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TITLE: PPQ Sampling plan based on Bayesian dynamic borrowing

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ABSTRACT: Process validation is the collection and analysis of data, starting from the design of the process all through the manufacturing phase, aiming at demonstrating that the process is capable of producing quality products. This means the process should output products which reliably meets predefined quality standards, as per the guidance of regulatory bodies such as the FDA and EMA. It is a lifecycle-based and continuous activity.

Process validation can be divided into three stages which are as follows: (1) Stage 1 - Process Design: In this stage development data is used to define the commercial process and strategy. Tools such as Design of Experiments, Quality by Design and/or Process Analytical Technology are applied to identify and set limits for both Critical Quality Attributes (CQAs) and Critical Process Parameters (CPPs); (2) Stage 2 - Process Performance Qualification (PPQ): Demonstrating that the designed process and included equipment can meet the predefined manufacturing criteria under commercial manufacturing conditions; and (3) Stage 3 – Continued Process Verification (CPV): Continued monitoring of production to ensure continued control of the required quality levels.

Prior to carrying out the PPQ Stage, there is a need to come up with a within-batch sample size that is sufficient to confirm that the process is capable of producing quality products at a commercial scale. An undersized sample may not adequately capture process variability or accurately estimate product quality attributes, increasing the chance of wrongly rejecting or accepting a batch. Conversely, an overly large sample is costly and waste validation resources. Therefore, it is essential to choose a sample size that is neither too small nor too large to ensure accurate and cost-effective process validation. To develop a sampling plan for the PPQ stage, historical data from process design batches (such as formulation and/or process development batches, design space batches, characterization batches, clinical batches, registration batches, engineering batches, and other applicable sources) can be leveraged through Bayesian (partial) borrowing methods (e.g., power priors and meta-analytic-predictive priors dynamic borrowing). Dynamic borrowing is a Bayesian statistical method that uses historical data to inform the analysis of a new study but dynamically adjusts the amount of borrowed historical information based on its similarity to the current data.

Unlike standard borrowing methods that assume historical and current data are equally comparable, dynamic borrowing downweighs prior information that is inconsistent with new data, which helps reduce bias and maintain statistical rigor. This is particularly useful in situations with small populations, where historical data is crucial but may not be perfectly aligned with current studies. The use of Bayesian borrowing can lead to the benefit of smaller PPQ sample sizes.