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Beyond sensitivity: Improving the performance, productivity and compliance of the bioanalytical assay process

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The modern bioanalytical laboratory is charged with task of providing project teams with high quality, high sensitivity data in a timely manner. This information is often extremely time critical; for example in an escalating dose study where the derived PK information from the previous dosing stage is required to determine the next dosing level. Providing high sensitivity information, at the pg/mL level can often be extremely challenging. This is due to the fact that high resolution chromatograms and complicated sample preparation are often needed to reach the specified levels of sensitivity. All of this must be achieved in an environment of strict regulatory compliance and high productivity.

In this presentation we will discuss the application of a new Ultra High Sensitivity System for the quantification of small and large molecules at sub pg/mL levels. To illustrate this we will discuss the analysis of corticoid steroid inhaled therapeutic, fluticasone propionate. Fluticasone propionate is dosed by the inhaled route, with the majority of the drug directed to the lungs. The remainder is eliminated in the liver to via hydrolysis of the S-fluoromethylcarbothioate function to form the inactive 17β-carboxylic acid metabolite. These factors result in circulating levels at the 0.5pg/mL – 1pg/mL level. The high protein binding, greater than 99%, also present a challenge when developing a high sensitivity bioanalyticalassay. A high sensitivity method using solid-phase extraction (SPE) combined with high resolution LC/MS/MS was employed to quantify the compound. The extraction efficiency was determined to be more than 95%. The sub 2um separation resolved the active compound from endogenous interferences and metabolites. The assay cycle time was 5.5 mins with a peak width of 2 secs at base. The novel ion guide optics in the MS resulted in sufficient sensitivity to detect and quantify the compound at very low levels. The limit of quantification fluticasone was determined to be 0.25pg/mL.

Biography

Dr. Robert Plumb is senior manager in the Waters Pharmaceutical Business Operations Division, based in Milford, Massachusetts.

Dr. Plumb has published over 90 papers on the subject of HPLC/MS and NMR for pharmaceutical analysis, bioanalysis, metabolite identification and metabonomics. He is a recognized expert in the use of liquid chromatography with mass spectrometry, capillary scale LC, purifications scale LC and metabonomics, giving many invited papers at international meetings around the world.

After obtaining an honors degree in Chemistry from the University of Hertfordshire in 1992, he started work in at Glaxo Research and Development Drug Metabolism Department. During his time at Glaxo and later GlaxoWellcome he continued his research in liquid chromatography combined with NMR and mass spectrometry for metabolite identification and bioanalysis obtaining his PhD in 1999. Dr Plumb continued his work for GlaxoWellcome with the responsibility of metabolite identification using HPLC/MS/NMR and new analytical technology development. In 2001 he moved to Waters Corporation in Milford, MA, USA where he was responsible for the Life Science Chromatography group and latterly LC/MS applications in the Pharmaceutical Market Development Group. He is currently an visiting Professor in Analytical Chemistry at Kings College London, visiting Professor in Metabonomics at Imperial College and a Fellow of the Royal Society of Chemistry.

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