



H3D Foundation and Ersilia Present

Bringing data science and AI/ML tools to infectious disease research

Session 3: Skills session

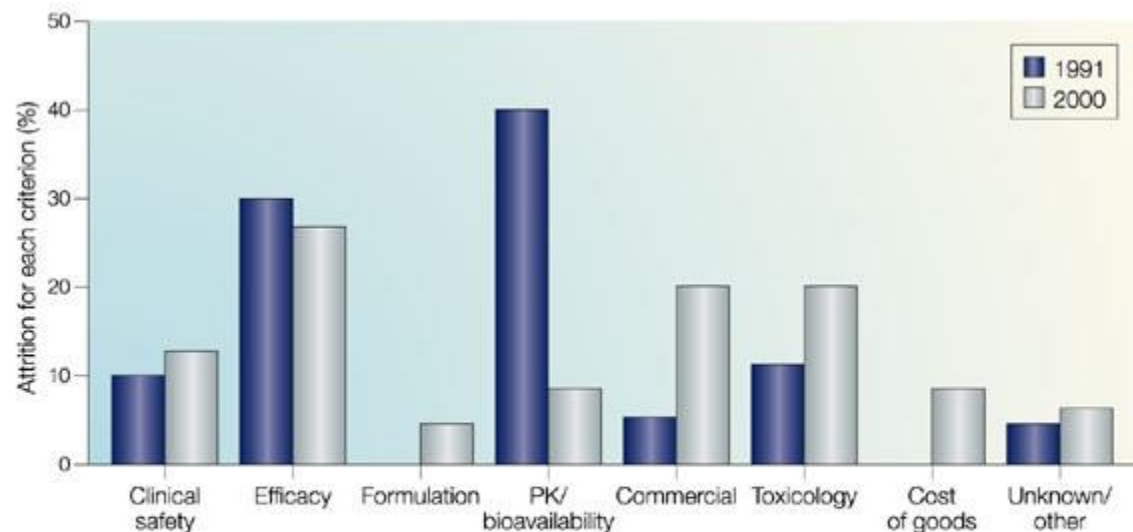
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Evolution of DMPK



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Nature Reviews | Drug Discovery

1950s – 1980s
Pharmacodynamic drug
discovery

1990s
High throughput DMPK driven
by revolution in analytical tools
and robotics

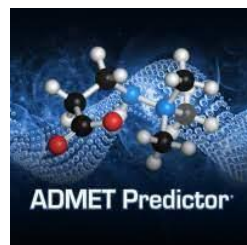
2000s
Assay refinement for IVIVC +
QSAR + mechanistic models

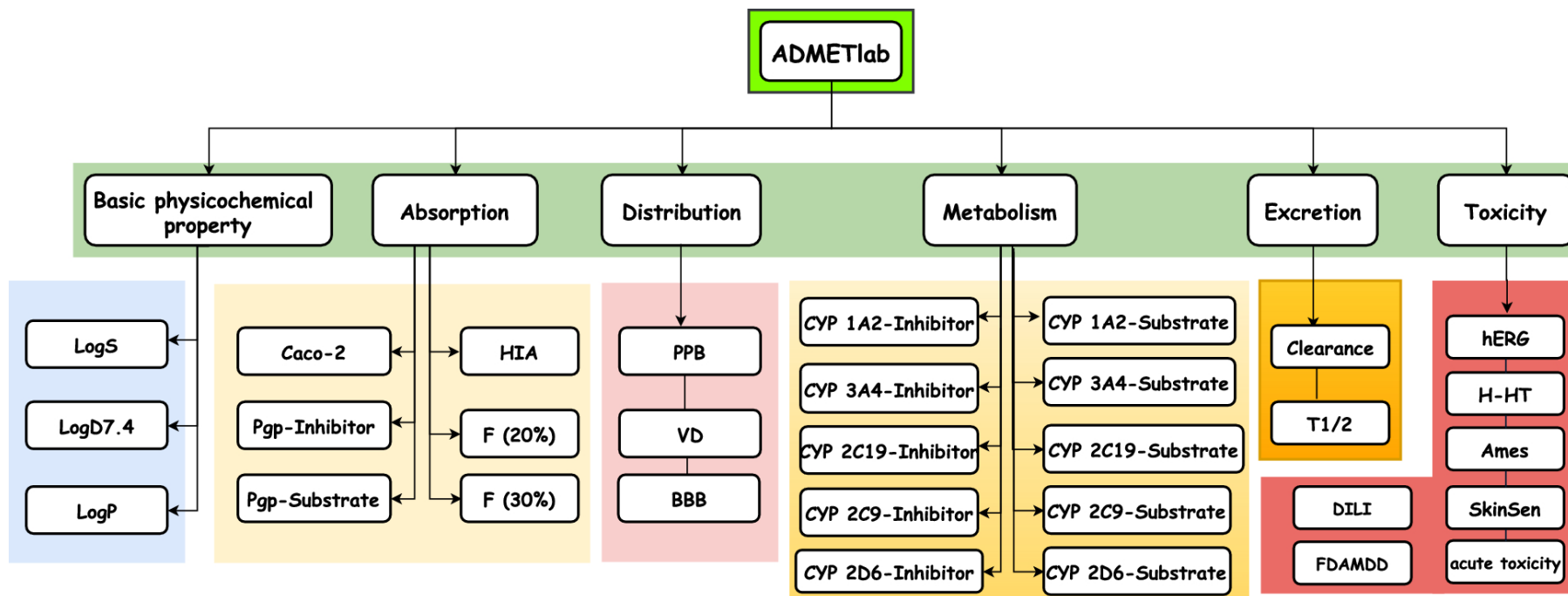
Modern era
High throughput DMPK +
Modelling and Simulation +
AI/ML-based predictions for
compound design etc

Computational Tools in DMPK



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Dong et al. *J Cheminform* (2018) 10:29
<https://doi.org/10.1186/s13321-018-0283-x> 

SOFTWARE  

ADMETLab: a platform for systematic ADMET evaluation based on a comprehensively collected ADMET database

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Abstract

Current pharmaceutical research and development (R&D) is a high-risk investment which is usually faced with some unexpected even disastrous failures in different stages of drug discovery. One main reason for R&D failures is the efficacy and safety deficiencies which are related largely to absorption, distribution, metabolism and excretion (ADME) properties and various toxicities (T). Therefore, rapid ADMET evaluation is urgently needed to minimize failures in the drug discovery process. Here, we developed a web-based platform called ADMETLab for systematic ADMET evaluation of chemicals based on a comprehensively collected ADMET database consisting of 288,967 entries. Four function modules in the platform enable users to conveniently perform six types of drug-likeness analysis (five rules and one prediction model), 31 ADMET endpoints prediction (basic property, 1, absorption, 6, distribution, 3, metabolism, 10, elimination, 2, toxicity, 7), systematic evaluation and database/similarity searching. We believe that this web platform will hopefully facilitate the drug discovery process by enabling early drug-likeness evaluation, rapid ADMET virtual screening or filtering and prioritization of chemical structures. The ADMETLab web platform is designed based on the Django framework in Python, and is freely accessible at <http://admet.scbdd.com/>.

ADMETLab 2.0: an integrated online platform for accurate and comprehensive predictions of ADMET properties

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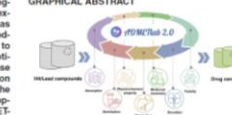
Received January 30, 2021; Revised March 20, 2021; Editorial Decision March 29, 2021; Accepted March 30, 2021

ABSTRACT

Because undesirable pharmacokinetics and toxicity of candidate compounds are the main reasons for the failure of drug development, it has been widely recognized that absorption, distribution, metabolism, excretion and toxicity (ADMET) should be evaluated as early as possible. In silico ADMET evaluation models have been developed as an additional tool to assist medicinal chemists in the design and optimization of leads. Here, we announced the release of ADMETLab 2.0, a completely redesigned version of the widely used ADMETLab web server for the predictions of pharmacokinetics and toxicity properties of chemicals, of which the supported ADMET-related endpoints are approximately twice the number of the endpoints in the previous version, including 17 physicochemical properties, 13 medicinal chemistry properties, 23 ADME properties, 27 toxicity endpoints and 8 toxicophore rules (751 sub-

server is freely available, without registration, at <https://admetmesh.scbdd.com/>.

GRAPHICAL ABSTRACT



INTRODUCTION

A successful drug should achieve a finely tuned combination of biochemical behavior, pharmacokinetics and safety

- ADMETLab is implemented on the Ersilia Model Hub (eos2re5)

ADMETLab skills workshop



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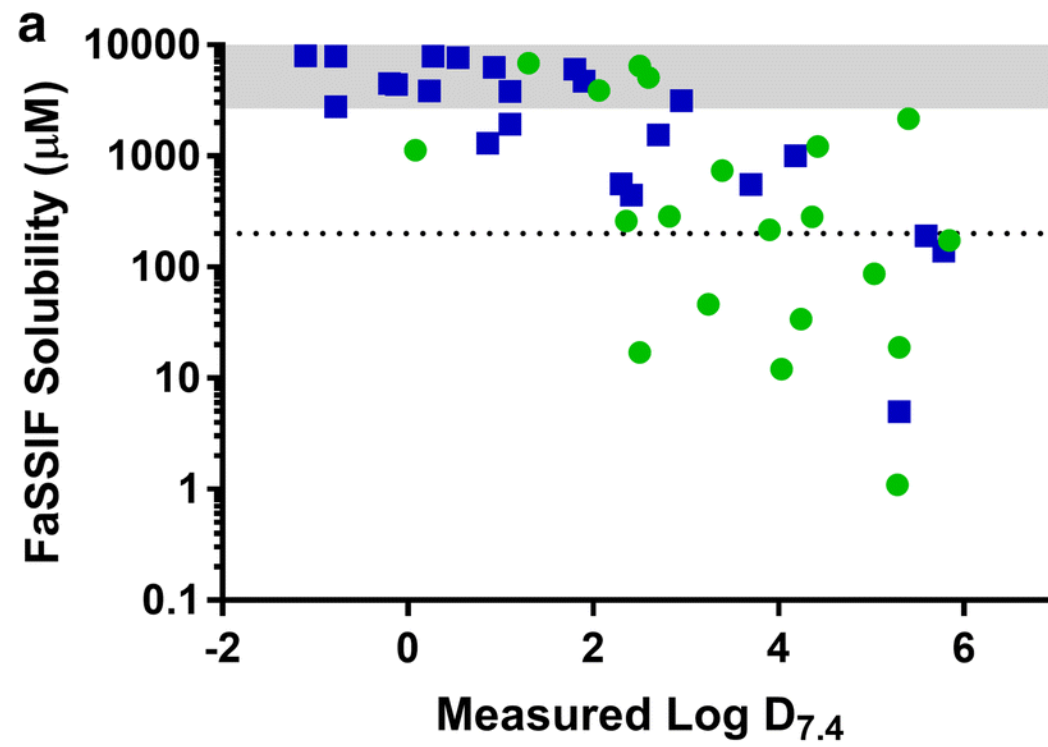
- We will now evaluate the ADMET properties of a series of clinically used drugs to demonstrate the process

Quinine
Chloroquine
Amodiaquine
Desethylamodiaquine
Artemether
Lumefantrine
Amlodipine
Nifedipine
Ritonavir

Solubility and Log D



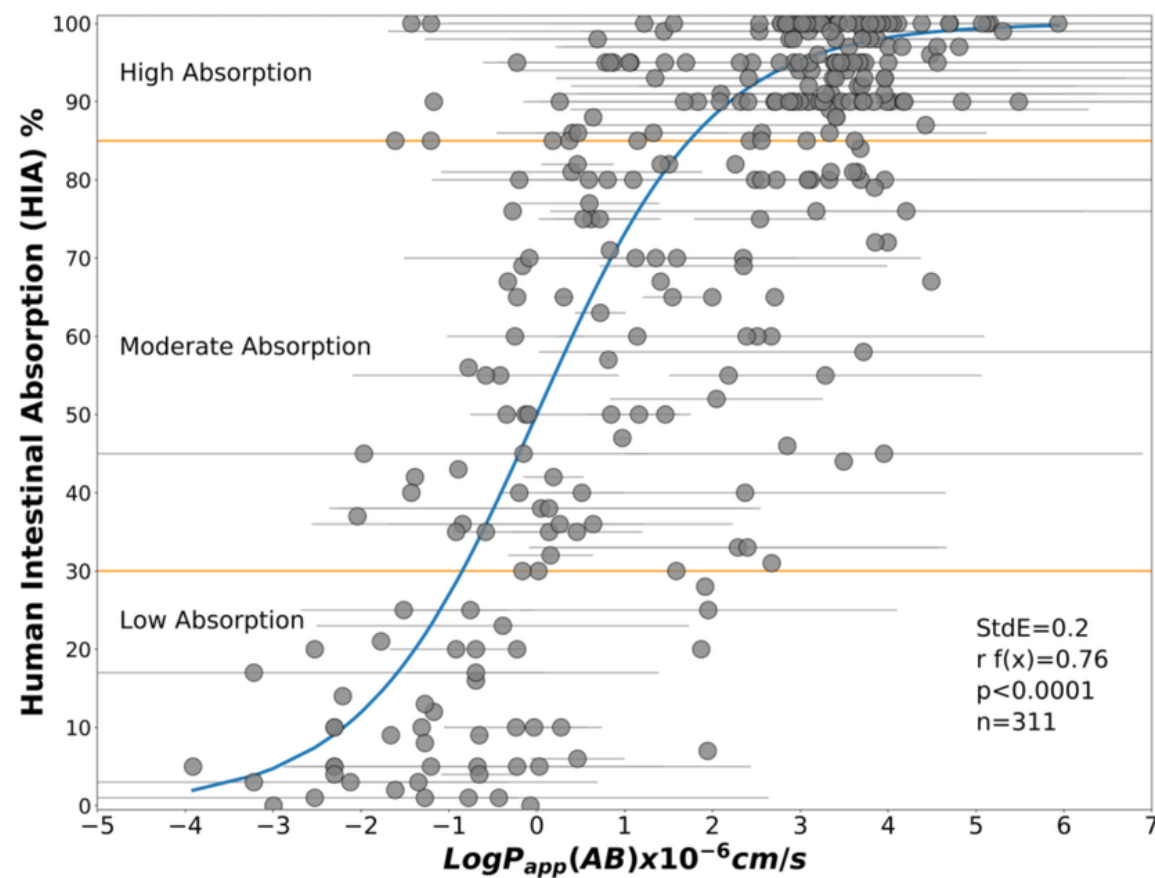
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Caco-2 vs HIA



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Clearance and unbound clearance



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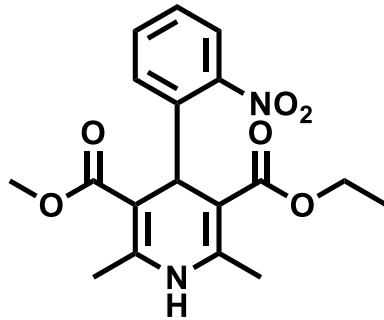
- Unbound clearance and its use for compound ranking

	CL	Fu	CLu
Quinine	3.3	18.49%	17.9
Chloroquine	5.8	25.79%	22.6
Amodiaquine	7.5	1.42%	529.5
Desethylamodiaquine	5.4	7.63%	70.7
Artemether	15.9	3.64%	436.3
Lumefantrine	5.6	0.67%	832.5
Amlodipine	6.9	42.93%	16.1
Nifedipine	10.1	19.50%	51.6
Ritonavir	6.4	0.74%	867.2

VD, half-life and dose



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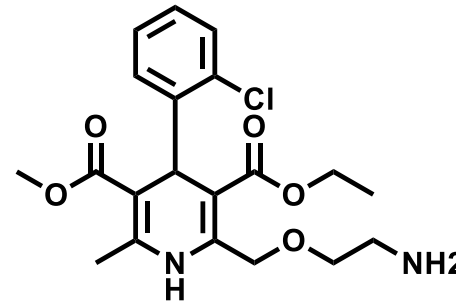
Nifedipine

Vd_u 19.5 L/kg

CL_u 175 ml/min/kg

$t_{1/2}$ 1.8h

Dose: 10 mg x 3 times a day



Amlodipine

Vd_u 228 L/kg

CL_u 85 ml/min/kg

$t_{1/2}$ 40h

Dose: 10 mg once a day

$$t_{1/2} = \frac{\ln 2 * Vd}{CL}$$



Dose prediction on MMVSola

- The impact of ADME/PK on the clinical efficacy of a compound can be described using mathematical equations allowing human dose prediction from *in vitro* data.
- Let's explore this using ADME/PK data of a hypothetical compound.
- Navigate to <https://www.mmvsola.org/>

MMVSola Predictor Basic Parameters Advanced Parameters

Upload Science Cloud or MMVSola Input file
Browse... No file select

Reset inputs

CLINICAL PK DATA	PRECLINICAL PK DATA	DOSING & PD DATA
H Plasma Binding [%] <input type="text"/>	R R Plasma Binding [%] <input type="text"/>	Simulated Dose [mg] <input type="text" value="100"/>
H Blood to Plasma Ratio <input type="text" value="1"/>	NF54 72h IC50 [nM] <input type="text"/>	Hill Slope <input type="text"/>
LogD (or LogP for bases) <input type="text"/>	R Plasma CL [mL/min/kg] <input type="text"/>	Log10 In-vitro PRR / 48h <input type="text"/>
H Hep. CLint [$\mu\text{L}/\text{min}/10^6$ cells] <input type="text"/>	R Plasma Vss [L/kg] <input type="text"/>	Molecular Weight [Da] <input type="text"/>
	R Hep. CLint [$\mu\text{L}/\text{min}/10^6$ cells] <input type="text"/>	

To get an initial prediction you need to input:

- Plasma Protein Binding in Human
- Hepatocyte or Microsome Human CLint
- Vss in at least one preclinical species

Parameter	Estimate
Predicted plasma hepatocyte CL (No IVIV) (mL/min/kg)	Not Available
Predicted Plasma microsome CL (Mic Based) (mL/min/kg)	Not Available
in-vitro under-prediction (HEP)	Not Available
in-vitro under-prediction (MIC)	Not Available
Selected in-vitro assay	Human Hepatocytes
Final Predicted Plasma CL (mL/min/kg)	Not Available
Human Vss (L/kg)	Not Available
C _{max} (nM)	Not Available



Dose prediction on MMVSola

- Navigate to <https://www.mmvsola.org/>
- Load the data saved under your project folder

MMVSola Predictor

Basic Parameters

Advanced Parameters

Upload Science Cloud or MMVSola Input file

Browse... No file select

Reset inputs

CLINICAL PK DATA

PRECLINICAL PK DATA

DOSING & PD DATA

H Plasma Binding [%]

H Blood to Plasma Ratio

LogD (or LogP for bases)

H Hep. CLint [μL/min/10⁶ cells]

R

R Plasma Binding [%]

R Plasma CL [mL/min/kg]

R Plasma Vss [L/kg]

R Hep. CLint [μL/min/10⁶ cells]

Simulated Dose [mg]

NF54 72h IC50 [nM]

Hill Slope

Log10 in-vitro PRR / 48h

Molecular Weight [Da]

To get an initial prediction you need to input:

- Plasma Protein Binding in Human

- Hepatocyte or Microsome Human CLint

- Vss in at least one preclinical species

Parameter

Estimate

Predicted plasma hepatocyte CL (No IVIV) (mL/min/kg)

Not Available

Predicted Plasma microsome CL (Mic Based) (mL/min/kg)

Not Available

in-vitro under-prediction (HEP)

Not Available

in-vitro under-prediction (MIC)

Not Available

Selected in-vitro assay

Human Hepatocytes

Final Predicted Plasma CL(mL/min/kg)

Not Available

Human Vss (L/kg)

Not Available

C_{max} (ng/mL)

Not Available

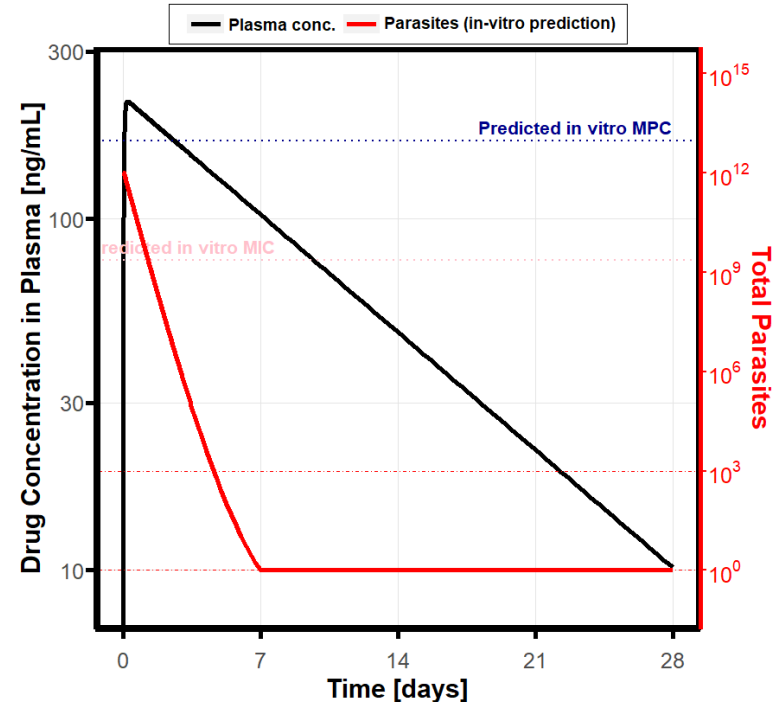
MMVSola dose prediction



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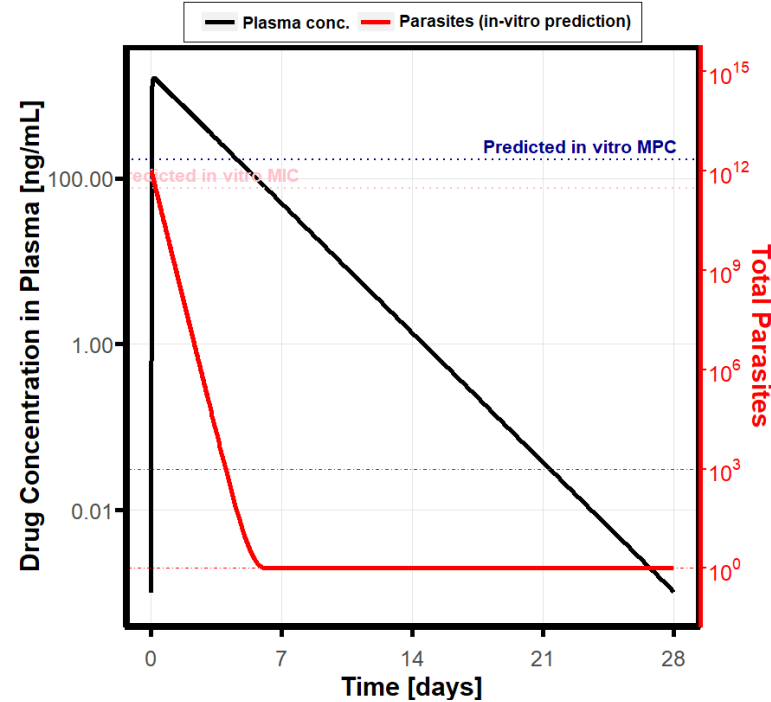


Predicted Plasma Exposure & Parasite Dynamics (WT0=55kg)
Dose: 62mg --- Clearance Method: Human Hepatocytes with IVIV correction



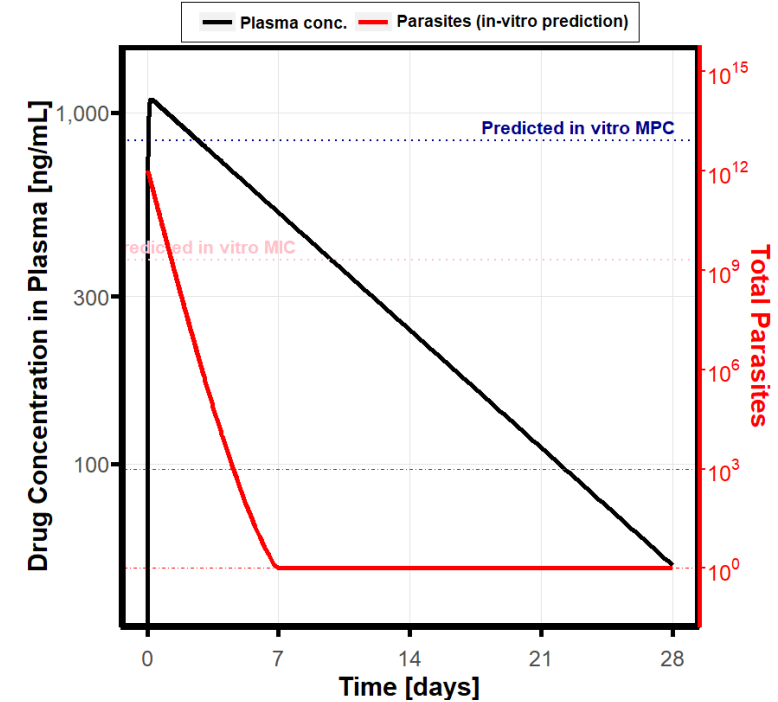
Heps CL_{int}: 1 µl/min/e6 cells
NF54: 20 nM
Predicted dose: 62 mg

Predicted Plasma Exposure & Parasite Dynamics (WT0=55kg)
Dose: 525mg --- Clearance Method: Human Hepatocytes with IVIV correction



Heps CL_{int}: 5 µl/min/e6 cells
NF54: 20 nM
Predicted dose: 525 mg

Predicted Plasma Exposure & Parasite Dynamics (WT0=55kg)
Dose: 313mg --- Clearance Method: Human Hepatocytes with IVIV correction



Heps CL_{int}: 1 µl/min/e6 cells
NF54: 100 nM
Predicted dose: 313 mg

ADME/PK and Dose



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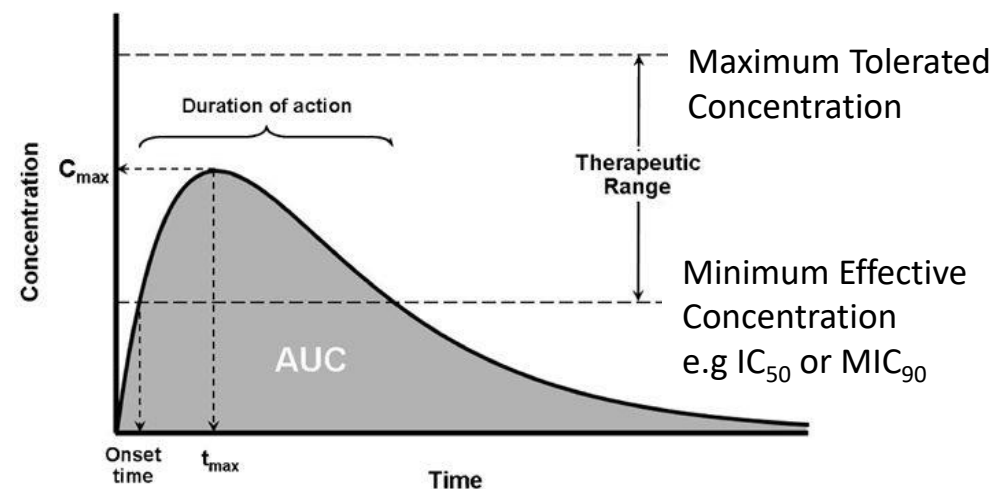
- The unbound Area Under the Curve (AUC_u) is one of the key measures of how much compound is in circulation

- For an oral drug;

$$AUC_u = F_{abs} \cdot F_{gut} \cdot \frac{\text{Dose}}{CL_{int,u}}$$

Therefore:

$$\text{Dose} = F_{abs} \cdot F_{gut} \cdot \frac{AUC_u}{CL_{int,u}}$$



- Increasing clearance increases the dose since more compound is required to achieve a similar AUC
- With an increase in IC₅₀ and increase in exposure levels is required resulting in an increased dose.