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# Prediction of AUCpo in humans - A modern in-silico-based system that outperforms traditional in-vitro- and animal-methods

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**Introduction** The aims were to investigate limitations with lab methodologies for prediction of area-under-the-curve following oral dosing ($AUC_{po}$) in man, and to benchmark the performances of these methods versus our proprietary, validated *in-silico*-based prediction system.

**Method** Lab-based predictions of $AUC_{po}$ (n=107) were taken from an investigation of 66 different *in-vitro*- and animal-methods by 11 big pharmas and one university (1). The literature was searched for data demonstrating limitations with lab methods. Results were compared to *in-silico*-predictions for several hundred compounds (molecular weight ~150-750).

**Results** A significant portion of commonly used *in-vitro* and animal-based prediction methods are associated with >1000-fold maximum prediction errors and systemic errors (1). Million-fold errors have been shown for some methods, allometry inclusively (1-3). A large portion of non-quantifiable compounds (>50%) and large maximum errors (at least ~2,000-fold) are among limitations with human hepatocyte-based predictions (2,4). Binding to material, low solubility, methodological differences (up to ~200-fold for $f_u$ (2)) and contribution by efflux, conjugation and excretion are other limitations/challenges with *in-vitro* methods. Consequences include jeopardized safety in early clinical trials (a 5,800-fold underprediction of AUC following iv dosing with allometry is reported (3)), poor understanding of drug candidate characteristics, additional costs and delays. In benchmarking studies the *in-silico* system succeeded in predicting hundreds of drugs inaccessible to *in-vitro* methods, and outperformed *in-vitro* methods in 56 out of 57 difficult cases. The Prosilico *in-silico* system was also comparable, or better than, the best of animal-based prediction methods.

**Conclusions** Limitations with lab-methods for prediction of $AUC_{po}$ in man were explored and highlighted. With our new proprietary *in-silico* system predictions can be improved, with the potential to enhance human safety, reduce animal experiments, costs and time, frontload decision-making (predictions before compound synthesis) and find better drugs.

## References

1. Ring BJ et al. (2011). *J Pharm Sci* **100**: 4090-4110.

2. Prosilico. Data on file.

3. Fuse E et al. (1998). *Cancer Res* **58**: 3248-3253.

4. Stringer R et al. (2008). *Xenobiot.* **38**: 1313-1329.