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CHALLENGES AND CONSIDERATIONS FOR QUANTITATIVE ANALYSIS OF CHOLESTEROL PRECURSORS AND METABOLITES IN HUMAN PLASMA BY LC-MS/MS METHODOLOGY

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Concentrations of Cholesterol Precursors and Metabolites in human body are very closely related to human cognitive performance and human heart health as well. Many new drugs are developed to improve the rations of among the precursors or metabolites in human body for human health needs. Because they are so important biomarkers that sensitive and accurate determinations of all concentrations of the precursors and metabolites are critical during the drug developments and studies. For such purpose, Bio-analytical methods were developed and fully validated following US FDA and European EMA guidance for Cholesterol three precursors: Lathosterol, Lanosterol and Desmosterol, and four Cholesterol metabolites: 4β-Hydroxycholesterol, 24S-Hdroxycholesterol, 25-Hdroxycholesterol and 27-Hdroxycholesterol by LC-MS/MS methods at our laboratories. Since such marker molecule structures and polarities are very similar or the same with only a double bond position different, the bio-analytical methodology faced extremely challenge during our method development stage, which include all extraction procedures, HPLC conditions and Mass Spectrometer parameters. Especially in human plasma samples, Cholesterol is dominate marker that had significant interference with the analysis. During the method validations, we have considered that the methods need to be conducted from regulatory point of view, that is, "method validation for biomarker assays should address the same questions as method validation for PK assays……" so that the method accuracy, precision and all stabilities were completed for all assessments to meet acceptance criteria from the regulatory agencies, instead, not reference methods "fit-for-purpose" for diagnostic. In this presentation, all above scientific challenges and regulatory considerations are introduced and discussed. All methods were successfully applied to our several clinical studies, and with later on the methods for phytosterol have provided very useful insights for the drug developments.