A comprehensive understanding of the safety and efficacy profile of a novel candidate pharmaceutical is necessary for the successful registration and eventual marketing of the candidate compound.

A significant proportion of lead candidates continue to fail in clinical development because of metabolic or pharmacokinetic 'defects'. Such failures should now be regarded as largely avoidable, by first conducting predictive \textit{in vitro} and \textit{in vivo} (preclinical) studies. While these tests are very helpful, metabolic fate and pharmacokinetic parameters \textit{in vivo} in man should be studied at the earliest stage possible, to avoid wasted time, effort and expense.

Regulatory Authorities correctly expect that appropriate investigations will be carried out, but are not usually prescriptive in exact design or timing of such studies, although all require a resultant understanding of key pharmacokinetic parameters and metabolic profile, principally in support of safety.

Phase I (usually volunteer) Clinical Trials incorporating these aims are often conducted in Western countries, particularly in the United Kingdom. A variety of scientific methodologies can be used, to detect and quantify at low levels, parent compound and individual metabolites; including conventional chromatographic separation (\textit{eg HPLC}) and detection (uv, fluorescence, electrochemical, \textit{etc}), stable isotope MS techniques, tracer $^{14}$C/$^3$H Accelerator Mass Spectrometry,
or more conventional $^{14}\text{C}/^{3}\text{H}$ mass-balance and LC-MS/MS investigations. Each has advantages and drawbacks and should be selected carefully in each case on the basis of knowledge gained from preclinical investigations. The situation is made more complex in many cases by the need, for example, to consider the impact of polymorphic isozymes in relation to therapeutic window, by potential drug-drug interactions, or by the particular challenges posed in investigations of biologically active macromolecules.

Volunteer safety is paramount; both in terms of drug safety and radiation safety. Current and impending regulations and practice will be reviewed in detail, and the role of expert bodies and committees explained (LEC, ARSAC etc). Specifically, the control of radioactive dosing in UK will be examined and categories of risk and benefit reviewed. The role of microdosing will be examined, and potential benefits and disadvantages proposed. These aspects will be discussed, keeping in mind that the eventual aim is to create most efficiently a well understood safe and effective new medicine which will bring health and economic benefits, both to society, and to stakeholders.