Evaluation of Drug-Drug Interactions in Drug Development

Dipti AMIN*1 Jean-Pierre ISAL*2

Introduction
Approximately 10-30% of hospital admissions are due to adverse Drug reactions, which have been shown to be between the 4th and 6th leading cause of death in hospitalised patients in the USA(1). Various studies report that between 5 and 30% of adverse reactions are as a result of drug-drug interactions (DDIs) although considered avoidable.

A DDI is defined as occurring whenever the effects of one drug are modified in or on the body by the prior or concurrent administration of another pharmacologically active substance(2). Regulatory authorities in the USA, Europe and Japan have issued guidance documents(5, 6, 7, 8) for the evaluation of potential DDIs.

Experimental Design in Clinical Development
DDI studies should maximise the possibility of finding an interaction so the experimental design is important. Select a design involving multiple dose administration to achieve steady state whenever possible, particularly when single dose (SD) pharmacokinetics (pk) does not predict the multiple dose pk, when enzyme induction is suspected, and where several weeks are needed for enzyme synthesis.

SD studies may be sufficient where the pk interaction is at the level of absorption, elimination or competitive inhibition, or with pharmacodynamic (pd) concentration related effects, or when tolerance develops after repeated dosing. Dose selection depends on whether the effect of a specific drug is sought where the approved therapeutic regimen may be sufficient, or if the effect sought is that of inhibition or induction where a dose higher than the approved regimen may be necessary to obtain a full effect.

The two drugs may be either administered concomitantly or staggered to obtain a peak concentration/effect at the same time. In order to demonstrate a statistically significant interaction on clinical and pd end points, a randomised, double-blind four-way crossover, placebo-controlled design can be utilised. A double blind or open, two-way crossover design is sufficient to assess the effect of one drug e.g. a cytochrome P450 inhibitor or inducer on the other drug. In order to assess a reciprocal pk interaction of two drugs, an open label, randomised, three-way crossover, placebo-controlled design may be employed. When analysing the results, confidence intervals should be used, and where an interaction is clearly present, specific recommendations regarding the clinical significance of the interaction based on what is known about the dose response relationship and/or the pk/pd relationship for the compounds involved should be provided; consider not just the mean of the interaction effect, but also the observed and theoretically conceivable extreme effects in individual subjects, resulting in possible toxicity.

*1 Guy's Drug Research Unit Quintiles Phase I Services Europe
6 Newcomen Street London SE1 1YR UK
*2 Quintiles Limited
A Practical Drug-Drug Interaction Strategy
In developing a practical strategy for carrying out DDI studies, consider the context, the mechanism, the likely cost, and the timing. For example, if a test drug is likely to be co-prescribed with other drugs or likely to be prescribed in a population which is at risk of polypharmacy e.g. the elderly, if it has a low therapeutic index, if it is in a class associated with DDIs, e.g. anticonvulsants, or there is a need for a drug with a lower potential for DDIs in current therapies, then there is likely to be a strong need to carry out several DDI studies with the test compound in question. For a drug for which the mechanism of action is understood with well defined predictable pk characteristics in human clinical studies and a lack of a theoretical basis for DDI, then it is likely that few, if any, interaction studies will be required in clinical development and any needed may be safely deferred at least to Phase 2, if not, Phase 3 trials. Although cost will not be the determining factor for whether DDI studies are conducted, they may influence the timing, particularly in relation to the cost of the clinical studies, the cost of the non-clinical assessments, and the level of internal resource which will be required to manage these studies. Where a decision not to conduct DDI studies is being considered it is important to factor in the cost of managing adverse events associated with DDIs the costs of managing undertreatment associated with DDIs, and the relative value of a drug with the DDI potential in the commercial market.

The timing of the individual studies will depend on the time that studies are likely to take, whether the DDI studies will be rate limiting in the drug development timetable, the need for early information for candidate selection in critical go/no go decision making, and the need for appropriate clinical drug-drug interaction studies to clarify the potential for an interaction identified by non clinical studies and thus prevent restrictive labelling.

Conclusion
In clinical drug development, the majority of DDI studies are carried out to clarify a metabolism interaction, in particular involving cytochrome P450 enzymes. In vitro studies may identify the potential for metabolic interaction between two drugs whereby if no interaction is seen in vitro, in vivo human studies may not be necessary although, if an interaction is seen in vitro, this data should be used only qualitatively and in vivo studies are needed to prevent a warning statement on the data sheet. When an interaction is identified, it is important to pay particular attention to individual data and not just to the mean values in order to identify potential at risk patients who are outliers. The timing of DDI studies within a practical drug development strategy as outlined should produce optimum data within realistic timelines.

References