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Biomarkers of CYP3A activity: What have we learned and are we ready to utilize biomarkers to replace clinical DDI studies?

Perspectives and case examples from industry

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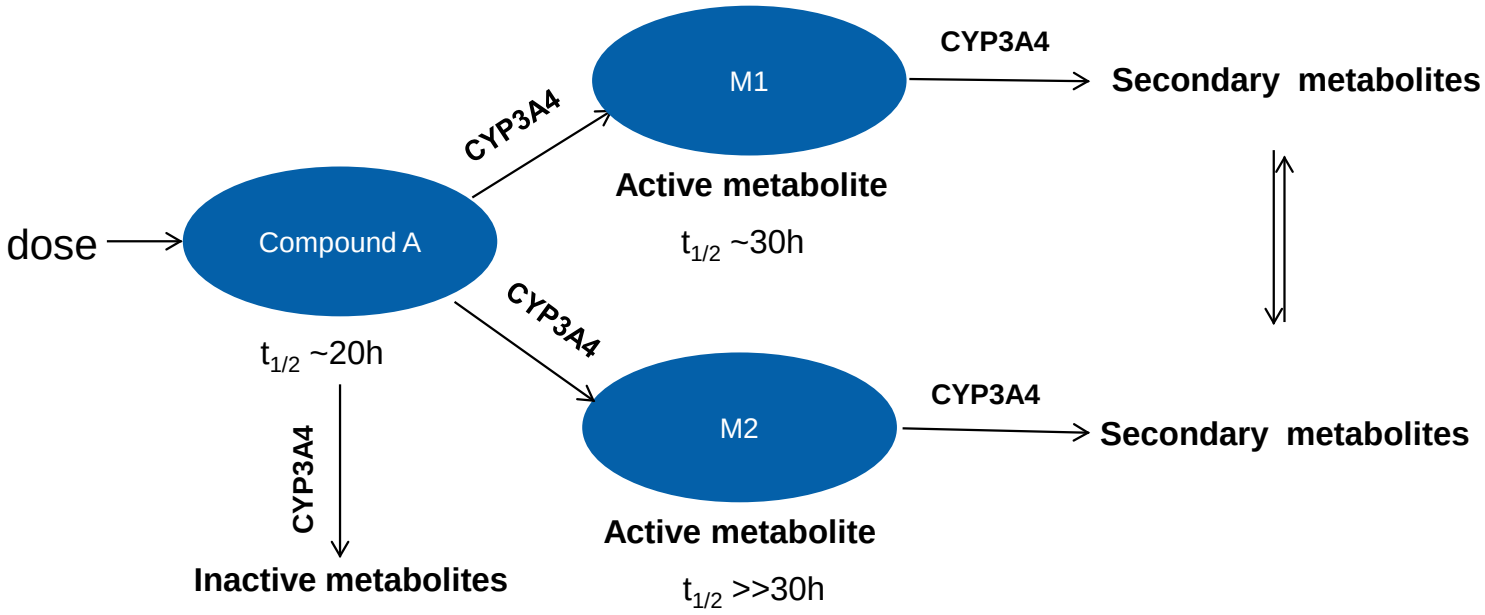
Compound A



Complex *in vitro* DDI properties: CYP3A4 substrate, mixed time-dependent inhibition, reversible inhibition and induction of CYP3A

<u>Question</u>: What is the net effect of parent + metabolites on midazolam exposure at steady-state in patients?

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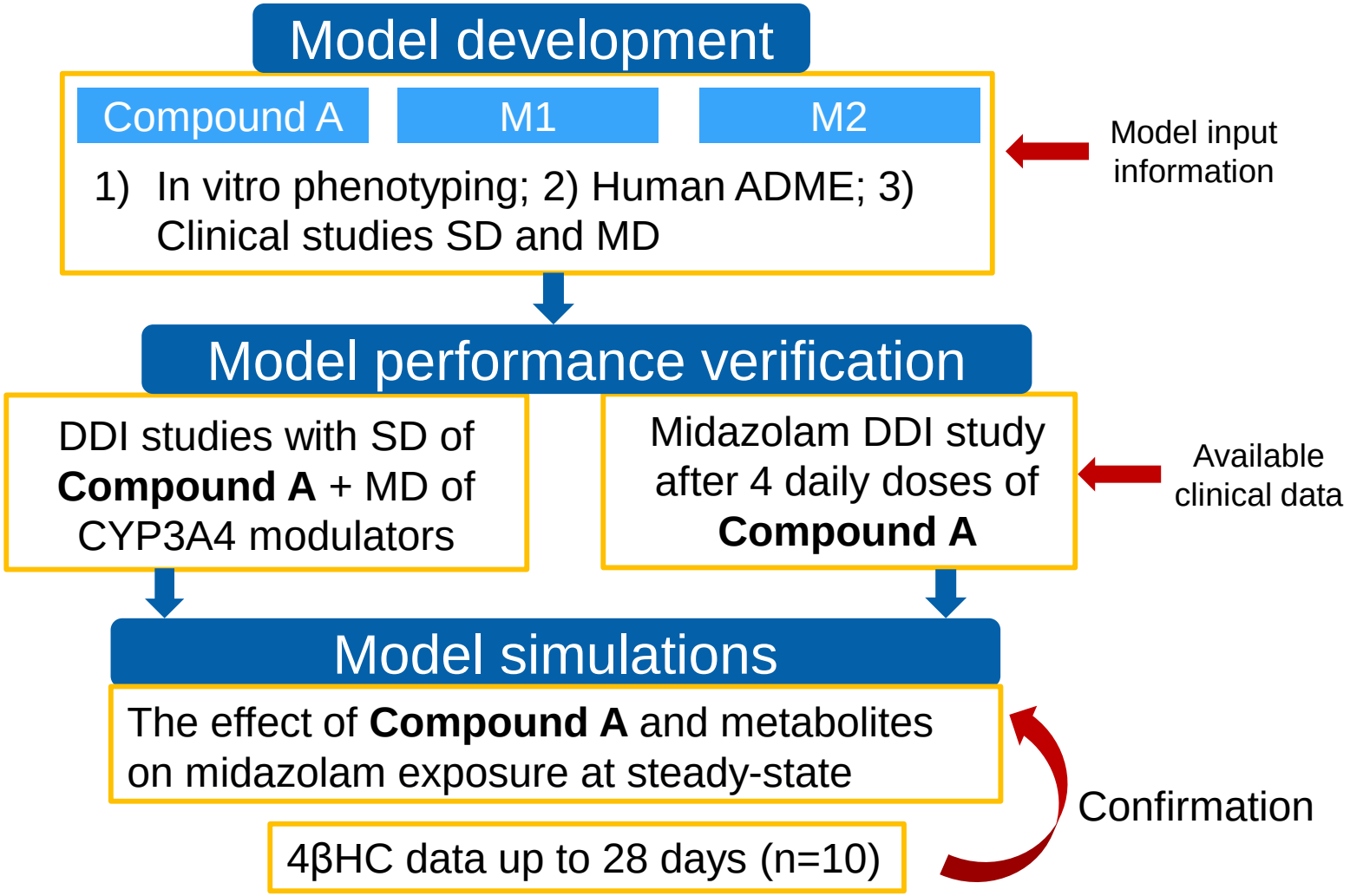
An integrated PBPK approach



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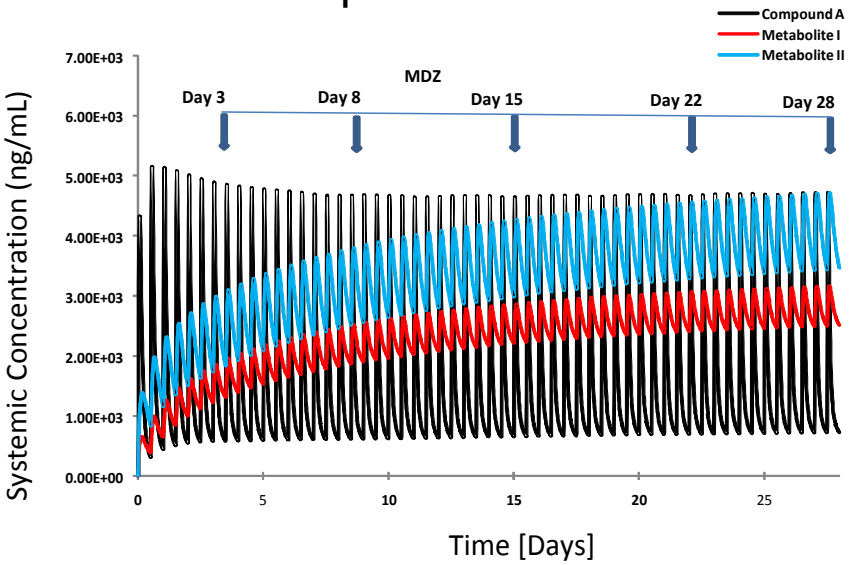
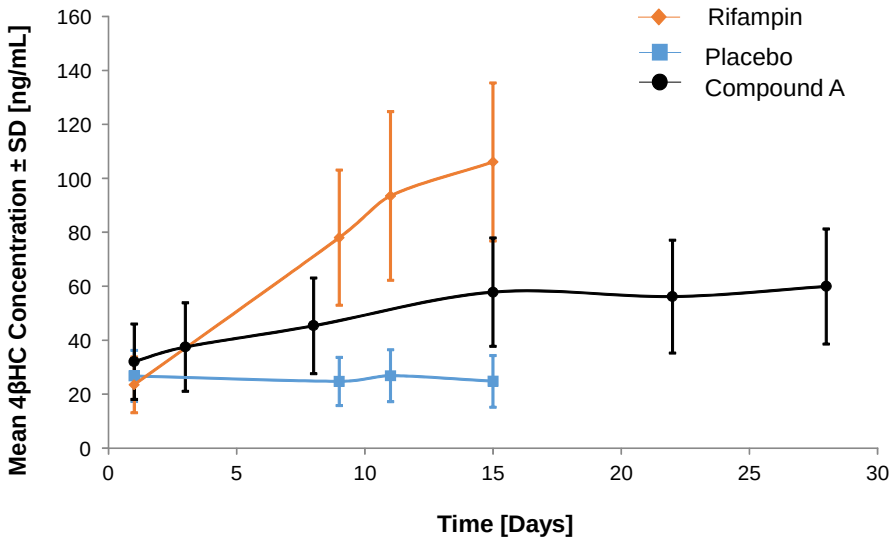
Assessment of net effect

Simulated PK profiles



Time course of plasma 4ßHC



Time [Days]	3	8	15	22	28
Predicted midazolam AUC GMR	0.84	0.60	0.55	0.54	**0.54**
Median Plasma 4βHC ratio relative to baseline (n=10)	1.2	1.4	1.8	1.9	**1.8**

Best case = weak induction (FDA, 2012)

Worst case = moderate induction (Mangold et al 2016)

Limitation of 4βHC to differentiate weak and moderate induction given the complexity of TDI/induction by parent + metabolites

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Compound A conclusions

- PBPK model predicted a weak induction of CYP3A (best case scenario).
- Inducer classification based on model predicted 4βHC changes classified Compound A as moderate CYP3A inducer (worst case scenario).
- An integrated approach increased our confidence in DDI predictions.

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Compound B: available data

- *In vitro* studies
  - CYP3A4-mediated metabolism
  - Weak CYP3A4 inducer
- Clinical PK and DDI studies
  - Study with itraconazole: fmCYP3A4 of ~0.8
  - Long $t_{1/2}$ (~160 hr); 28 days to steady-state
  - Plasma 4βHC levels (multiple ascending dosing, 90 days)

***Question**: Is it possible to determine the CYP3A4 induction potential clinically using 4βHC data from FIH study?*

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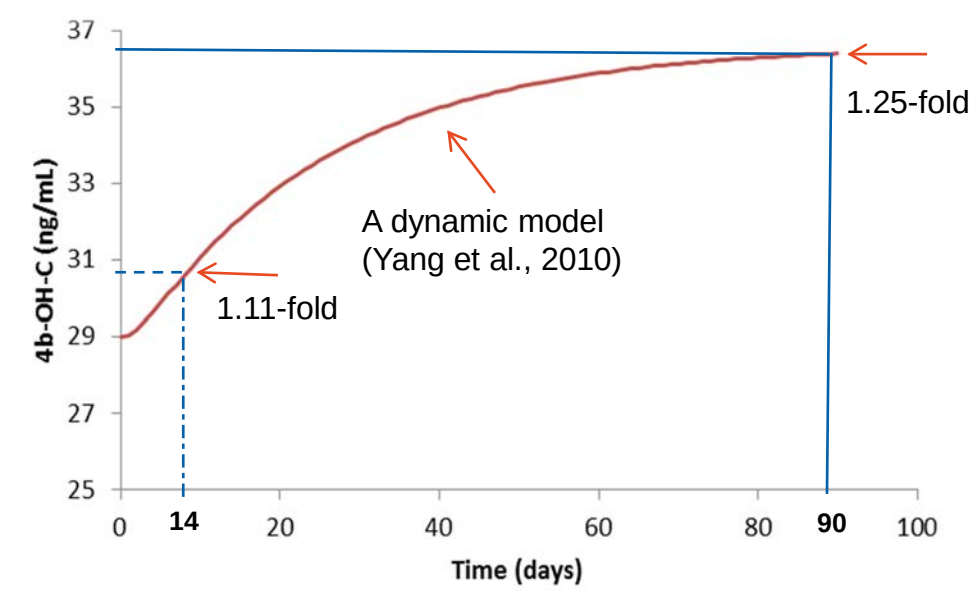
Method

Application of plasma 4βHC data ⟷ **PBPK model**



Days	Regulatory CYP3A inducer classification based on model-predicted 4βHC increase (MDZ AUC GMR)		
	Mechanism–based PK/PD (Leil et al., 2014)	Emax-Imax (Mangold et al., 2016)	Population PK/PD (Jiang et al., 2016)
90	Moderate	Weak	Moderate
14	**Weak (0.62)**	**Weak (0.79)**	**Weak**

Bottom-up approach using in vitro EC_{50} predicted midazolam AUC GMR of 1

↓

Top-down approach used to calculate optimized EC_{50} (~13-fold reduction)

↓

Optimized PBPK model predicted that **Compound B** would result in midazolam **AUC GMR of 0.66 (weak)**

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Compound B conclusions

- PBPK model predicted MDZ AUC ratio of 0.66 (weak)
- The prediction was confirmed by biomarker data quantitatively.
- Compound B advanced to POC testing without the need of midazolam DDI study.
- Is it important to measure 4βHC levels at late time point (after 2-week) for compounds with long $t_{1/2}$ to capture PK steady state of perpetrator as well as 4βHC?

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