

Drug-Drug Interaction (DDI) Calculator

Streamline DDI predictions using available *in vitro* and clinical PK data

The DDI Calculator within DIDB is a tool designed to quantitatively assess clinical DDI risk of a compound acting as a precipitant or perpetrator based on the compound properties and early *in vitro* results.

Using both basic and mechanistic static models, the DDI calculator can predict enzyme inhibition and induction as well as transporter inhibition.

Greater productivity

Automated calculations and pass/fail indicators allow users to work more efficiently

Built-in compliance

Promotes regulatory compliance by incorporating ICH M12 final guideline and other guidances from global regulatory agencies

Push-button Report Generation

Enables easy export of submission-ready PDF documents with footnote citations based on your calculations



The challenge

Evaluating DDI risk requires integrating enzyme and transporter data, selecting appropriate parameters (e.g., C_{max} , $f_{u,p}$, K_i , EC_{50}), and applying regulatory equations across multiple mechanisms.

This process is often manual, time-consuming, and difficult to standardize.



The solution: DIDB DDI Calculator

The DDI Calculator consolidates key regulatory models and parameters into a single environment, enabling rapid evaluation of DDI risk based on compound-specific inputs.

Key features

Mechanistic enzyme and transporter DDI assessment

The screenshot shows the DIDB DDI Calculator interface. At the top, there are tabs for 'Enzyme inhibition and induction', 'Transporter inhibition', 'View all', and 'Constants'. A 'Print / Save as PDF' button is on the right. Below the tabs, there are sections for 'Regulatory agencies' (with checkboxes for ICH, FDA, EMA, PMDA, NMPA) and 'General precipitant properties' (with a dropdown arrow). The 'General precipitant properties' section includes a 'Compound name' field (containing 'didb123') and several input fields for 'Molecular weight', 'Dose', 'Route', 'I_{gut}', 'C_{max}', 'f_{u,p}', 'C_{max,u}', 'F_s', 'F_g', 'k_a', 'R_B', and 'C_{max,intest,u}'. Each input field has a unit or a small icon indicating its type.

- Evaluate enzyme reversible inhibition, time-dependent inhibition, induction, and transporter inhibition
- Apply basic and mechanistic static models to predict AUCR and net interaction effects
- Assess combined hepatic and intestinal contributions to DDI risk

Regulatory-aligned calculations

- Implement equations and thresholds from ICH M12 and global regulatory guidance (FDA, EMA, PMDA, NMPA)
- Use standardized system parameters (e.g., enzyme turnover, blood flow) for consistency
- Ensure alignment with expectations for DDI risk assessment and regulatory submissions

ICH M12 Guideline

2.1.2 Drug as an Inhibitor of CYP Enzymes

An investigational drug's potential to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A in both a reversible manner and time-dependent manner (TDI) should be evaluated.

2.1.2.1 Reversible Inhibition

In the reversible inhibition experiments, a K_i (inhibition constant) is usually determined experimentally or estimated based on half-maximal inhibitory concentration (IC_{50}) using unbound concentrations (refer to Section 7.3.3). If the initial experiments testing a sufficiently high concentration of the investigational drug already indicate that the $K_{i,u}$ will be markedly higher than the cutoffs given (see below), the risk for clinical inhibition can normally be excluded without further data.

The risk for reversible enzyme inhibition can be excluded based on *in vitro* data ("basic method") if:

$$K_{i,u} > 50 \times C_{max,u} \text{ (i.e., } \frac{C_{max,u}}{K_{i,u}} < 0.02)$$

$K_{i,u}$ is the unbound inhibition constant.

$C_{max,u}$ is the unbound C_{max} at the highest recommended dose at steady state.

Automated, submission-ready reporting

Reversible inhibition

Enzyme	Substrate name	IC ₅₀	K _i	f _{u,in vitro}
CYP1A2	phenacetin	70 μ M	35 μ M	0.9
CYP3A4	midazolam	20 μ M	10 μ M	0.9

Enzyme	Basic model		Cut-off limit	DDI guideline
CYP1A2	$C_{max,u}/K_{i,u}$	0.003	passes cut-off limit	≥ 0.02 ICH
CYP1A2	dose/250 mL/ $K_{i,u}$	—	≥ 10	ICH
CYP3A4	$C_{max,u}/K_{i,u}$	0.009	passes cut-off limit	≥ 0.02 ICH
CYP3A4	dose/250 mL/ $K_{i,u}$	14.815	fails cut-off limit	≥ 10 ICH

Comments

The K_i values were calculated using $IC_{50}/2$, assuming competitive inhibition

- Perform real-time calculations with immediate pass/fail risk indicators
- Generate structured PDF reports with inputs, outputs, and supporting notes
- Maintain full transparency with linked equations referenced from guidelines and auto-generated footnotes

Integrated with DIDB

The Drug Interaction Database (DIDB®) is the industry's most comprehensive resource for evaluating drug interactions. Trusted by over 200 pharmaceutical and biotech companies, as well as regulatory agencies. The DDI Calculator is easily integrated with DIDB tools including the Concomitant Meds Navigator.

Request a demo to see DDI Calculator in action

See DDI Calculator in action

