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The role of glomerular filtration and active tubular secretion in predicting renal clearance of drugs in children using population pharmacokinetic and physiology-based pharmacokinetic modeling approaches: unspinning the yarn

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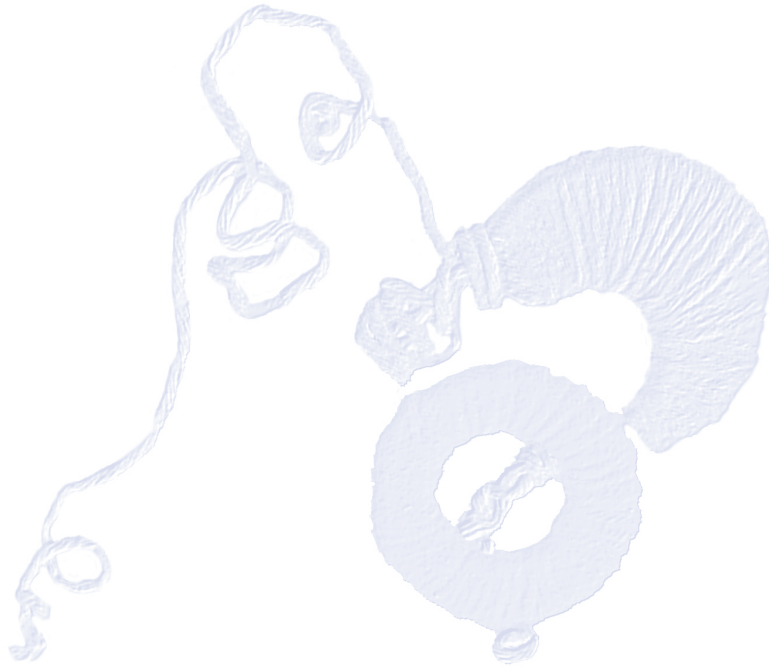
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Section VI. Appendices



Curriculum vitae

Sinziana Cristea (1988, Suceava, Romania) started her academic education in 2007 with the Faculty of Pharmacy program at the University of Medicine and Pharmacy “Carol Davila” in Bucharest Romania. Sinziana obtained her Pharmacy degree in 2012 after completing her research internship at the Department of Physical-Chemistry on formulation studies for complexes with antitumoral action under the supervision of Dr. Mihaela Ghica and Prof. Dr. Cristina Dinu-Pirvu.

In 2013 Sinziana started her Master of Science program Bio Pharmaceutical Sciences with an internship at the Department of Pharmacology under the supervision of Dirk-Jan van den Berg and Prof. Dr. Elizabeth de Lange where she was trained in developing analytical analysis methods. Her second internship was at the Centre for Human Drug Research under the supervision of Dr. Jasper Stevens where she gained experience in modeling clinical data.

In 2015 Sinziana became a Research Assistant at Simcyp (a Certara company) in Sheffield, UK, where she further developed her skills in modeling approaches and contributed to the dermal absorption module of the Simcyp Simulator. In December 2015 Sinziana returned to Leiden University as a PhD student under the supervision of Dr. Elke Krekels, Prof. Dr. Karel Allegaert and Prof. Dr. Catherijne Knibbe where she applied modeling and simulation techniques to optimize pediatric drug dosing.

In April 2020 Sinziana joined the Integrated Drug Development team at Certara as a pharmacometrician and is specializing in using modeling and simulation to identify and address key decisions in drug development.

List of publications

Publications related to this thesis

Cristea, S., Krekels, E.H.J., Allegaert, K., De Paepe, P., de Jaeger, A., De Cock, P.A.J.G., Knibbe, C.A.J. Estimation of ontogeny functions for renal transporters using a combined population pharmacokinetic and physiology-based pharmacokinetic approach: application of OAT3. *AAPS J* 23, 65 (2021) <https://doi.org/10.1208/s12248-021-00595-9>

Cristea, S., Krekels, E.H.J., Rostami-Hodjegan, A., Allegaert, K., Knibbe, C.A.J. The Influence of Drug Properties and Ontogeny of Transporters on Pediatric Renal Clearance through Glomerular Filtration and Active Secretion: a Simulation-Based Study. *AAPS J* 22, 87 (2020). <https://doi.org/10.1208/s12248-020-00468-7>

Cristea, S., Krekels, E.H.J., Allegaert, K., Knibbe, C.A.J. The Predictive Value of Glomerular Filtration Rate-Based Scaling of Pediatric Clearance and Doses for Drugs Eliminated by Glomerular Filtration with Varying Protein-Binding Properties. *Clin Pharmacokinet* (2020). <https://doi.org/10.1007/s40262-020-00890-2>

Cristea S, Allegaert K, Falcao AC, Falcao F, Silva R, Smits A, Knibbe CAJ, Krekels EHJ. Larger Dose Reductions of Vancomycin Required in Neonates with Patent Ductus Arteriosus Receiving Indomethacin versus Ibuprofen. *Antimicrob Agents Chemother*. 2019 Jul 25;63(8):e00853-19.

Cristea S, Smits A, Kulo A, Knibbe CAJ, van Weissenbruch M, Krekels EHJ, Allegaert K. Amikacin Pharmacokinetics To Optimize Dosing in Neonates with Perinatal Asphyxia Treated with Hypothermia. *Antimicrob Agents Chemother*. 2017 Nov 22;61(12):e01282-17.

Publications unrelated to this thesis

Shimizu S., Hoedt S.M. den, Mangas-Sanjuan V., **Cristea S.**, Geuer J.K., Berg D.-J. van den, Hartman R., Bellanti F. & Lange E.C.M. de. Target-Site Investigation for the Plasma Prolactin Response: Mechanism-Based Pharmacokinetic-Pharmacodynamic Analysis of Risperidone and Paliperidone in the Rat. *Drug Metabolism and Disposition* February 2017, 45 (2) 152-159

Patel, N.K.; Clarke, J.; Arora, S.; Martins, F.; Salem, F.; Abdulla, T.; Tsakalozou, E.; Hodgkinson, A.; Tash, O.A.; **Cristea, S.**; et al. Multi-Phase Multi-LAYER Mechanistic Dermal Absorption (MPML MechDermA) Model to Predict Local and Systemic Exposure of Dermally Applied Drug Products 1: Model Structure and Parameterization (*Manuscript under Preparation*).

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