

Comparative Evaluation of Pharmacologically Guided Approaches (PGA) to Determine Maximum Recommended Starting Dose (MRSD) of Monoclonal Antibodies for First Clinical Trial

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Abstract : First-in-human (FIH) studies are a critical step in clinical development of any molecule that has shown therapeutic promise in preclinical evaluations, since preclinical research and safety studies into clinical development is a crucial step for successful development of monoclonal antibodies for guidance in pharmaceutical industry for the treatment of human diseases. Therefore, comparison between USFDA and nine pharmacologically guided approaches (PGA) (simple allometry, maximum life span potential, brain weight, rule of exponent (ROE), two species methods and one species methods) were made to determine maximum recommended starting dose (MRSD) for first in human clinical trials using four drugs namely Denosumab, Bevacizumab, Anakinra and Omalizumab. In our study, the predicted pharmacokinetic (pk) parameters and the estimated first-in-human dose of antibodies were compared with the observed human values. The study indicated that the clearance and volume of distribution of antibodies can be predicted with reasonable accuracy in human and a good estimate of first human dose can be obtained from the predicted human clearance and volume of distribution. A pictorial method evaluation chart was also developed based on fold errors for simultaneous evaluation of various methods.

Keywords : clinical pharmacology (CPH), clinical research (CRE), clinical trials (CTR), maximum recommended starting dose (MRSD), clearance and volume of distribution

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