CHEMICALLY REACTIVE METABOLITES IN DRUG DISCOVERY AND LEAD OPTIMIZATION

Thomas A. Baillie

School of Pharmacy, University of Washington, Box 357631, Seattle, WA 98195-7631, USA

The past decade has witnessed a transformation in the use of drug metabolism and pharmacokinetic (DMPK) data to support the discovery and development of novel therapeutic agents. In contrast to the traditional role of such information in qualifying candidates already selected for development, the DMPK characteristics of new chemical entities (NCEs) play a key role, together with evaluations of potency and selectivity against the biological target, in the selection process itself. Criteria such as appropriate PK of the NCE in animal species, interactions with drug metabolizing enzymes and transporters, plasma protein binding, identities and pharmacological activities of mammalian metabolites, and formation of chemically-reactive, potentially toxic, metabolites all contribute to the choice of candidates for development. This presentation will highlight one integrated approach to drug discovery, originally established at Merck Research Laboratories, in which chemical, pharmacological, and DMPK data all play a key role in the selection of drug candidates whose properties have been optimized for successful development. Particular emphasis will be placed on studies aimed at the early identification of chemically reactive metabolites, using a combination of in vitro systems and animal models in vivo, and examples will be given of the use of metabolic activation data in the lead optimization stage of drug discovery (1,2).

References:


Biography
Dr. Thomas A. Baillie is Dean of the School of Pharmacy at the University of Washington. He was educated at the University of Glasgow, Scotland, where he earned B.Sc. (Hons) and Ph.D. degrees in Chemistry in 1970 and 1973, respectively. He also holds an M.Sc. degree in Biochemistry from the University of London (1978) and was awarded the degree of D.Sc. in Chemistry from the University of Glasgow in 1992. Dr. Baillie’s research interests center on the application of mass spectrometry and allied techniques to mechanistic studies on the metabolism of foreign compounds, with particular emphasis on the generation of chemically-reactive, potentially toxic products of biotransformation.