

1. J Pharm Sci. 2015 Jan;104(1):191-206. doi: 10.1002/jps.24214. Epub 2014 Nov 12.

A systematic evaluation of the use of physiologically based pharmacokinetic modeling for cross-species extrapolation.

Thiel C(1), Schneckener S, Krauss M, Ghallab A, Hofmann U, Kanacher T, Zellmer S, Gebhardt R, Hengstler JG, Kuepfer L.

Author information:

(1)Computational Systems Biology, Bayer Technology Services GmbH, Leverkusen, Germany; Institute of Applied Microbiology, RWTH Aachen, Aachen, Germany.

Transfer of knowledge along the different phases of drug development is a fundamental process in pharmaceutical research. In particular, cross-species extrapolation between different laboratory animals and further on to first-in-human trials is challenging because of the uncertain comparability of physiological processes. Physiologically based pharmacokinetic (PBPK) modeling allows translation of mechanistic knowledge from one species to another by specifically considering physiological and biochemical differences in between. We here evaluated different knowledge-driven approaches for cross-species extrapolation by systematically incorporating specific model parameter domains of a target species into the PBPK model of a reference species. Altogether, 15 knowledge-driven approaches were applied to murine and human PBPK models of 10 exemplary drugs resulting in 300 different extrapolations. Statistical analysis of the quality of the different extrapolations revealed not only species-specific physiology as the key determinant in cross-species extrapolation but also identified a synergistic effect when considering both kinetic rate constants and gene expression profiles of relevant enzymes and transporters. Moreover, we show that considering species-specific physiology, plasma protein binding, enzyme and transport kinetics, as well as tissue-specific gene expression profiles in PBPK modeling increases accuracy of cross-species extrapolations and thus supports first-in-human trials based on prior preclinical knowledge. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:191-206, 2015.

[PMID: 25393841 \[PubMed - in process\]](#)