FACTORS LEADING TO ERRONEOUS PKPD INTERPRETATION

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The ultimate goals of preclinical and early clinical studies are to characterize a drug’s efficacy and safety, and in so doing, assess the medical utility and chance of success in a respective target patient population as early and accurately as possible. Over the last decade, various approaches have been proposed and exercised to address this goal, which has recently been termed “translational science” in pharmaceutical development. Several state-of-the-art technologies in this area were highlighted in JSSX’s official journal (DMPK) in the first 2009 (Theme) Issue. These articles introduce translational pharmacokinetic and pharmacodynamic (PKPD) approaches with modeling and simulation tools. They consider biologic, physiologic and mechanistic insight to both inform decisions and identify key parameters to be investigated in early exploratory stages.

Challenges in the design and interpretation of PKPD studies can be traced to insufficient or even erroneous assumptions in establishing the “exposure – response (E-R)” relationship, particularly in defining “exposure”. The most relevant exposure causing a drug response (efficacy or safety) is the unbound drug concentration around the target leading to the response. Initially this relationship can be measured by in vitro pharmacology assays where drug binding is negligible, however many confounding factors arise when performing this assessment in vivo. Plasma or blood concentrations are considered routinely as a surrogate for available concentration, often without detailed study of the equivalence between the two. Unique blood binding properties, including species difference, nonlinearity, and their potential change in experimental/disease conditions, can dramatically alter the apparent E-R relationships across species, doses or populations. Often neglected is the dependence of measured concentration on sampling site due to the fact that drug concentration is not uniform within the whole body vascular system, e.g., artery, common vein, venous outflow from specific organ, or a mixture from multiple organs. The higher organ extraction of a drug (i.e., high distribution volume or clearance), the larger impact this factor causes in projecting the response-relevant exposure. Where feasible, tissue concentrations may be directly measured in drug target organs, e.g., tumor for anticancer drug, lung for inhaled respiratory drugs, or other specific organ for toxicological targets. However, a careful interpretation is still necessary regarding what form of drug are measured and how the measurement are related to drug responses.

Unexpected or seemingly anomalous PKPD observations in the laboratory are indeed opportunities to identify the key factors specific to a given compound which may inform the decision to test the candidate clinically or not and further help optimize early (or even late) clinical study design. In general, we should revisit all assumptions and analyze the gaps or discrepancies in our understanding based on well understood PKPD principles, specific for each drug rather than by comparison to general rules. Modeling and simulation is an effective aid in this regard for translational stage of development, offering a framework to integrate the knowledge and commonly usable database.


Biography: Ryosei (Leo) Kawai, Ph.D, is a Senior Expert Modeler in Modeling & Simulation Dept., Novartis Global Development. He acquired his Ph.D at Chiba University in 1986 in biopharmaceutical science; post-doc in Nuclear Medicine, as imaging data modeler, CC, NIH Bethesda, USA (1987-1990); then, joined Novartis (Sandoz; 1990 to present), serving in multiple roles (mainly DMPK and clinical pharmacology) at multiple global sites (Basel/Switzerland; Tokyo,Tskuba/Japan; Cambridge/USA)