Qualification of a Human 3D Liver-on-Chip Model: Establishing a Cross-pharma trial to evaluate ADME and Toxicity Predictions in Pre-clinical Development

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INTRODUCTION

Safety concerns, particularly drug-induced liver injury, often lead to the discontinuation of drug candidates during preclinical development. Less than 10% of drugs that reach Phase I clinical trials obtain FDA approval, highlighting the need for better preclinical testing methods. Traditional animal models have limited relevance to humans, prompting the development of complex in vitro models (CIVM). In this context, we have established a pathway to validate a 3D liver-CIVM according to the guidelines outlined by the MPS Affiliate of the International Consortium for Innovation and Quality in Drug Development (IQ-MPS). This study describes a Liver Ring Trial (LRT) as a joint effort by 6 international pharma companies, a platform developer, and a computational expert company to test the overall reproducibility of a liver microphysiological system (MPS) across different labs. An overview of the intrinsic clearance experiment is provided here.

EXPERIMENTAL DESIGN PRINCIPLES

The qualification strategy starts with validating the liver-CIVM's biological function and reproducibility of the assay using hepatic biomarkers (albumin, urea, ALT, AST) and ATP for viability, in a context-of-use agnostic manner. In a second stage, nine reference compounds were selected to validate the reproducibility of predictive results in two contexts: i) drug-induced liver-injury (DILI) and ii) intrinsic clearance. LC-MS measurements are performed to measure loss of parent compound and non-specific binding during the screening phase to correlate observed toxic/clearance effects to actual concentrations and improving the predictability of the outcome. To address interlaboratory variability, a regulatory-aligned SOP randomly and blindly assigns test compounds for qualification rounds.

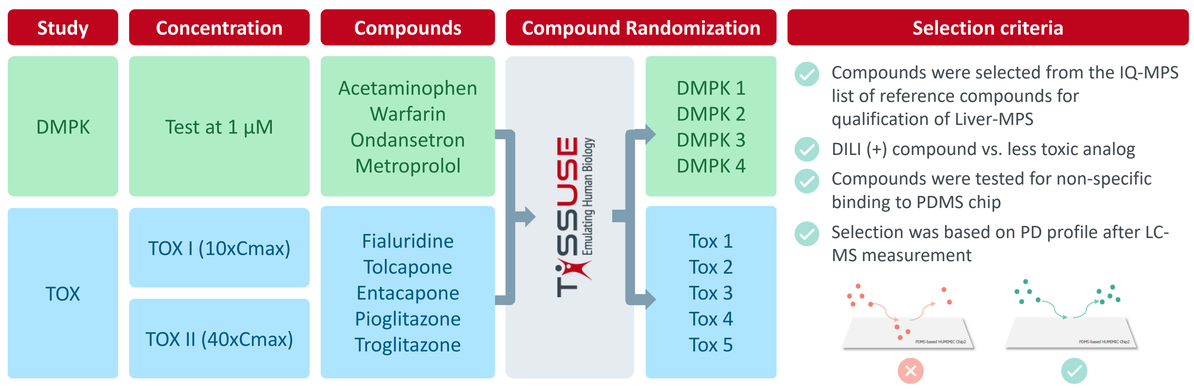


Fig. 1 Study arms of the Liver-Ring-Trial. Intrinsic clearance (DMPK, green) and drug-induced liver injury (TOX, blue) with corresponding test compounds and concentrations.

RESULTS

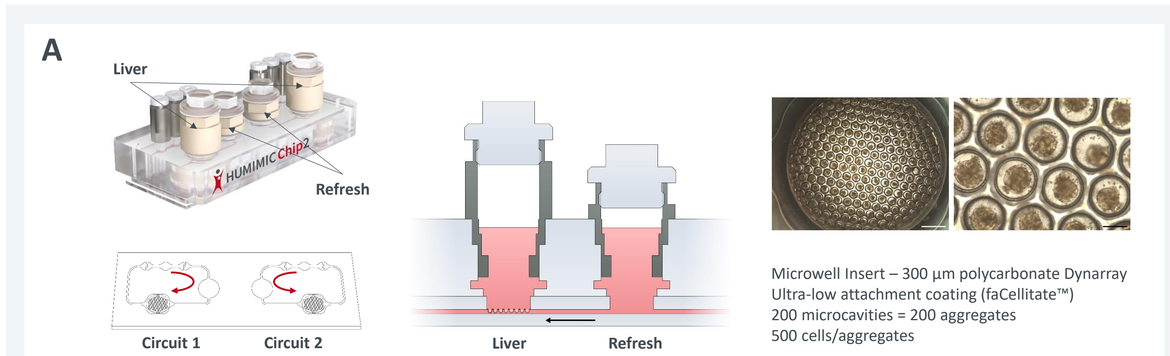
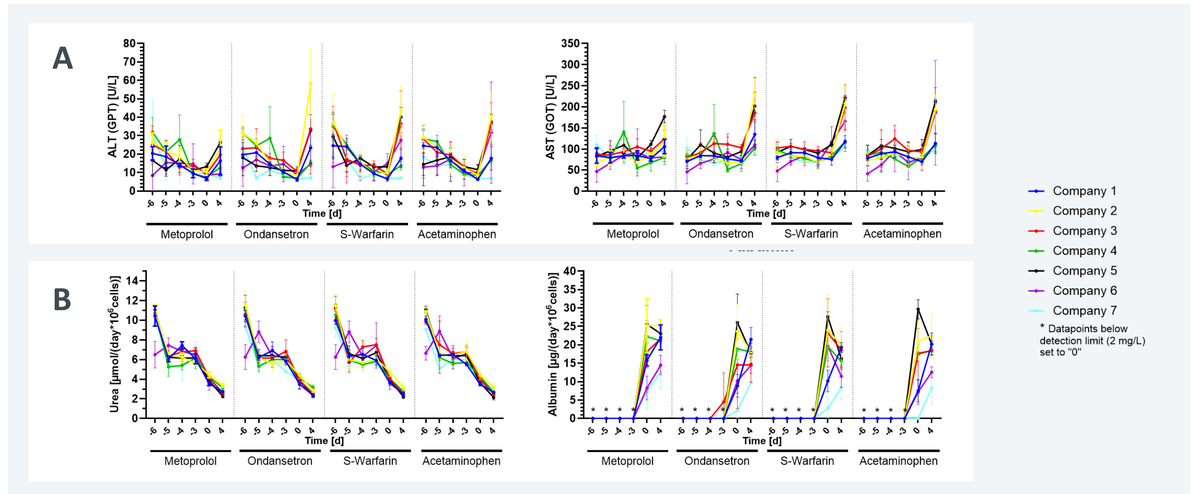
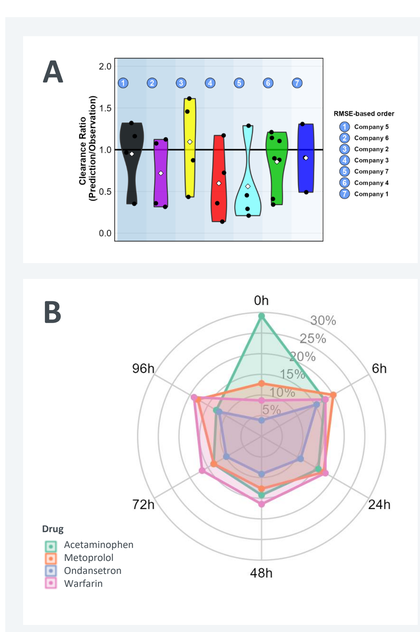


Fig. 2 Human liver spheroid formation in organ-chip using microwells. A: HUMIMIC Chip2 96-well setup with spheroids formed by seeding 100,000 cells onto microwell inserts. B: Each member is equipped with 2 HUMIMIC starters which can operate 16 circuits per study. C: Experimental timeline of the DMPK study.



↑ **Fig. 3 Biomarker characterization of the liver-chip over time.** A: ALT/AST release in the medium of the different treatment conditions over time produced in 7 independent labs. The data is shown as the amount of ALT/AST present in the medium (U/L). Data represents mean +/- standard deviation of the mean. N = 3-4. B: albumin and urea production in the different treatment conditions over time produced in 7 independent labs. Data represents mean +/- standard deviation. N=3-4



← **Fig. 4 Human clearance variability and prediction accuracy across labs. A:** Violin plot of prediction accuracy (clearance ratio = predicted/observed) for seven independent labs. Each shape shows a company's distribution; white diamonds indicate medians. Black line at 1.0 represents perfect predictions. Companies are ranked by overall accuracy. **B:** Radar plot of inter-company variability in drug concentration (coefficient of variation, CV) over time (0h–96h). Each polygon represents one drug; longer radii indicate higher variability. Variability was highest for acetaminophen at 0h, suggesting inconsistencies in initial dosing or media preparation. Intra-company CV = 11.1% (good within-lab replicate consistency); inter-company CV = 14.8% (acceptable site-to-site reproducibility).

SUMMARY & OUTLOOK

Inter-lab variability was notably higher for acetaminophen, indicating potential inconsistencies in early experimental steps across sites. The remaining drugs showed more uniform results between labs, and technical variability within labs was low—demonstrating strong assay reliability. By addressing interlaboratory variability and thoroughly qualifying the 3D MPS liver model, our study advances its use as a standard tool in drug development, ensuring reliable, reproducible results across labs and supporting more accurate, cost-effective preclinical testing.

References 1- Cox et al., Biomater. Biosyst. 2022

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