Intergration of Pharmacokinetics and Pharmacodynamics in Early Phase Clinical Evaluations

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The design of Phase I studies may be more flexible than those for Phase 2 and 3 studies. The regulatory review to narrow the focus in Phases I protocol to issues of safety alone reflects the desirability of reducing impediments to scientific creativity at this early phase drug development(Fed. Reg., IND Rewrite, 1987).

The traditional Phase I goals of defining dose tolerability in normal volunteers or patients can be efficiently extended to include initial characterization of PK and PD of acute toxic effects or measurble pharmacological responses. PK studies incorporated into Phase I clinical single and multiple dose trials can yield baseline information on drug bioavailability, distribution, metabolism, elimination, protein binding, their variabilities among subjects, and associated linear or nonlinear pharmacostatistical models. Linking measured plasma drug concentrations with observations of acute toxic effects(PD) enables preliminary definition of maximum safe drug concentrations. Taken together, this PK/PD integration can be used to define candidate dosage forms and regimens for evaluation in Phase 2 clinical trials and may be infuential in choice of clinical trial designs(e.g. dose-controlled vs. concentration-controlled trials).

It is important to incorporate PK/PD studies in the very first dose-tolerance studies in humans since this offers a unique(possibly one-time only) opportunity to evaluate drug concentration-acute toxic effect relationships of poorly tolerated doses which will be avoided in subsequent studies.