FROM PBPK TO PBFTPK (PHYSIOLOGICALLY BASED FINITE TIME PHARMACOKINETIC) MODELS

WEBINAR: 28th June 2022, 9.00 am (CET)

THIS IS A SATELLITE WEBINAR OF THE 30th PAGE MEETING: Welcome to the Population Approach Group in Europe (page-meeting.org)

REGISTRATIONS:

https://afea.eventsair.com/athena-satellite-meeting/register/Site/Register

Summary

This webinar is intended for Academics/students or scientists working in pharmaceutical industries, regulatory agencies, and contract research organizations.

The first talk will focus on the false hypothesis used for oral drug absorption since the inception of pharmacokinetics in 1953. The impact of the false concepts on the fundamental aspects of bioavailability and bioequivalence will be underlined. Relevant references: *i) Pharmaceutical Research.* 36:94 (2019) https://doi.org/10.1007/s11095-019-2633-4 *ii) Pharmaceutical Research* **37,** 187 (2020). https://doi.org/10.1007/s11095-020-02894-w

The second talk will describe the science behind the development of the Physiologically Based Finite Time Pharmacokinetic (PBFTPK) models. The models were built on two principles i) drugs are absorbed passively for a finite period of time, τ and ii) time absorption constrains linked with the gastrointestinal transit times of drug in the stomach, the small intestines and the colon were applied. Relevant references: i) *Pharmaceutical Research* **37,** 187 (2020). https://doi.org/10.1007/s11095-020-02894-w ii) *Pharmaceutical Research* 38, 1345–1356 (2021) [DOI: 10.1007/s11095-021-03078-w]

The third talk will be about the application of PBFTPK models to the analysis of pharmacokinetic data. Several case studies for data set analyses using the PBFTPK software will be presented. The PBFTPK software used in all model fittings relies on user defined functions in Igor programming environment. Relevant reference: *Pharmaceutical Research* Re-writing oral pharmacokinetics using physiologically based finite time pharmacokinetic (PBFTPK) models. In press https://doi.org/10.1007/s11095-022-03230-0.

The fourth talk will be centered on the implications of Finite Absorption Time (FAT) concept for bioavailability and bioequivalence. Both compartmental and non-compartmental considerations will be addressed. Approaches towards the unthinkable estimation of absolute bioavailability from oral data exclusively will be presented. Relevant references: i) *Pharmaceutical Research* 38, 1345–1356 (2021) [DOI: 10.1007/s11095-021-03078-w] ii) . *Pharmaceutical Research* 38, 2185 (2021) [DOI: 10.1007/s11095-021-03121-w]

The fifth talk will be about the application of Finite Absorption Time (FAT) to the analysis of bioequivalence data. The current approach based on the traditional metrics using $(AUC)_{0-\infty}$ and C_{max} will be questioned. Analysis of a bioequivalence pilot study of axitinib with two tests and one reference formulation under the prism of FAT will be presented.

The sixth talk will be about the variability of the gastrointestinal tract properties, such as fluid volume, the concentration of bile salts, gastrointestinal transit time, and pH in the fasted and fed states, and how these are captured in virtual clinical trials conducted by PBPK models. The usefulness of incorporating these variabilities into PBPK models to evaluate the impact of gastrointestinal properties on drug behavior *in vivo* will be discussed and shown for two drug products.

The seventh talk will address possibilities and limitations of PBPK modeling for inhaled drugs. The selected case studies will describe the key steps in pulmonary PBPK modeling, and illustrate the impact of input parameters on the model performance. Also, a combined in silico approach (using linked software) for the prediction of inhaled drugs performance will be presented. Relevant references: i) *Asian Journal of Pharmaceutical Sciences* 16(3), 350-362 (2021) [DOI: 10.1016/j.ajps.2020.12.001], ii) *European Journal of Pharmaceutical Sciences* 113, 171-184 (2018) [DOI: 10.1016/j.ejps.2017.10.022]

The eighth talk will relate to population PK modeling of complex absorption profiles using empirical functions, including Weibull, inverse Gaussian, transit compartments model, and convolution-based models with nonparametric input functions. The application of the approach in the model-integrated evidence for bioequivalence assessment will also be demonstrated. Relevant reference: International Journal of Pharmaceutics 437, 170-178 (2014). [https://doi.org/10.1016/j.ijpharm.2014.07.013]

The ninth talk will focus on PBPK modeling approaches to inform virtual bioequivalence trials. The concept of in vitro in vivo extrapolation (IVIVE) in biopharmaceutics as well as the role of inter-occasion variability in virtual bioequivalence assessments will be discussed.

The final talk will be centered on the food effect mechanisms and incorporation in PBPK models. Case studies of application of PBPK models for food effect predictions in industry and regulatory applications will be presented. The gaps and opportunities will be underlined.

Scientific Programme:

Time	Speaker	Topic
08:55	**Panos Macheras** *Department of Pharmacy, National & Kapodistrian Univeristy of Athens*	Welcome – Introduction
09:00	**Panos Macheras** *Department of Pharmacy, National & Kapodistrian Univeristy of Athens*	The false assumption that breaks pharmacokinetics of oral drug absorption.https://www.athena-innovation.gr/en/announce/pressreleases/274-1stmeetingofpharma-informaticsunit.html
09:30	**Panos Macheras** *Department of Pharmacy, National & Kapodistrian Univeristy of Athens*	The rise of physiologically based finite time pharmacokinetic (PBFTPK) models
10:30	*Coffee Break*	
11:00	**Athanasios Tsekouras** *Department of Chemistry, National & Kapodistrian Univeristy of Athens*	Analysis of pharmacokinetic data using the PBFTPK software

11.30	**Panos Macheras** *Department of Pharmacy, National & Kapodistrian Univeristy of Athens*	Implications of finite absorption time on Bioavailability and Bioequivalence
12.00	*Light lunch*	
13.00	**Nikos ALimbertis** *Department of Pharmacy, National & Kapodistrian Univeristy of Athens*	Analysis of bioequivalence data using the finite absorption time (FAT) concept
13.30	**Rebeka Jereb** *Sandoz development center, Ljubljana, Slovenia*	Evaluating the impact of gastrointestinal tract properties on drug *in vivo* performance using PBPK modeling and virtual clinical trials
14.00	**Filippos Kesisoglou** *Merck & Co., Inc., Rahway, NJ, USA*	Can PBPK Modeling Streamline Food Effect Assessments?
14:30	*Coffee Break*	
15:00	**Iztok Grabnar** *Faculty of Pharmacy, University of Ljubljana*	Modeling complex absorption in a population analysis using empirical functions
15:30	**Ioannis Loisios Konstantinidis** *Novartis, Basel, Switzerland*	PBPK-IVIVE linked models to inform virtual bioequivalence trials
16:00	**Di Wu** *Merck & Co., Inc., Rahway, NJ, USA*	Physiologically based pharmacokinetic models under the prism of the finite absorption time concept

16.30 Wrap-up & end of workshop

Short Bios (in alphabetical order)

Filippos Kesisoglou is a Distinguished Scientist at Merck & Co., Inc., (Rahway, NJ) where he is currently leading the Biopharmaceutics team and oversees the translational biopharmaceutics efforts in the Pharmaceutical Sciencesdepartment. Filippos has more than 15 years of industry experience in the fields of biopharmaceutics and formulation development and has been a keycontributor to more than 10 new drug applications across therapeutic areas. He holds a Pharmacy diploma from Aristotle University of Thessaloniki, Greece and MSc and PhD degrees in Pharmaceutics from University of Michigan.

Dr Ioannis Loisios Konstantinidis studied Pharmacy in the National and Kapodistrian University of Athens, Greece and did his thesis in Pharmacometrics in the Aix Marseille University. He did his PhD in PBPK modeling at Goethe University in Frankfurt am Main.

Previous position: Senior scientist M&S in the clinical PBPK/PD group at Novartis
Currently: Principal Scientist M&S in the clinical PBPK/PD group at Novartis

Iztok Grabnar studied pharmacy and obtained his PhD degree in pharmacokinetics at University of Ljubljana. Currently he is a Full Professor of biopharmaceutics and pharmacokinetics at University of Ljubljana, Faculty of Pharmacy, where he also served as a Vice-Dean (2015-2019). For more than 20 years his research is in pharmacometrics, focused on the development of modeling and simulation methods in the fields of biopharmaceutics, pharmacokinetics and clinical pharmacology.

Nikos Alimpertis is currently pursuing his PhD in the field of Modelling & Simulation of oral drug absorption in the Department of Pharmacy, National and Kapodistrian University of Athens. He completed the undergraduate degree in Informatics at the Athens University of Economics and Business [Final Grade: 8.85/10 (Excellence)]. He studied Computational Biology and Bioinformatics at ETHZ and he completed the M.Sc thesis at IBM Research in Zurich in the department of Computational systems biology.

Panos Macheras is Emeritus Professor (after obligatory retirement September 2014) of the Department of Pharmacy, National and Kapodistrian University of Athens. He is the Founder (1991) of the Laboratory of Biopharmaceutics and Pharmacokinetics at the University of Athens. He established in 2016 the PharmaInformatics Unit of the Research and Innovation Center ATHENA; he is currently the Head of the Unit. He is Adjunct Professor, Department of Pharmaceutical Sciences, State University of New York (SUNY), Buffalo, USA.

Rebeka Jereb studied pharmacy at the University of Ljubljana, Faculty of pharmacy, Slovenia, where she also did her Ph.D. thesis in PBPK modeling. She is currently a scientist in the Clinical development department at Sandoz, focusing on PBPK modeling used during generic drug development and exploring the potential use of PBPK models for regulatory purposes.

Di Wu is a Senior Scientist at Merck & Co., Inc., (Rahway, NJ), where she serves as a biopharmaceutics representative in oral and parenteral drug development. Before Merck, Di was an Orise Fellow in the division of Biopharm, FDA, where she worked on PBPK modeling and IVIVC. Di holds a bachelor degree from China Pharmaceutical University, and a PhD degree in Pharmaceutical Sciences from Temple University, focusing on drug delivery systems.