FROM PBPK TO PBFTPK (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:  

ii) *Pharmaceutical Research* 37, 187 (2020). [https://doi.org/10.1007/s11095-020-02894-w](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, $\tau$ 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](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 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](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 $C_{\text{max}}$ 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 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:

<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>08:55</td>
<td>Panos Macheras</td>
<td>Welcome – Introduction</td>
</tr>
<tr>
<td></td>
<td>Department of Pharmacy, National &amp; Kapodistrian University of Athens</td>
<td></td>
</tr>
<tr>
<td>09:00</td>
<td>Panos Macheras</td>
<td>The false assumption that breaks pharmacokinetics of oral drug absorption.</td>
</tr>
<tr>
<td></td>
<td>Department of Pharmacy, National &amp; Kapodistrian University of Athens</td>
<td></td>
</tr>
<tr>
<td>09:30</td>
<td>Panos Macheras</td>
<td>The rise of physiologically based finite time pharmacokinetic (PBFTPK) models</td>
</tr>
<tr>
<td></td>
<td>Department of Pharmacy, National &amp; Kapodistrian University of Athens</td>
<td></td>
</tr>
<tr>
<td>10:30</td>
<td>Coffee Break</td>
<td></td>
</tr>
<tr>
<td>11:00</td>
<td>Pavlos Chrysafidis</td>
<td>Analysis of pharmacokinetic data using the PBFTPK software</td>
</tr>
<tr>
<td></td>
<td>Department of Pharmacy, National &amp; Kapodistrian University of Athens</td>
<td></td>
</tr>
<tr>
<td>11.30</td>
<td>Panos Macheras</td>
<td>Implications of finite absorption time on Bioavailability and Bioequivalence</td>
</tr>
<tr>
<td></td>
<td>Department of Pharmacy, National &amp; Kapodistrian University of Athens</td>
<td></td>
</tr>
</tbody>
</table>
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 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.

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.