Physiologically-Based In Vitro-In Vivo Extrapolation of Tubular Reabsorption in Kidney
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Purpose
A large gap currently exists in the mechanistic translation of in vitro data to human renal excretion clearance (CLR) in vivo. While the major focus for reducing this gap has been on drug transporters, the accurate prediction of passive tubular reabsorption and its contribution to CLR has largely been ignored. In the current study, minimal physiologically-based model is applied to predict renal tubular reabsorption (Freab) and non-secretion CLR (CLR, Non-Sec) of selected drugs, using in vitro permeability data generated in Caco-2 and MDCK models.

Methods
A database of CLR values was collated from clinical reports. Passive permeability and transporter information were collated from literature and AstraZeneca in house database. Minimal physiologically-based model was used to assess the impact of changes in tubular flow rate and surface area in a stepwise manner on the prediction of Freab and CLR, Non-Sec.

Results
CLR for 63 drugs in the database ranged from 0.02 (isoxicam) to 119 mL/min (varenicline). Assuming glomerular filtration clearance (CLR,filt) was the only contributing mechanism to CLR led to an over-prediction (> 3-fold error) of CLR for 21 drugs. The minimal model of reabsorption reduced the over-prediction of CLR(z) (from 21 to 14). Accounting for proximal tubule microvilli and incorporation of water reabsorption alone or in combination improved prediction accuracy of CLR, Non-Sec (5, 11 and 2 drugs over-predicted, respectively). However, incorporation of CLR, Non-Sec resulted in under-prediction of CLR for 13 kidney transporter substrates. Similar trend was seen for 19 drugs with unknown or negative transporter affinities, of which nearly 70% were weak bases. Consideration of effects of ionisation of weak bases due to pH differences between the in vitro assay and urine reduced under-prediction of CLR for this class of drugs.

Conclusion
The proposed minimal physiologically-based model represents a promising tool for the in vitro-in vivo extrapolation of tubular reabsorption and renal clearance. Further refinement and ability of the model to account for active secretion is ongoing.