

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

Congress Centre, Ljubljana, Slovenia, 28th June 2022, 9.00 pm (CET)

Summary

This seminar is intended for Academics/students or scientists working in Academia, 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 (PBFTP) 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](https://doi.org/10.1007/s11095-021-03078-w)]

The third talk will be about the application of PBFTP models to the analysis of pharmacokinetic data. Several case studies for data set analyses using the PBFTP software will be presented. The PBFTP 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 (PBFTP) 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](https://doi.org/10.1007/s11095-021-03078-w)] ii) *Pharmaceutical Research* 38, 2185 (2021) [DOI: [10.1007/s11095-021-03121-w](https://doi.org/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 <i>Department of Pharmacy, National & Kapodistrian University of Athens</i>	Welcome – Introduction
09:00	Panos Macheras <i>Department of Pharmacy, National & Kapodistrian University of Athens</i>	The false assumption that breaks pharmacokinetics of oral drug absorption.
09:30	Panos Macheras <i>Department of Pharmacy, National & Kapodistrian University of Athens</i>	The rise of physiologically based finite time pharmacokinetic (PBFTPk) models
10:30	<i>Coffee Break</i>	
11:00	Pavlos Chrysafidis <i>Department of Pharmacy, National & Kapodistrian University of Athens</i>	Analysis of pharmacokinetic data using the PBFTPk software
11.30	Panos Macheras <i>Department of Pharmacy, National & Kapodistrian University of Athens</i>	Implications of finite absorption time on Bioavailability and Bioequivalence

- 12.00** *Light lunch*
- 13.00** **Nikos Alimbertis**
Department of Pharmacy, National & Kapodistrian University 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** **Sandra Cvijic**
Department of Pharmaceutical Technology, University of Belgrade Tackling the challenges of PBPK modeling for inhaled drugs
- 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** **Filippos Kesisoglou**
Merck & Co., Inc., Rahway, NJ, USA Can PBPK Modeling Streamline Food Effect Assessments?

16.30 Wrap-up & end of workshop

Registration-Fees

- Industry, CROs : 300 €
- Academia-Government: 200 €
- Student : 100 €

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 Sciences department. Filippos has more than 15 years of industry experience in the fields of biopharmaceutics and formulation development and has been a key contributor 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 Loisis 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.

Pavlos Chryssafidis is a dental surgeon based in Athens. He is currently pursuing his PhD at the Department of Pharmacy, National and Kapodistrian University of Athens in the field of Modelling & Simulation of oral drug absorption. He holds an MSc in Computational Mechanics from the National Technical University of Athens and a BSc in Physics from the National and Kapodistrian University of Athens

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.

Sandra Cvijic (maiden name: Grbic) holds a PhD in Medical Sciences - Pharmacy (2011) and Specialization in Pharmaceutical Technology (2015) from the University of Belgrade-Faculty of Pharmacy. She has been working at the University of Belgrade-Faculty of Pharmacy, Department of Pharmaceutical Technology and Cosmetology from 2003, and currently holds a position of associate professor.