Accelerated PK Screening Study of Formulation Design Space in Early Drug Development

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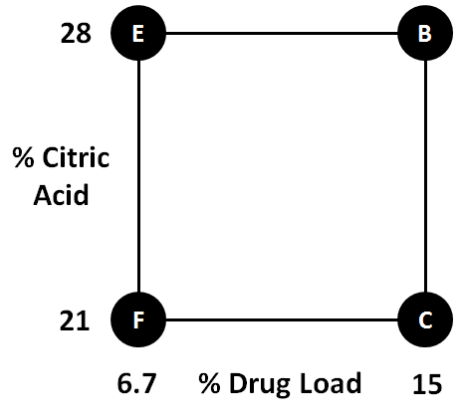
A key element of new drug product development is to achieve desirable formulation bioavailability (BA) to meet the pharmacokinetic target. The BA of a drug product formulation can be impacted by critical quality attributes (CQAs), critical material attributes (CMAs) and critical processing parameters (CPPs). A non-conventional approach of BA study can apply a formulation design space rather than specific formulations during drug product development, where a quantitative range of variables expected to have in-vivo impact on exposure, including formulation composition, API /excipient attributes, and process parameters will be evaluated.

There have been recent efforts in Rapid Formulation development and Clinical Testing (RapidFACT) to exploit the benefits of Translational Pharmaceutics in the clinical screening and optimization of drug products.[1] Merck has successfully conducted a formulation design space study in United Kingdom for development compound B in 2016 following the consultation with MHRA.

Merck Compound A is in early phase clinical development. As a crystalline freebase and BCS class II compound, the pH dependent solubility of Merck Compound A presents an increased risk of drug-drug interactions with proton pump inhibitors (PPI). The project team leveraged the innovative approach of “Spring and Parachute” to design the drug product to improve the exposure of prototype tablets under acholorhydric condition. To understand the clinical relevance of the tablet drug loading and citric acid level, an adaptive clinical study is proposed that includes a formulation design space covering specified range of drug load and citric acid levels. ‘Real-time’ decisions will be based on emerging human PK data to inform the next clinical formulation, which will be manufactured just in time to enable expedited dosing cycle of every 2 weeks. This approach will enable a better understanding of the dosage form’s biopharmaceutical properties and drive more efficient formulation selection decisions.



Representative drug product stability data of Merck compound A was generated for the corner point formulations, which brackets the active-to-excipient ratio of the clinical formulations. This approach is analogous to a stability bracketing design strategy following ICH Q1D. Any formulations within the formulation design space are expected to have the similar quality and stability as the corner formulations in the design space. This approach enables any possible formulation within the proposed design space to be manufactured and assessed in the adaptive clinical study. Just in time manufacture of clinical formulations, testing, packaging, and dosing will allow rapid PK screening study period within 14 day cycle. Clinical PK data for each study period will be reviewed in real time and used to guide the formulation to be manufactured for evaluation in the next study period.

Standard Biocomparison (BC) study will take cycle time of 9-12 months between formulation permutations. Accelerated PK Screening study will drive better efficiency of relative BA evaluation and reduce the lead time to inform formulation selection based on human PK data.

Reference:

1. McDermott, J., & Scholes, P. 2015. Formulation design space: a proven approach to maximize flexibility and outcomes within early clinical development. Therapeutic Delivery, 2015, **6**(11):1269-1278.