

## De-convolution Based IVIVC Correlation for Tacrolimus ER Tablet (Narrow Therapeutic Index Drug) With Widening of Dissolution Prediction for Virtual Bioequivalence

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**Abstract :** Background: Development of modified-release oral dosage formulations (OSD) like tacrolimus in narrow therapeutic categories, together with high levels of intra-individual variability, impose greater challenges. The risk assessment for bioequivalence studies requires developing a suitable design through pilot studies involving the comparison of multiple formulations of the same product with a marketed product to understand the in-vivo behaviour. These formulations could have varying coating levels and other minor quantitative differences to achieve the desired release rate for the final product. Although small-scale studies are critical before the conduct of full-scale Pharmacokinetic (PK) studies, regulatory agencies evaluate critical bioavailability attributes (CBA) before approving the submitted dossiers. Since Tacrolimus is a BCS Class II drug, therefore developing the extended-release formulation, in addition to associated challenges, provides an opportunity to present the In vitro-in vivo correlations (IVIVC) to regulatory agencies, not only to exhibit product quality but also to reduce the burden of additional human trials and cost involved to them for bringing the product to market. Objective: The objective of this study was to develop a Level-A In vitro - In vivo Correlation (IVIVC) model for Sun Pharma's test formulation Tacrolimus ER tablet 4mg and extend its application to a widened dissolution window of 25% at 2.5 hours (critical release time) sampling time point. Experimental Procedure: Post the conduct of two in-vivo studies, a pilot study evaluating two test prototypes on 24 subjects (under fasting) and a pivotal study having 50 subjects (under fasting), the observed pharmacokinetic profile was used for IVIVC model development. The dissolution media used was 0.005% HPC + 0.25% SLS in Water 900 mL at pH 4.50 using USP II (Paddle) apparatus with alternative sinkers operated at 100 RPM. The sampling time points were chosen to mimic the drug absorption in vivo. The dissolution best fit to data was obtained using Makoid Banakar kinetics. Then deconvolution, anchoring to concepts of the single compartment by Wagner Nelson method was applied for tacrolimus slow-release formulation batch with film coating weight build-up of 5.4% (used in pilot bio study), medium release with Hypromellose (retard-release exhibit batch used in the pivotal study) and fast release formulation batch with film coating weight build-up of 5.05% (used in pilot bio study). Results and Conclusion: The results were deemed acceptable as prediction errors for internal and external validation were < 3% depicting in-vitro drug release mimics in-vivo absorption. Moreover, the prediction result for the Test/Reference ratio was <15% for all test formulations and widening dissolution (i.e., 39%-64% drug release at 2.5hrs) predictions were well within 80-125% when compared against Envarsus XR (reference drug). This IVIVC-validated model can be used in the futuristic exploration of dose titration with 1mg tacrolimus ER OSD as a surrogate for In-vivo bioequivalence trials.

**Keywords :** pharmacokinetics, BCS, oral dosage form, Bioavailability, intra-individual variability

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