Towards Virtual Exposure Assessment of Dermally Applied Drugs - PBPK Model of Buprenorphine Transdermal Patches

Sebastian Polak1,2,*, Nikunjkumar Patel1, Karen Rowland-Yeo1, Masoud Jamei1

1Simcyp (part of Certara), Sheffield, UK; 2Jagiellonian University Medical College, Kraków, Poland

Objectives: To develop and assess a PBPK model for buprenorphine dermal patches using available physicochemical, in vitro ADME and formulation specific data for prediction of systemic exposure.

Methods: Prior ADME and formulation specific in vitro data of buprenorphine and its main metabolite norbuprenorphine were collated from publicly available sources. This includes the enzyme specific metabolism information (intrinsic clearances for CYP3A4, CYP2B6, and UGT1A1). The data were used in the Simcyp Simulator (V16) to develop the parent and metabolite compound files. The parent-metabolite model was qualified against published clinical studies using intravenous (bolus and infusion) administration of buprenorphine and the observed plasma concentration of buprenorphine and when available norbuprenorphine. After addition of the formulation (in vitro release rate from the patch, dose, thickness) and application (location and area) specific data the qualified compound files were used to predict the plasma exposure after single and multiple dermal patch application using the Multi-Phase Multi-Layer (MPML) Mechanistic Dermal absorption model.

Results: For intravenous administration and dermal patch application of buprenorphine, visual checks indicated that the model adequately predicted the buprenorphine and norbuprenorphine concentrations (Figure 1A and 1B).

Conclusions: Verified PBPK models can be used for virtual assessment of various clinical scenarios including long-term use or misuse and overdose. The ability to simulate and analyze individual profiles for different populations makes such models potentially useful for assessing exposure and safety aspects of dermal formulations, in particular, the in silico based cardiac safety assessment.