**TUESDAY MORNING WORKSHOP (8:30 am – 11:30 am)**

**D. (CHEMICAL MANUFACTURING CONTROL) Control Strategies in CMC**

**Organizer/Chair: Mark Johnson, AbbVie**

1. Attribute Sampling and Acceptance Criteria Control Strategies to Assess PPQ Batches

Speaker:  Mark Johnson, AbbVie

When product process validation is completed, continued monitoring of quality attribute performance from initial marketed product batches must be initiated, to ensure they continue meeting product requirements.

This presentation reviews acceptance sampling practices useful to evaluate pharmaceutical product batches during late process validation, continued process verification and product performance qualification stages. This activity is critical to confirm that manufactured batches continue to meet expected acceptance criteria beyond process validation into the commercial manufacturing stage.

Support for this presentation was provided by AbbVie. AbbVie participated in the review and approval of the content.

2. Linearity of Measurement Methods, AKA, Don’t get twisted up over linearity

Speaker:  Brent Harrington, Pfizer

TBA

3. Analytical QbD – Method Development of Ion Exchange Chromatography for a Monoclonal Antibody

Speaker:  Ming-Ching Hsieh and Jingming Zhang, Eli Lilly

Ion exchange chromatography is a powerful tool to separate large molecules, including proteins, nucleotides, and viruses. It is not only used for purification in manufacturing but is also used in analytical laboratories to analyze a variety of analytes. In general, ion exchanger can be cation or anion exchangers with either strong or weak exchanger depending on the functional groups on the exchangers.

As part of Quality Target Product Profile (QTPP), product variants need to be well characterized and measured. A cation exchange (CEX) chromatography method was developed to characterize a therapeutic monoclonal antibody Mab1. The assay qualification study was performed to establish Analytical Target Profile (ATP) and to understand the parameters’ operating ranges. This study was to identify the robustness operation space for each parameter defined after screening study.

To assess the method robustness, eleven (11) parameters were evaluated, including five (5) categorical parameters and six (6) chromatographic (continuous) parameters. Due to a large number of parameters being evaluated, with the knowledge from the same method for the other molecules, a Plackett-Burman design was adopted for this study. The response included evaluation of percents of acidic peak group (APG), neutral peak group (NPG), and basic peak group (BPG). Generalized Linear Model (GLM) analyses of experiment results showed there were some statistically significant parameters for each response respectively. However, further analyses showed the effects of significant parameters could be tolerated practically. This study demonstrated that the method was robust for all eleven parameters within the selected ranges.

To understand the parameter effects crossing different molecules, further analyses were performed on peak resolution and retention time. Two peaks were selected to represent early peak (Peak 4) and late peak (Peak 16). The GLM analysis results revealed the actual impacts on resolution and retention time by the different categorical and chromatographic parameters. The retention times of both Peak 4 and Peak 16 were found to be dependent upon the initial mobile phase (A) pH and the steepness of salt gradient (gradient end of mobile phase B and salt concentration in mobile phase B). Interestingly, the resolutions of Peak 3/4 and Peak 15/16 were impacted by the different initial mobile phase pH conditions oppositely. This observation was confirmed by our experience in developing CEX methods for other therapeutic antibodies.

The Analytical QbD principles and statistical approach (DoE) helped analytical scientists to minimize the efforts during method development and robustness study. It can also provide pivotal information when further tweaks of the method, e.g., shortening run time and better separation, are implemented.

3. Panel Discussion

**TUESDAY AFTERNOON WORKSHOP (1:30 pm – 4:30 pm)**

**D. (CHEMICAL MANUFACTURING CONTROL) Bayesian Applications in CMC**

**Organizers/Chair: Jinxin (Jerry) Gao and Chao (Richard) Li, Eli Lilly**

1. A Bayesian Application in Process Monitoring – Establishing Limits for Dosage Units in Early Phase Process Control

Speaker: Ming Tang, AbbVie

TBA

2. A review of Bayesian power prior approaches to PPQ batch sample size estimation

Speakers: Stan Altan and Craig Bernier, JnJ

The FDA Process Validation guidance issued in 2011 lays out a 3-stage framework for process validation. Stage 1 is the Design Phase, where the manufacturing process is developed, implementing sufficient engineering controls to assure high quality. Stage 2 is the Process Performance Qualification (PPQ) intended to demonstrate the ability of the Phase 1 process to manufacture at full commercial scale. Stage 3 is the Continued Process Verification stage, which imposes an ongoing requirement to monitor quality for the life of the product. The objective of our presentation is to review Bayesian approaches to the question of justification of the number of batches at Stage 2, PPQ. The commercial motivation is to carry out the qualification phase in an efficient way. In the face of limited time and resources, the question of sufficient number of batches should be driven by severity of risk considerations, as well as resource limitations. Based on the review of methods, we give a Bayesian approach applying a power prior to provide additional flexibility in the inclusion of prior knowledge, and the nature of the prior experience to guide the choice of number of batches. The basic method relies on the Strawman 3 approach described by Lewis et al. (2014), with modifications to describe the impact of levels of severity of risk, and the nature of past or prior manufacturing experience in relation to the PPQ manufacturing process. We show some examples of the calculations for different risk levels, prior distributions on the parameters and the strength of borrowing in the power prior.

3. Panel Discussion