76a Approaches to Accelerating Pharmaceutical Process Development and Scale-up

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Ever increasing pressures to reduce pharmaceutical product development timelines have resulted in innovative approaches to extracting as much information as possible from every pilot-scale batch. Shorter development timelines have placed a premium on every batch as API (active pharmaceutical ingredient) quantities available for development are tight. In the recent process development and scale-up of a direct compression product, opportunities were sought to gain key process understanding from required clinical batch production. All critical process parameters defining the final product properties were evaluated using both active and surrogate formulations to conserve valuable API. Pilot scale predictive methods were developed and PAT (Process Analytical Technology) tools were used to gain the necessary process understanding for successful process scale-up.

Typical challenges with a direct compression process include attainment of blend uniformity, adequate formulation flow, minimization of API segregation and formulation sticking during compression. A non-invasive near infrared (NIR) probe was placed on the blender to obtain blend uniformity profiles. These data were used in conjunction with standard thief sampling to provide a more complete assessment of factors influencing blending performance and to help direct appropriate endpoint selection. Tablet compression studies were specially designed to assess formulation flow and segregation performance. Additional small scale methods were developed to evaluate the formulation sticking potential and sensitivity to changes in API particle size.

Limited API supply also constrained the process scale-up and removed the possibility of conducting commercial scale experimental batches to prepare for eventual process validation. A surrogate (blank) formulation was designed and characterized at both pilot and commercial scales to speed technology transfer to the commercial site. The bridge between active and blank performance at pilot scale, coupled with the bridge of blank performance across scales, enabled prediction of active formulation performance at the commercial site. Clinical batch production prior to process validation at the commercial site was possible as the inherent scale-up risk was minimized through the blank formulation experience. This clinical batch experience was then leveraged to prepare for the validation campaign. Through the development of key scale up approaches and characterization of a surrogate formulation, the pharmaceutical process development and scale-up was completed rapidly using minimal API dedicated for development.