Faculty of Pharmacy Guest Speaker Seminar

Taking a medicine or taking a risk? The dose rationale in first-time-in-humans and recent clinical trial disasters.

Prof. Oscar Della Pasqua
Senior Director Clinical Pharmacology, GlaxoSmithKline, UK
Chair Clinical Pharmacology & Therapeutics, UCL, London, UK

Abstract: Over the past 20 years, thousands of first-into-human (FIH) clinical trials have been performed across the world, with few major incidents or safety concerns. Despite the requirement for a comprehensive non-clinical safety and toxicology package, current guidelines do not fully consider the need for a dose rationale based on the anticipated concentration-effect (PKPD) relationships. In fact, the primary objective of most first-time-in-human studies continues to be tolerability, safety and pharmacokinetics. The potential flaws in this approach become evident only when things go wrong. The fatal incident in 2016 during the evaluation of a novel fatty acid amide hydrolase (FAAH) shows the limitations of this process. In this presentation, we revisit the dose rationale based on receptor and clinical pharmacology principles as the basis for the progression of an investigational product into humans. While non-clinical safety pharmacology and toxicology data remain important safeguards, dose selection, dosing regimen, and escalation procedures must be based on target engagement. A new reading is proposed to Theophrastus of Hohenheim’s, who in 1538 stated that all things are poison and nothing is without poison: only the dose makes a thing not to be poison.

About the speaker

Prof Oscar Della Pasqua is Senior Director Clinical Pharmacology at GlaxoSmithKline (GSK) and Chair Clinical Pharmacology & Therapeutics at University College London (UCL), United Kingdom. In addition to his extensive experience in late clinical development and life cycle management, he provides clinical pharmacology expertise for the implementation of first-time-in-humans and proof-of-concept studies. At UCL, he leads a research group focused on paediatric pharmacology, disease modelling and clinical trial design methodology. His has more than 120 publications in clinical and scientific journals.

Prof Della Pasqua is Executive Editor of the British Journal of Clinical Pharmacology and co-chair of the Medicines for Children Advisory Network (MCAN), an internal expert panel at GSK. He is also member of the of SMART, a EU-funded project, where he coordinates the efforts on the implementation of quantitative clinical pharmacology principles for the evaluation of paediatric efficacy and safety data.