ANALYSIS ON FACTORS ASSOCIATED WITH INCLUSION OF HUMAN INTRAVENOUS STUDY DATA IN NEW DRUG APPLICATION IN JAPAN
Haruo Imawaka1, Makiko Kusama1, Kiyomi Ito3, Shunsuke Ono2 and Yuichi Sugiyama2
1 Minase Research Institute, Ono Pharmaceutical Co., Ltd., 3-1-1 Sakurai, Shimamoto-cho, Mishima-gun, Osaka, 618-8585, Japan, 2 Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan, 3 Research Institute of Pharmaceutical Sciences, Musashino University, 1-1-20 Shinmachi, Nishitokyo-shi, Tokyo, 202-8585, Japan

[Purpose] Inclusion of human intravenous (iv) study data in new drug applications in Japan has been recommended, yet not mandatory, through the government notification of "Clinical Pharmacokinetic Studies of Pharmaceuticals" issued in June 2001. As a consequence, some new oral drugs are submitted with human iv data, while others are not. Inclusion of such data is generally believed to be attributed not only to the notification, but also to the feasibility to conduct iv studies which is restricted by solubility, but currently there is no comprehensive data on this topic. [Methods] We quantitatively investigated the association between the inclusion of human iv data in new drug application and factors such as this notification, human and animal pharmacokinetic data, and drug profiles, such as solubility, therapeutic class, originator, and the developer. Logistic regression was carried out on a data set of 117 new oral drugs approved in Japan between September 1999 and April 2009. [Results] Inclusion of human iv data conspicuously increased after the notification in the self-originated drugs of Japanese companies. Drugs with large inter-individual variation in pharmacokinetics and drugs for cardiovascular diseases showed significant association with frequent inclusion of human iv data, whilst significantly less inclusion was observed in gastrointestinal, anti-allergy, and anti-tumor drugs. Solubility was not associated with inclusion of human iv data. [Conclusions] The developer’s behavior towards regulatory compliance and corroborative data, rather than the feasibility of iv administration studies, seems to be a stronger factor in deciding whether or not to include human iv data in the dossier.

HUMAN DOSE PREDICTION FOR A FULLY HUMANIZED IgG2 MONOCLONAL ANTIBODY USING A MECHANISTIC PK/PD MODEL
Tomomi Matsuura1, Gai Ling Li2
Pfizer Global Research & Development 1 Pharmacokinetics, Dynamics & Metabolism, 2 Clinical Pharmacology, Sandwich, Kent, UK CT13 9NJ

[Purpose] PF-04427429 is a high-affinity human monoclonal anti-human calcitonin gene-related peptide (CGRP) antibody of the IgG2 isotype. A mechanism-based PK/PD model was developed to predict the range of clinical doses. [Methods] The PK/PD model consists of integrated components: a CGRP kinetic model that describes CGRP production, degradation and distribution; PF-04427429 plasma pharmacokinetics and its binding kinetics to CGRP; CGRP-receptor binding kinetics in biophase; Key parameter values were estimated in vitro or were obtained from the literature. Modeling and simulations were performed using Berkeley Madonna Version 8.0.1. [Results and Discussion] The CGRP baseline and turnover rate, and the elimination rate of its complex with PF-04427429, have been identified as most sensitive parameters that can significantly influence dose projection. The minimum anticipated biological effect level was determined to be 0.2 mg, where an inhibition of up to 20% in free plasma CGRP. [Conclusions] This mechanism-based PK/PD modeling and simulation enables the integrated use of a range of in vitro, in vivo, preclinical and clinical information that were available prior to the start of the first in human study, to effectively identify the potential clinical dose range for subsequent investigation.