**The Impact of Mass Spectrometry in Pharmaceutical Lead Optimization**

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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 selection of candidates for development. Mass spectrometry in general, and LC-MS/MS in particular, has played a key role in supporting the lead optimization phase of drug discovery, and the relatively recent introduction of high resolution mass analyzers and associated high-speed data processing systems has further enhanced the value of MS-based technologies in metabolite detection and identification through the provision of accurate mass data and corresponding elemental composition information. In this presentation, examples will be given of the application of contemporary MS techniques to the optimization of drug candidates in an industrial drug discovery setting, and the complementary roles of high resolution MS and high-field NMR spectroscopy in metabolite structure elucidation will be highlighted.