Process Validation Life Cycle. Contribution of variability due to inherent process represents process robustness (4M: Man, Machine, Mfg. Method, Material) under current manufacturing conditions. Therefore, Inherent Process Variability Contribution (IPV max) = Overall Variability- Analytical Method Variability. Once CPP vs CQA correlation and design space estimations has been re-established, parameters can be further tightened to produce the targeted quality attribute results, frequency of testing may be reduced during commercial manufacturing for certain quality attributes.

Conclusions:

The essentials documented in this article provide a much needed methodology in completing Stage 3A assessment for a newly launched product. The comprehensive assessment reviews data from process development stages through scale-up, qualification and commercial manufacturing. The conclusions made should provide sufficient information to **make a scientific and risk-based decision on Product Robustness and Product Quality.** The approach systematically evaluates material attributes, process parameters, quality characteristic data and

scientifically establishes evidence that a process is capable of consistently delivering quality product. Stage 3A assessment methods improve product, process knowledge and detect correlations on attributes that has significant impact to patient safety and efficacy. The knowledge gained is valuable in estimating product variability, prediction of change impact, utilizing data in Stage 1 development of similar products and to detect continuous improvement.

Keywords:
Continuous Improvement, Metrics, Continued Monitoring