

The evolution of ADME
prediction software
From “in vitro” to Human PK

noraymet
adme[™]

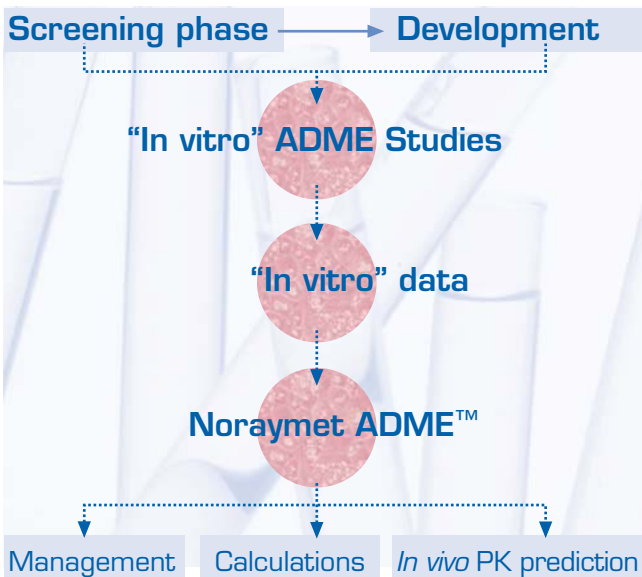
main features

From “in vitro” data to Human PK

Noraymet ADME™ software is a modular bioinformatics tool that allows you to:

- Predict pharmacokinetic parameters (Absorption, Distribution, Metabolism) using only *in vitro* data
- Conduct *in vitro* ADME studies

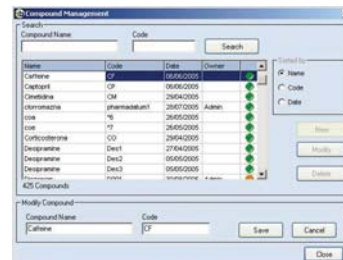
Noraymet ADME™ innovative software combines the capabilities of ADME predictive software with the functionalities of a LIMS: management of *in vitro* data and automatic calculations. All of these scientific aspects are covered with a user-friendly interface, resulting in one of the most accurate and reliable ADME prediction software.



Relevance of Noraymet ADME™ software in drug discovery

Overcome a current necessity in drug discovery

The implementation of ADME HTS methods has led in the necessity for maintaining high quality data and for automatic generation of *in vitro* results. In this field, it is necessary to have bioinformatics tools with the ability to generate accurate predictions of *in vivo* pharmacokinetic behaviour and with the capability to integrate, manage and compare large amount of data.



Noraymet ADME™ LIMS advantages:

- Single software with centralized data storage to manage and integrate *in vitro* ADME studies.
- Conduct *in vitro* experiments and rapid automatic calculations.
- Immediate enquiry of information per compound.
- Make the most of the results and comparative studies.

Noraymet ADME™ pharmacokinetic prediction advantages:

- Combination of mechanistically and physiologically based models.
- Most innovative approaches currently available to estimate human pharmacokinetic parameters.
- Human pharmacokinetic modelling using *in vitro* data as sole inputs.
- Exhaustive validation process following FDA guidelines.



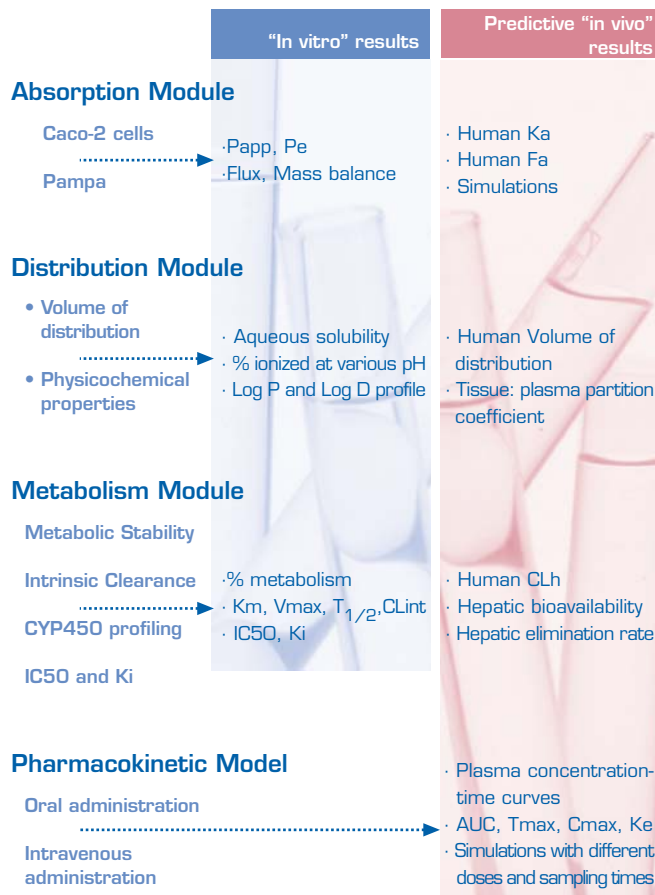
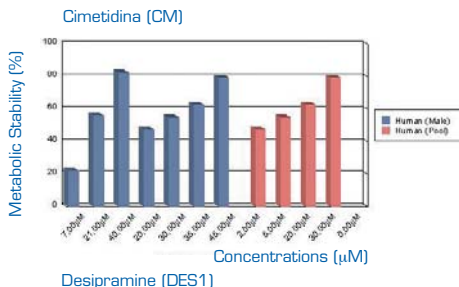
Support for the most important “in vitro” assays

Noraymet ADME™ has been developed to meet the specific needs of pharmaceutical screening and development departments. It manages and integrates ADME *in vitro* assays in a single environment. Noraymet ADME™ includes:

Why use Noraymet ADME™?

Noraymet ADME™ users will have benefits at various stages of the drug discovery process:

- Eliminates labour-intensive and time consuming calculations of *in vitro* ADME studies.
- Standardizes the way to conduct *in vitro* pharmacokinetics studies.
- Offers useful graphs and reports to facilitate results processing.
- Provides single software for both screening and development departments.
- Incorporates fully validated pharmacokinetics prediction models.
- Shows a complete pharmacokinetic model using just 5 *in vitro* inputs commonly obtained during screening phase.
- Enables to redesign compounds and reduces failures before preclinical and clinical studies.



Absorption Module

The measurement of intestinal epithelium permeability is one of the most important characteristics involved in the drug development process. The Absorption module includes 2 assays:

- Caco-2 permeability
- PAMPA permeability

Permeability in Caco-2 cells

This assay is specially designed to conduct experiments either kinetic or non-kinetic. The software includes all the calculations needed to obtain apparent permeability (Papp), flux and mass balance from primary data obtained by commonly used detection methods (HPLC or radioactive labelling). Due to the possibility of conducting apical-basolateral and basolateral-apical studies, the software helps to deduce the transport mechanism.

Noraymet ADME™ software includes a BCS (Biopharmaceutical Classification System) based on compounds recommended by the FDA. The user has the possibility to redesign BCS model with his/her own compounds.

From apparent permeability results, the software predicts:

- Human Absorption Rate Constant (Ka)
- Fraction of Absorbed Dose in human (Fa)
- Simulations of fraction of dose absorbed at different times.

Noraymet ADME™ does not assimilate Ka (absorption rate constant) as Kd (elimination rate constant); the predicted Ka value is directly the constant of drug appearance in plasma.

PAMPA permeability

PAMPA is a non-cell based permeability assay designed to evaluate first-line permeability properties of candidate drugs in early stages of drug discovery.

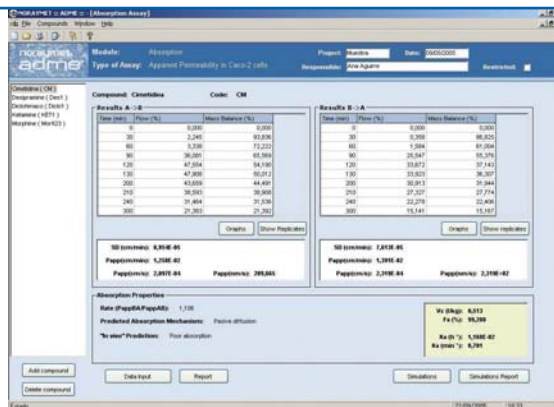
Noraymet ADME™ PAMPA permeability assay allows the researcher to manage this *in vitro* experiment. The software automates all the calculations and shows the % of transport and the effective permeability (Pe).

Distribution Module

This module is specially designed to conduct physicochemical assays commonly carried out during screening and development phases. The Distribution module includes 2 assays:

- Physicochemical properties
- Volume of Distribution

The software calculates aqueous solubility, % ionized and Log P profile at different pH. In addition to the results, the software shows the relevance of aqueous solubility and Log P in drug discovery.



For efficient screening efforts it is of particular importance to predict human volume of distribution. From drug lipophilicity and few common *in vitro* results and using tissue composition-based equations, the software predicts:

- Human Volume of Distribution (Vd)
- Tissue:Plasma partition coefficients

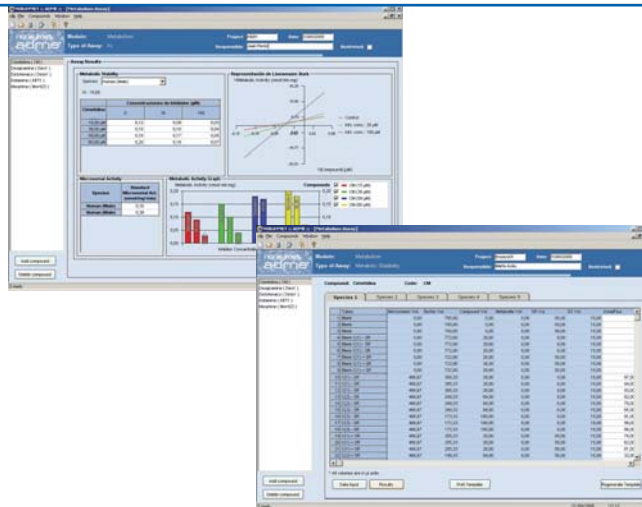


Metabolism Module

The assessment of metabolic stability of new potential drugs is essential in the discovery process as it influences on both oral bioavailability and elimination. The Metabolism module includes 5 assays:

- Metabolic stability
- Intrinsic Clearance
- CYP450 profiling
- IC50
- Inhibition constant

Noraymet ADME™ metabolism module provides the informatics tool to conduct a wide range of *in vitro* metabolism experiments, both drug metabolism and drug-drug interaction assays. This module provides an automated data analysis for metabolic stability, CYP450 phenotyping, intrinsic clearance and inhibition assays.

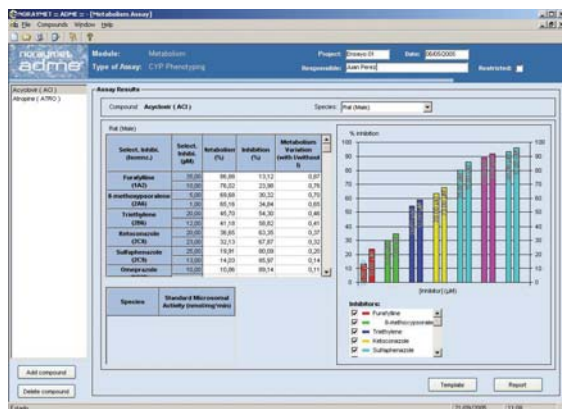


All the experiments can be carried out in microsomes or hepatocytes and conducted with up to 5 species at the same time, enabling to scan differences in metabolism between species. The software helps you creating a very useful template. Depending on the type of assay the software gives the number of tubes that have to be prepared and the content of each one. Templates can be printed and used as a guide of how to perform experiments in the laboratory.

Finally, with “just one click” the software calculates and shows main results of *in vitro* hepatic metabolism studies: % of metabolism, % of inhibition, IC50, Ki, Km and Vmax, half-life, etc.

From intrinsic clearance and using physiologically based pharmacokinetic models, the software predicts:

- Human Hepatic Clearance (CLh)
- Hepatic Elimination Rate
- Hepatic Bioavailability



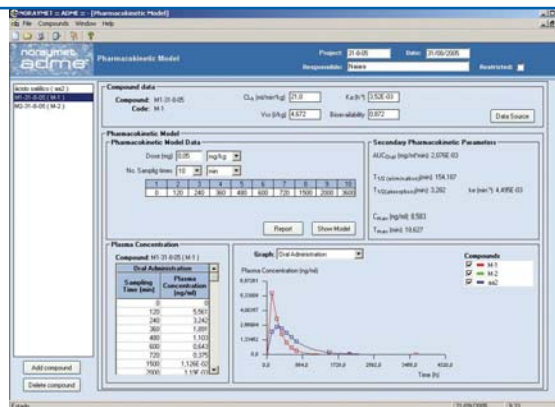
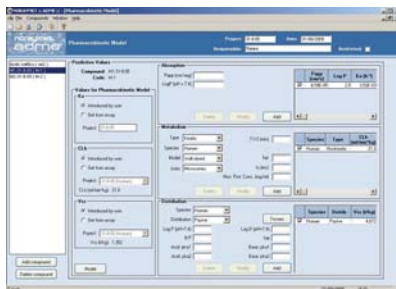
Pharmacokinetic Model

Noraymet ADME™ prediction of human pharmacokinetic parameters is based on assembly of several mathematical models (mechanistically and physiologically based models) that enables to estimate a value of human K_a , V_d and CL_h , providing only *in vitro* data. Using the previously estimated PK parameters, the Pharmacokinetic module predicts concentration-time data with a 1-compartment model.

With just two inputs, initial dose and sampling times, the software predicts and shows plasma concentration-time curves for oral or/and intravenous administration. The predicted pharmacokinetic model enables the researchers to evaluate how the pharmacokinetic parameters could modify the plasma concentration levels.

The simplicity of this pharmacokinetic model built in Noraymet ADME™ is the key aspect of its usability. Easy software means better understanding, and this is the main objective of Noraymet ADME™. The program needs just 5 *in vitro* inputs to predict the complete human pharmacokinetic behaviour of tested compound. The advantage is that these inputs are commonly obtained during screening phase. From primary pharmacokinetic parameters, the software calculates secondary parameters:

- AUC
- Elimination rate constant
- C_{max} and T_{max}



The final consequences of using Noraymet ADME™ Pharmacokinetic module are an improved decision making, better design of later experiments, better selection of species, and most likely a reduction of number of animals.

Validation of Noraymet ADME™

The simplicity of Noraymet ADME™ does not mean less efficiency. The software has been fully validated guaranteeing an optimized tool for practical use.

Validation process of Noraymet ADME™ was carried out following FDA guidelines. The statistical analyses include experimental-prediction correlation, mean prediction error and mean square error.

Over 160 compounds have been used to validate the predictive capability of Noraymet ADME™, divided in acid, base and neutral compounds.

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Support

NorayBio is always looking for its client satisfaction and the usability of its products. Our mission is to be innovative and to enhance working practices in pharmaceutical companies. For this reason, the company offers a support for advice, technical assistance, possible customizations and problem solving, building quality into all software we design. Personal attention and individual solutions are the key aspects of the collaboration with our customers.

Contact information



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Technical features

Noraymet ADME™ works as client/server application.

Server requirements

- Minimum:
 - Windows: NT, 2000 or 2003
 - Intel Pentium III or AMD Athlon 800MHz
 - 260MB RAM
 - 200 MB of free space in the Hard Disk
- Recommended:
 - Windows: 2000 or 2003
 - Intel Pentium IV or AMD XP 1.8GHz
 - 512MB RAM
 - 2GB of free space in the Hard Disk
 - Net Ethernet 100Mb

Workstation requirements

- Minimum:
 - Windows: NT, 2000 or XP
 - Intel Pentium 200MHz
 - 128MB RAM
 - 100 MB of free space in the Hard Disk
 - Screen resolution: 1024 x 768
- Recommended:
 - Windows: 2000 or XP
 - Intel Pentium III 800MHz
 - 512MB RAM
 - 150MB of free space in the Hard Disk
 - Net Ethernet 100Mb

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