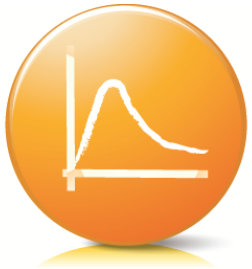


Vivo Drug Delivery
Pharma Consulting

The future in Pharma Development is simulation

APM Forum,

April 2-3, 2014
London, Royal Garden Hotel

Dr. Dieter Becker

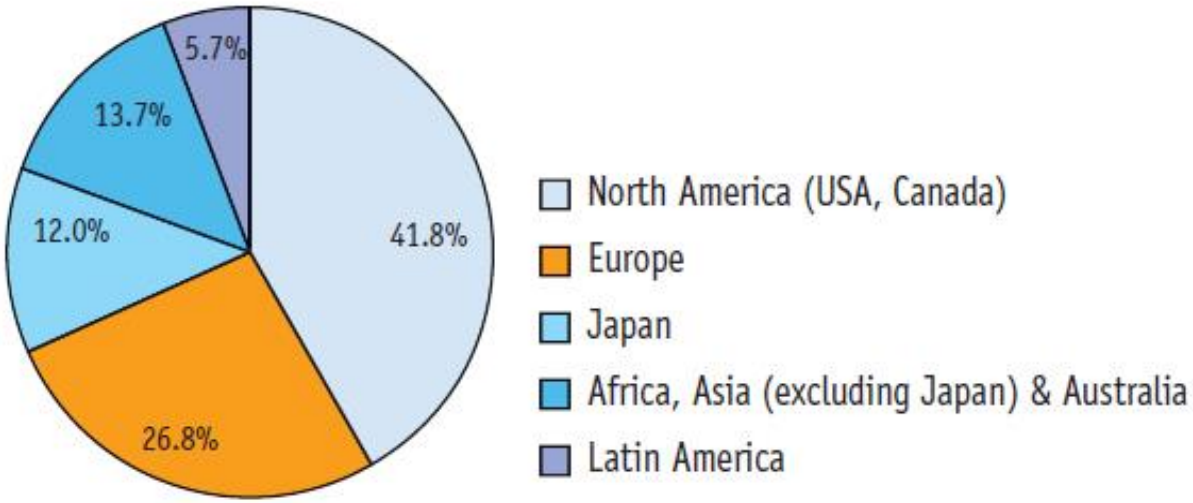
Vivo Drug Delivery GmbH, Roosstrasse 23, CH-8832 Wollerau, Switzerland
Phone +41 44 563 63 00, dieter.becker@vivodrugdelivery.com , © 2013

Overview

- Pharma Market
- Product Development Pharma
- How can Simulation (gCOAS) optimize Product Development
- Example of a Simulation Workflow using Atenolol as a Model Drug

Pharma Market

- 2011 world-wide sales 855.5 bn UDS



Note: Europe includes non-EU members and CIS markets
Source: IMS MIDAS, 2012 (data relate to the 2011 audited market at ex-factory prices)

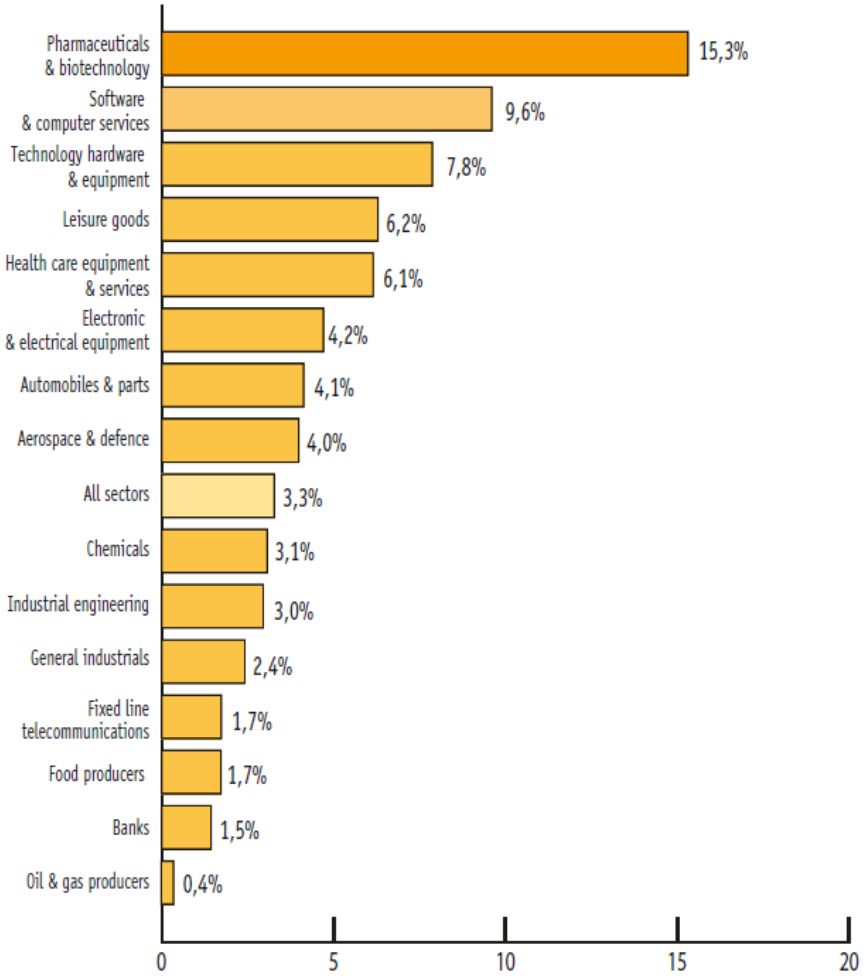
EFPIA report 2012: The pharmaceutical industry in figures

R&D spending in industry

Pharma 15.3 %

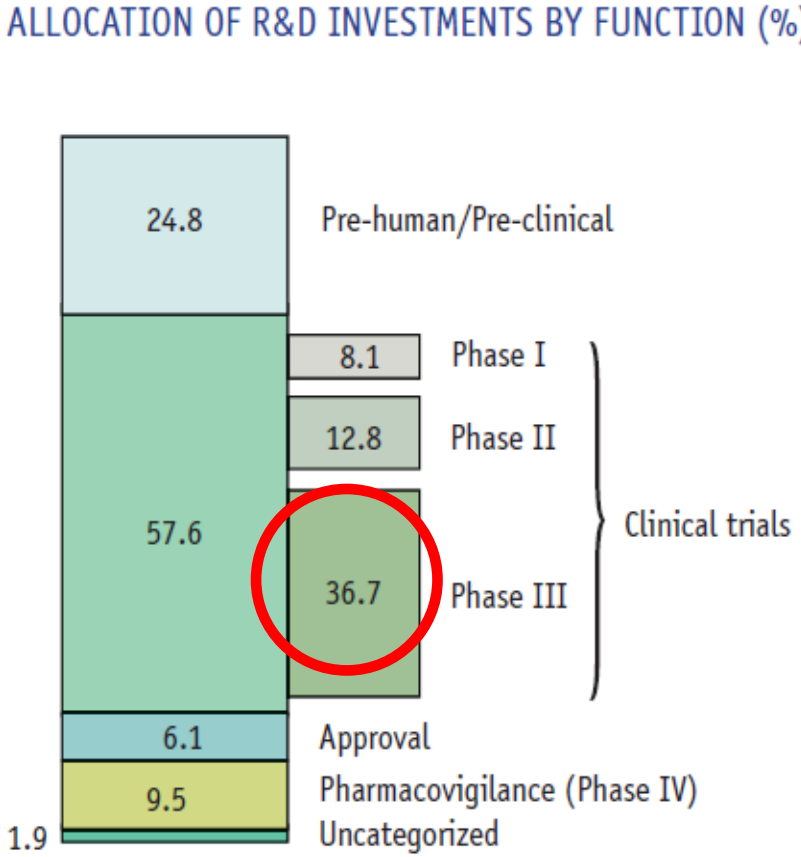
Automobile 4.1 %

Oil & Gas 0.4%



EFPIA report 2012: The pharmaceutical industry in figures

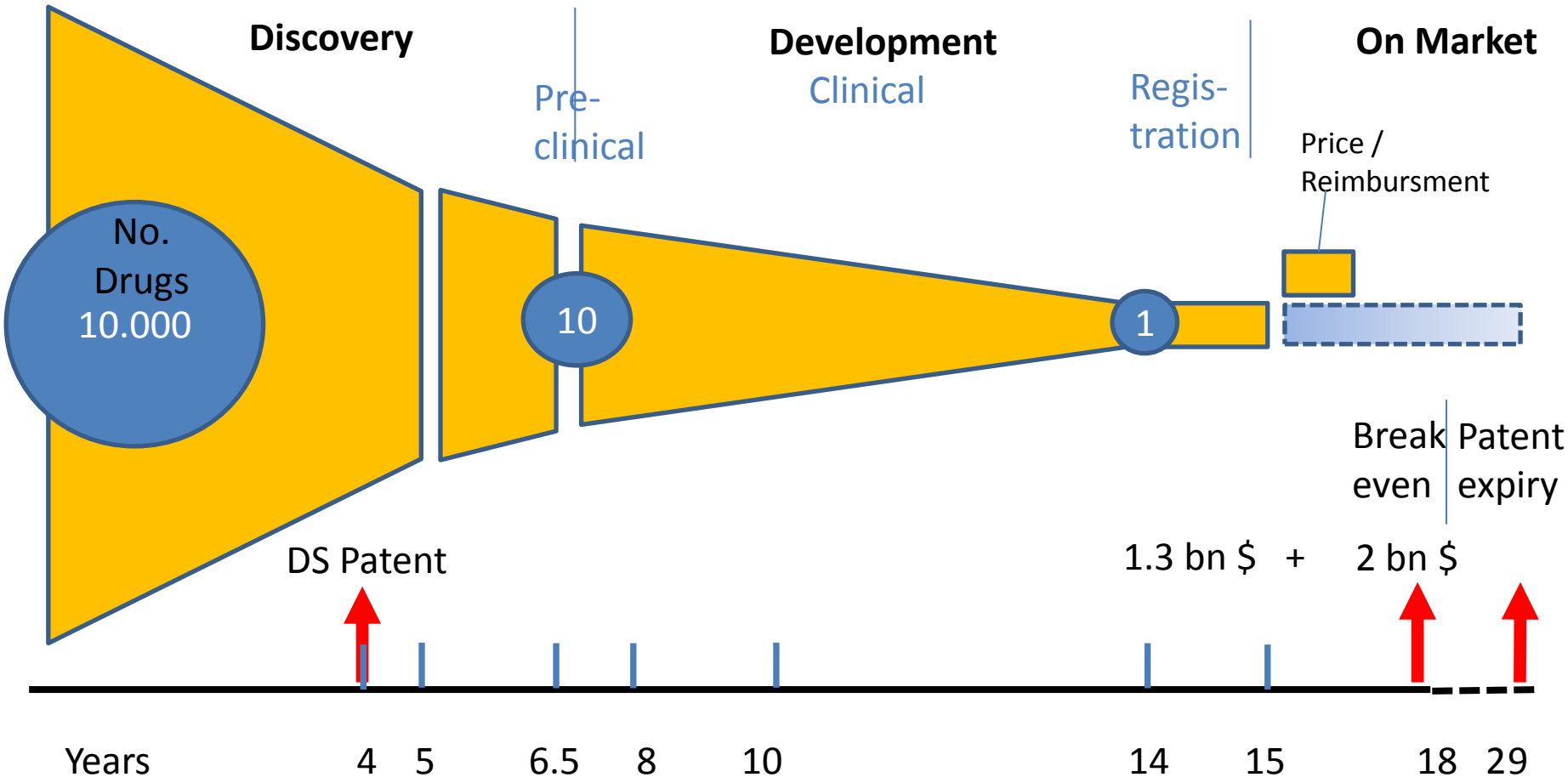
Pharma Market



- R&D cost 1 drug product 2005: 1.3 bn USD
- Main cost driver Dev. Clinical Ph 3 ~ 0.4 bn USD

EFPIA report 2012: The pharmaceutical industry in figures

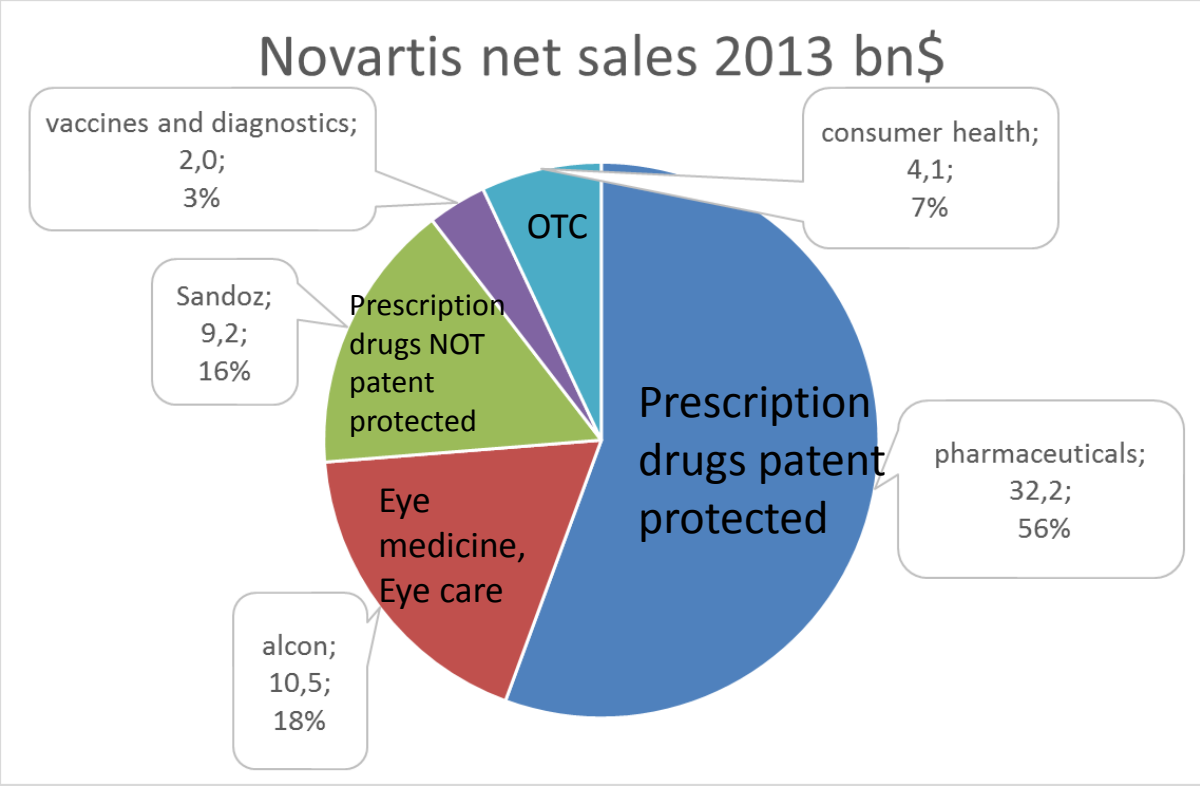
Drug Development Overview



EFPIA report 2012: The pharmaceutical industry in figures

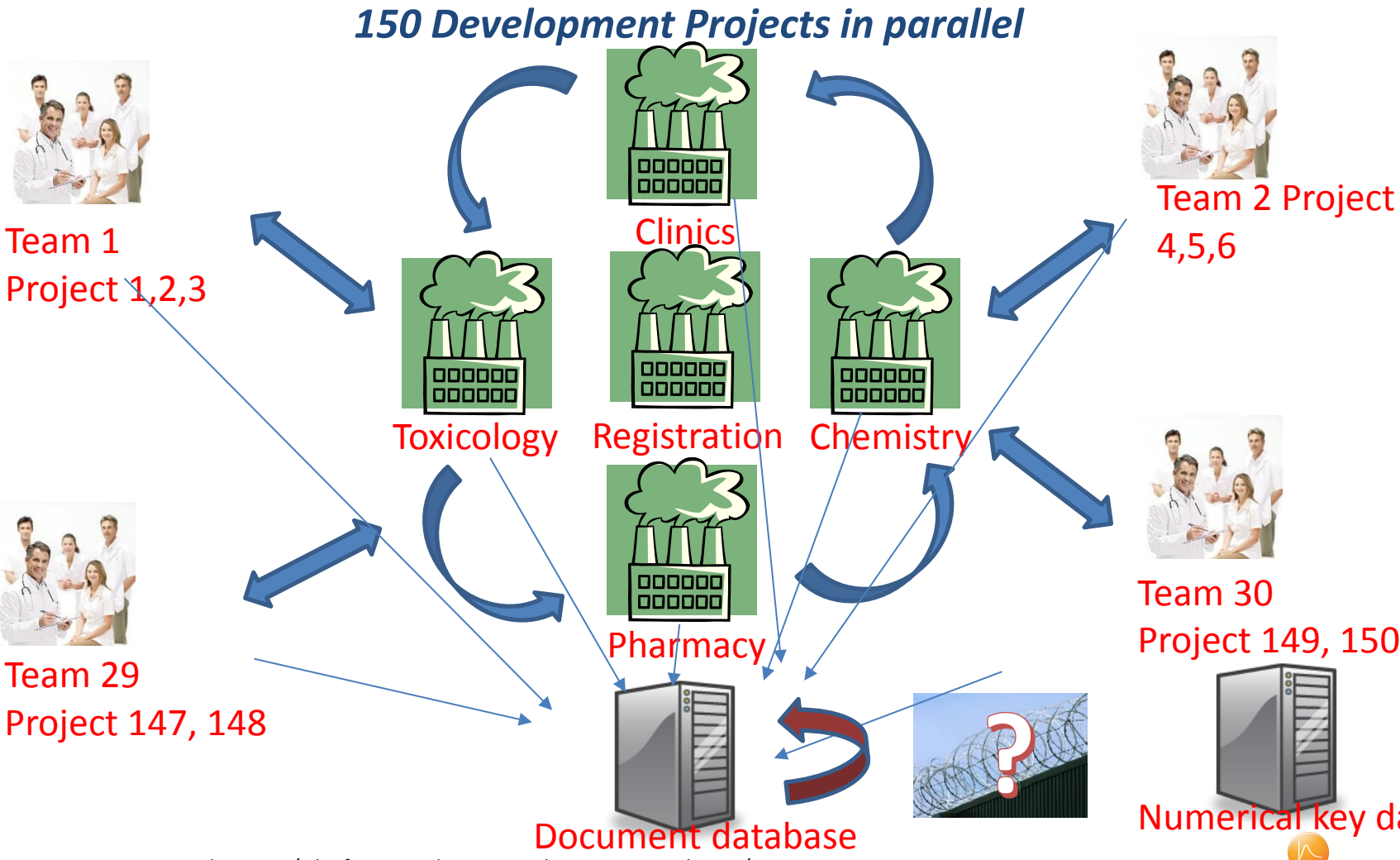
Big Pharma - Novartis

- 57.9 bn$ Sales
- ~120'000 Co workers
- ~350 drug substances in marketed products (only pharmaceuticals)
- ~ 150 Products in Development (only pharmaceuticals)



OTC = Over The Counter (non-prescription drugs

Product development Pharma Novartis



Product development Pharma

Know-how transfer hindered by:

- many project teams with high workload
- Unfocused because report based data exchange
- Reports of each department comprises all data but typically only a few data are important for the **other** departments (key data)

Product development Pharma

Document database

- Example: Registration dossier* for **1 product** consists of
  100 folders
  = 80'000 pages
  = 20 mio. words

Numerical key data to foster inter disciplinary or inter departmental knowledge exchange (1 product)

- ~150 data sets with ~30'000 data points
  ➔ 0.15 % of regis-tration dossier content

* Compiled by the Pharma company and submitted to ~ 40 health authorities to get marketing allowance in the country / region

Product development Pharma

- **~150** product developments in parallel at Novartis
- Involved main departments: clinics – toxicology - chemistry – pharmacy - regulatory
- Project teams: 30-40 at Novartis
- Reports clinic: ~1500 pages or more
- Report filing in document database

BUT

- Structured **inter-disciplinary** numerical product database missing to preserve expert knowledge which is easily and quickly available

What data is needed to make development more efficient

Inter-departmental data exchange is key!

Numerical data that one department is generating and another department needs

This is data on:

- Human clinical trials, animal trial (time drug plasma concentration, number participants, study no. ,..)
- Drug product properties (dissolution profile,..)
- Drug substance properties (solubility, particle size distribution, log P, …)

How many numerical data?

Numerical data	no data sets	no data points per set	no. data total
Drug substance			100
Drug product	15	25	375
Dissolution	100	10	1.000
animal trials PK mean	10	50	500
human trials PK mean	10	50	500
animal trials PK ind	10	1250	12.500
human trials PK ind.	10	1250	12.500
Total no. of data	**155**		**27.475**

- All data are already used in simulation software (gCOAS) to predict a products performance in men

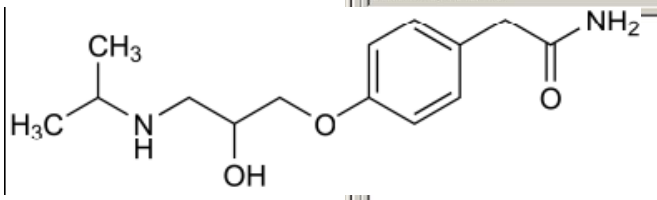
Example Simulation using Gastro+

Drug	Atenolol
Drug Product	oral solution
Dose mg	50
Indication	Anit-hypertensive drug
Mode of action	beta-blocker
Metabolism	no metabolism

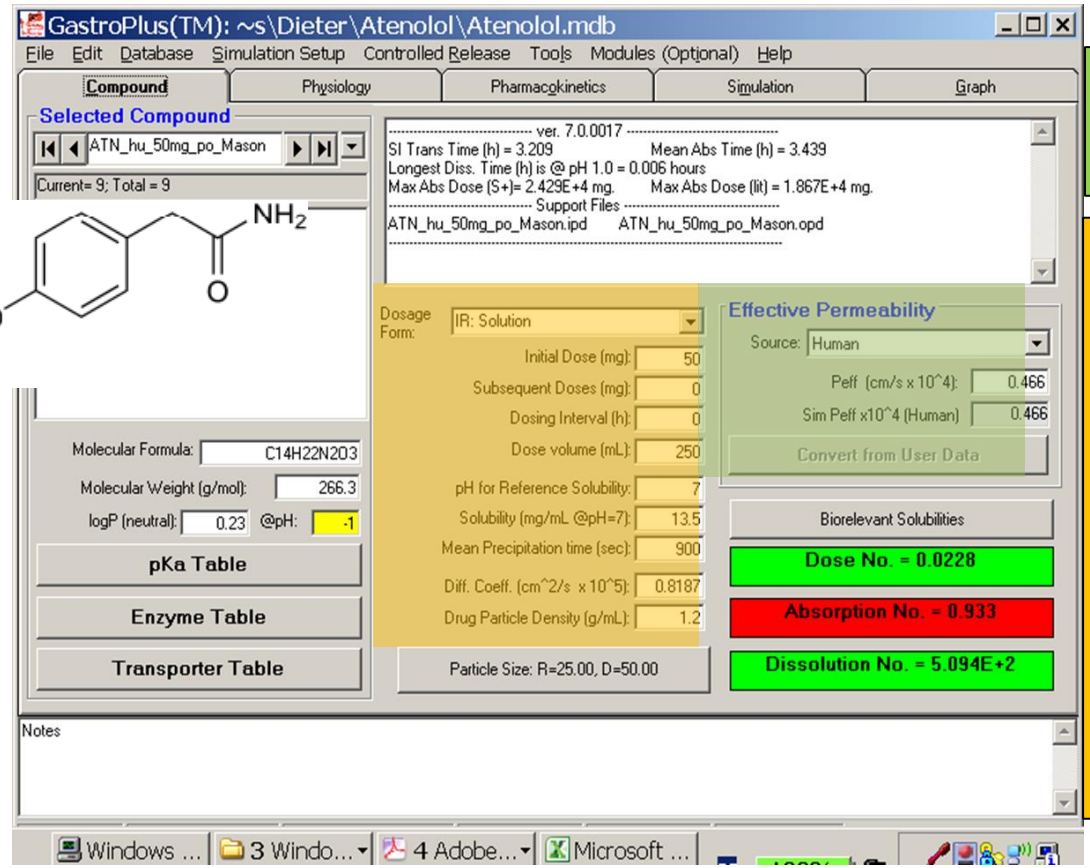
Simulation workflow

1. Enter basic data like MW, water solubility
2. Fit measured iv PK data to set up a 1, 2 or 3 compartmental model
3. Enter physiological data e.g. body weight
4. Select physiology (e.g. human fasted)
5. Enter time – plasma drug conc. data
6. Simulate
7. If the simulation fit observed data well
   ➔ model can be used

Example: Atenolol



$C_{14}H_{22}N_2O_3$
MW 266.3
logP 0.23



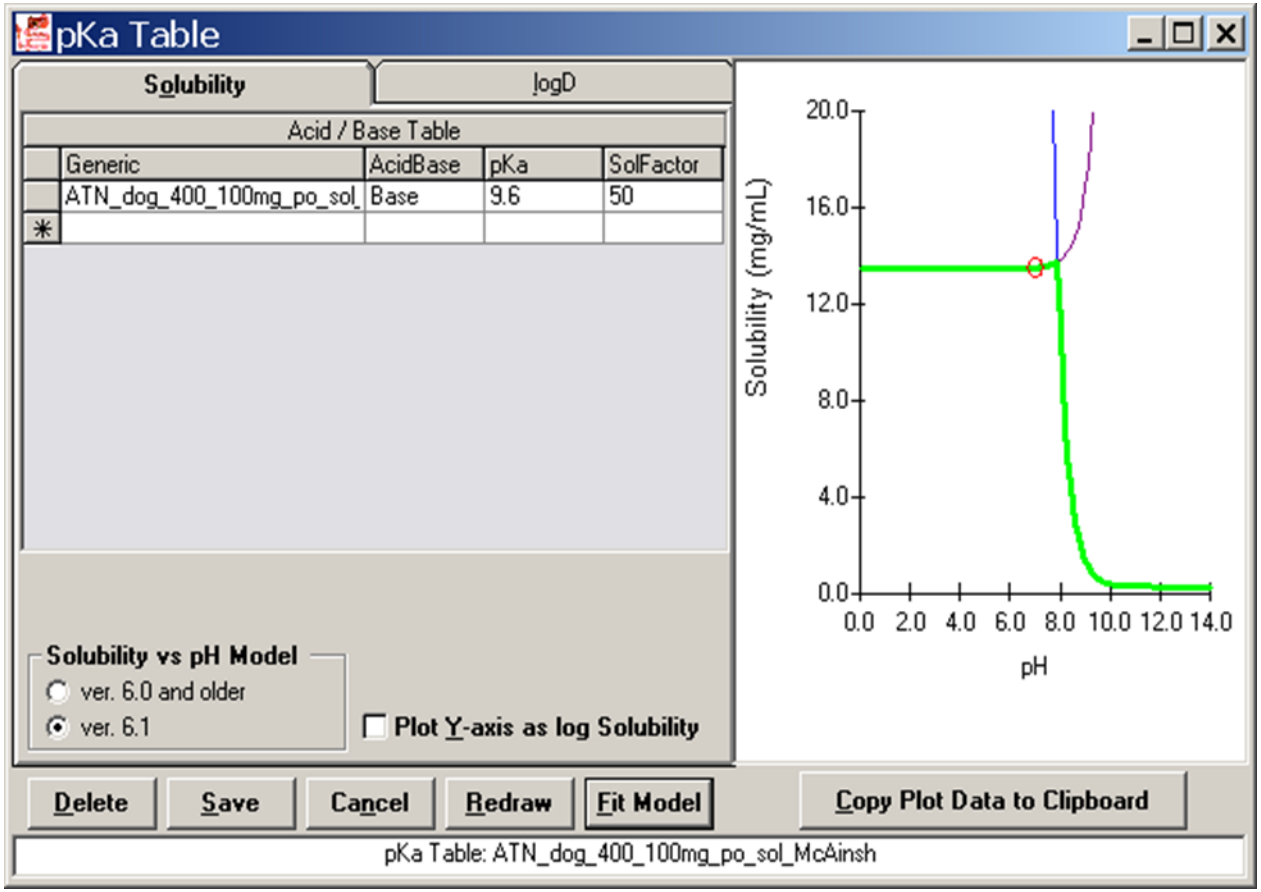
Human
Peff 0.466

Oral solution
Human
Dose mg 50
Inf time 0.2h
pH ref sol 7
Sol mg/ml 13.5
MPT sec 900
Diff Coef 0.818
Drug dens 1.2

W.D. Mason, N. Winer, G. Kochak, I. Cohen, R. Bell, Kinetics and absolute bioavailability of atenolol, Clin. Pharmacol. Ther. 25 (1979) 408.

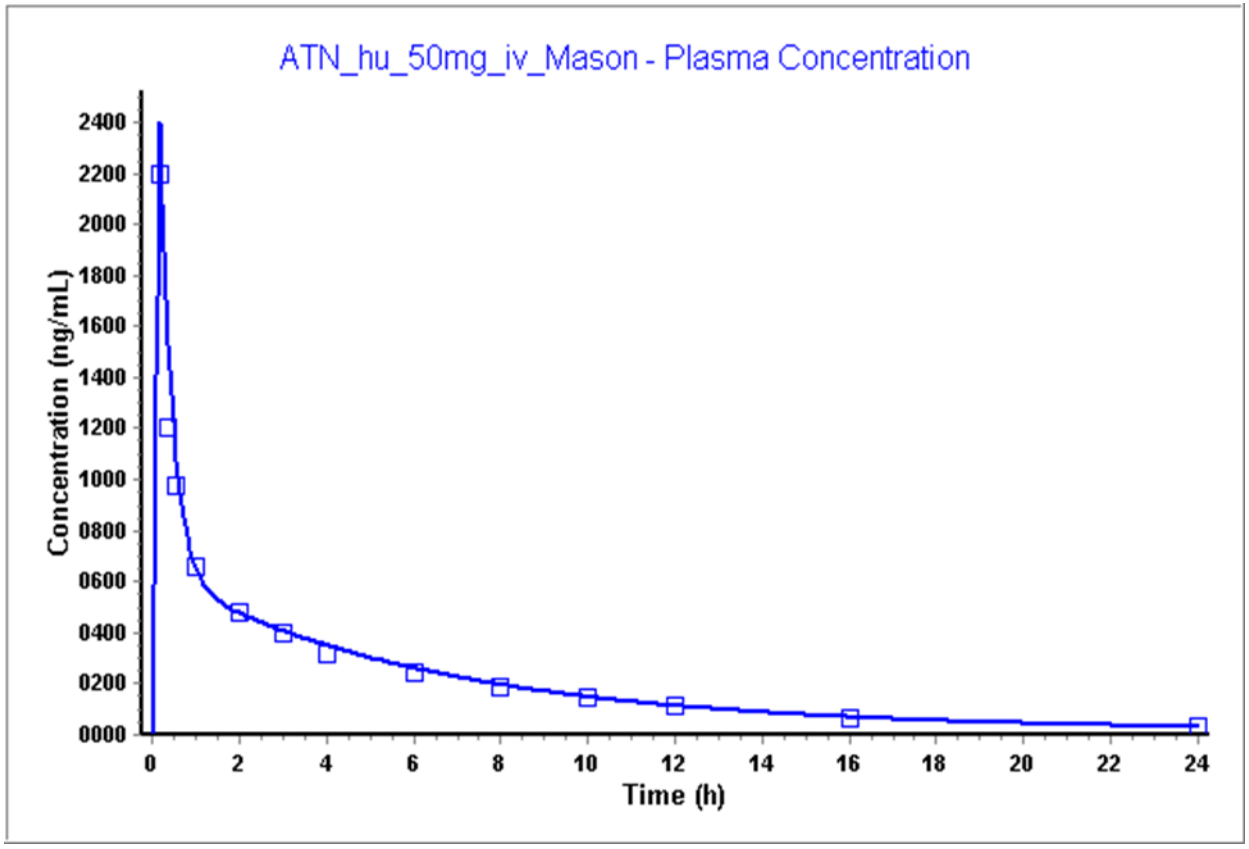
Example: Atenolol pKa

Base
pKa 9.6



Example: Atenolol iv human

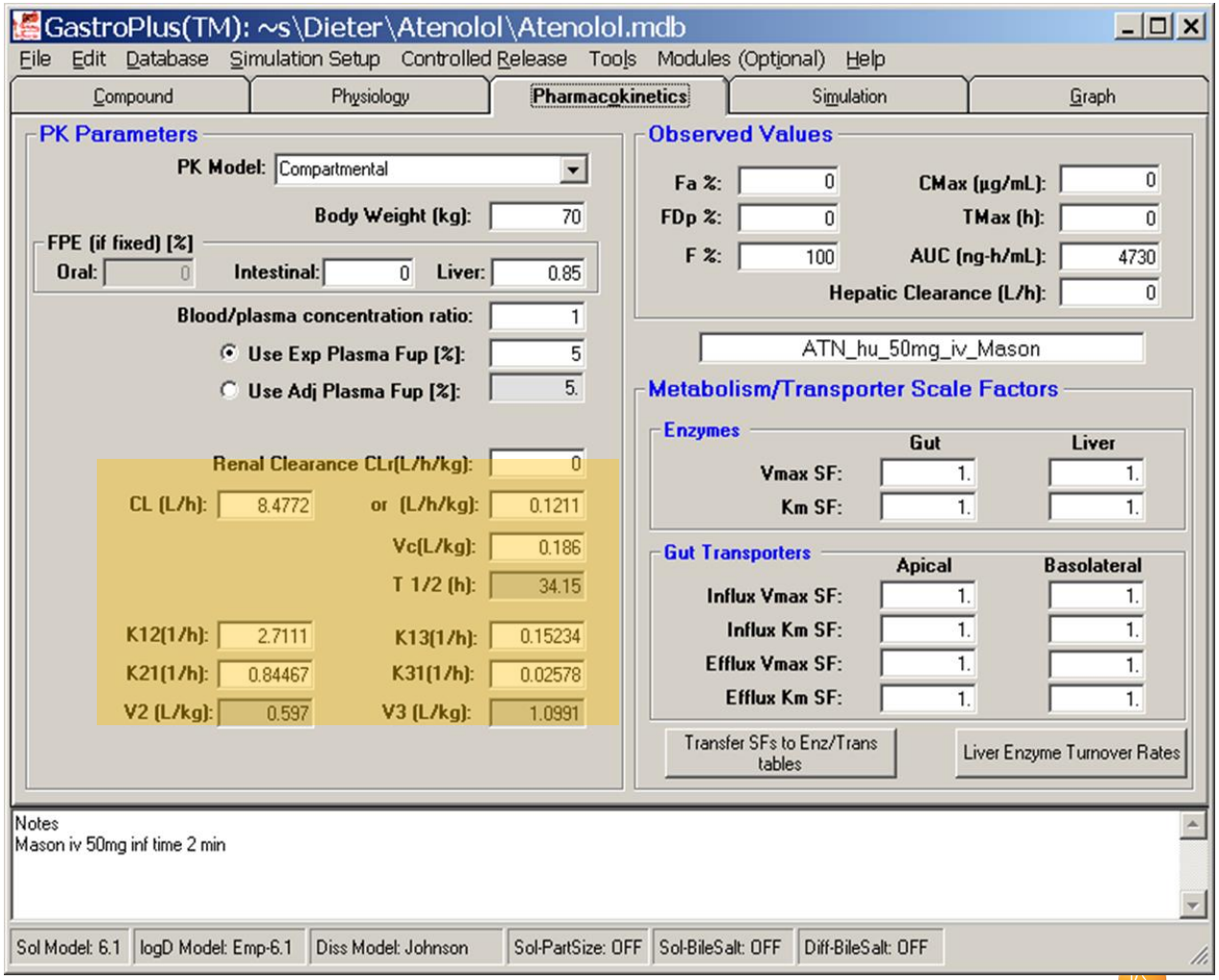
R^2=0.972



Example: Atenolol

3-compartment model calculated from iv data:

CL	0.1211
K_{12}	2.7111
K_{21}	0.84467
V_2	0.597
K_{13}	0.15234
K_{31}	0.02578
V_3	1.0991

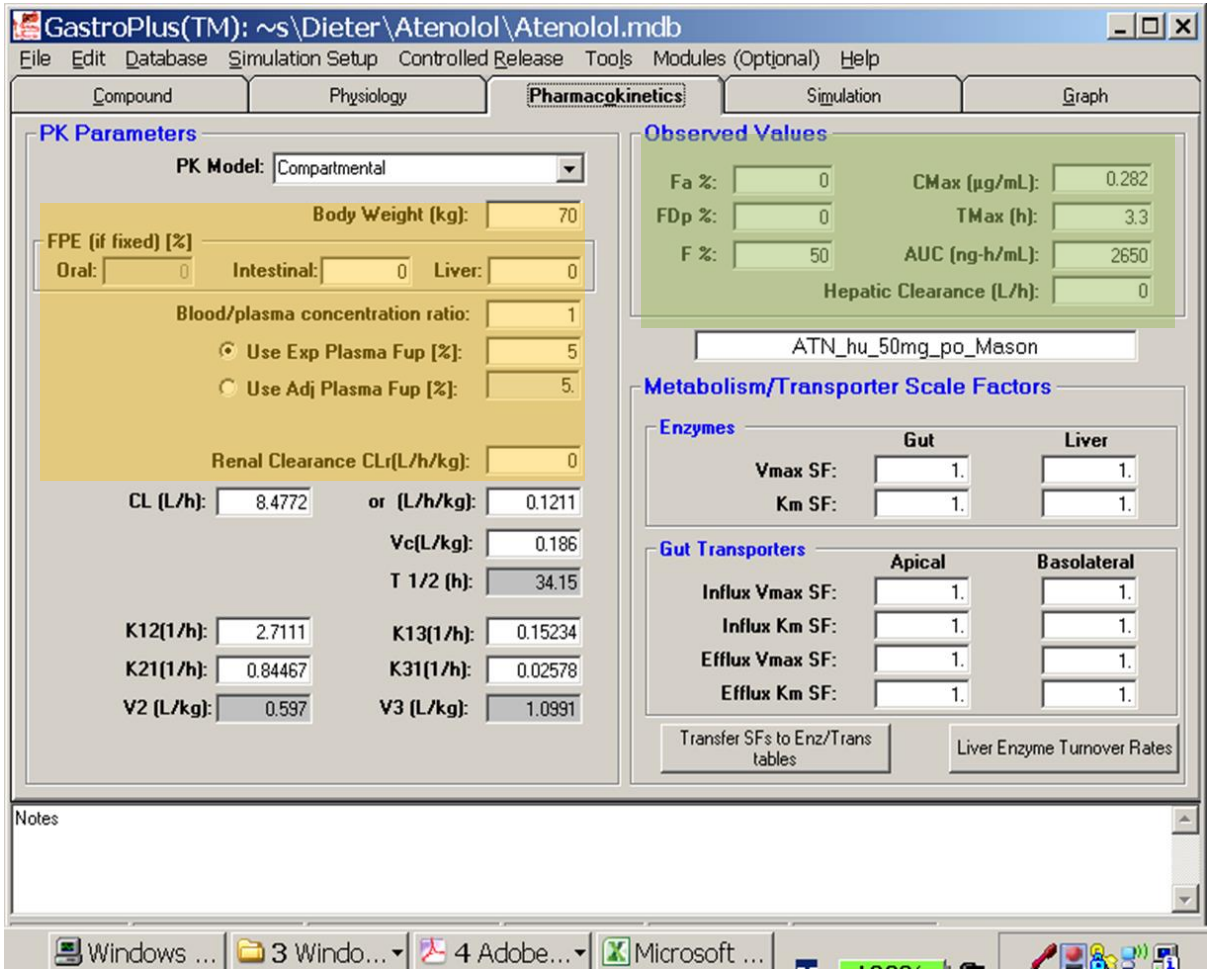


Example: Atenolol

Body weight kg	70
Blood/ Plasma ratio	1.0
F up	5

Obs. Values:

Cmax	0.282
Tmax	3.3
AUC	2650



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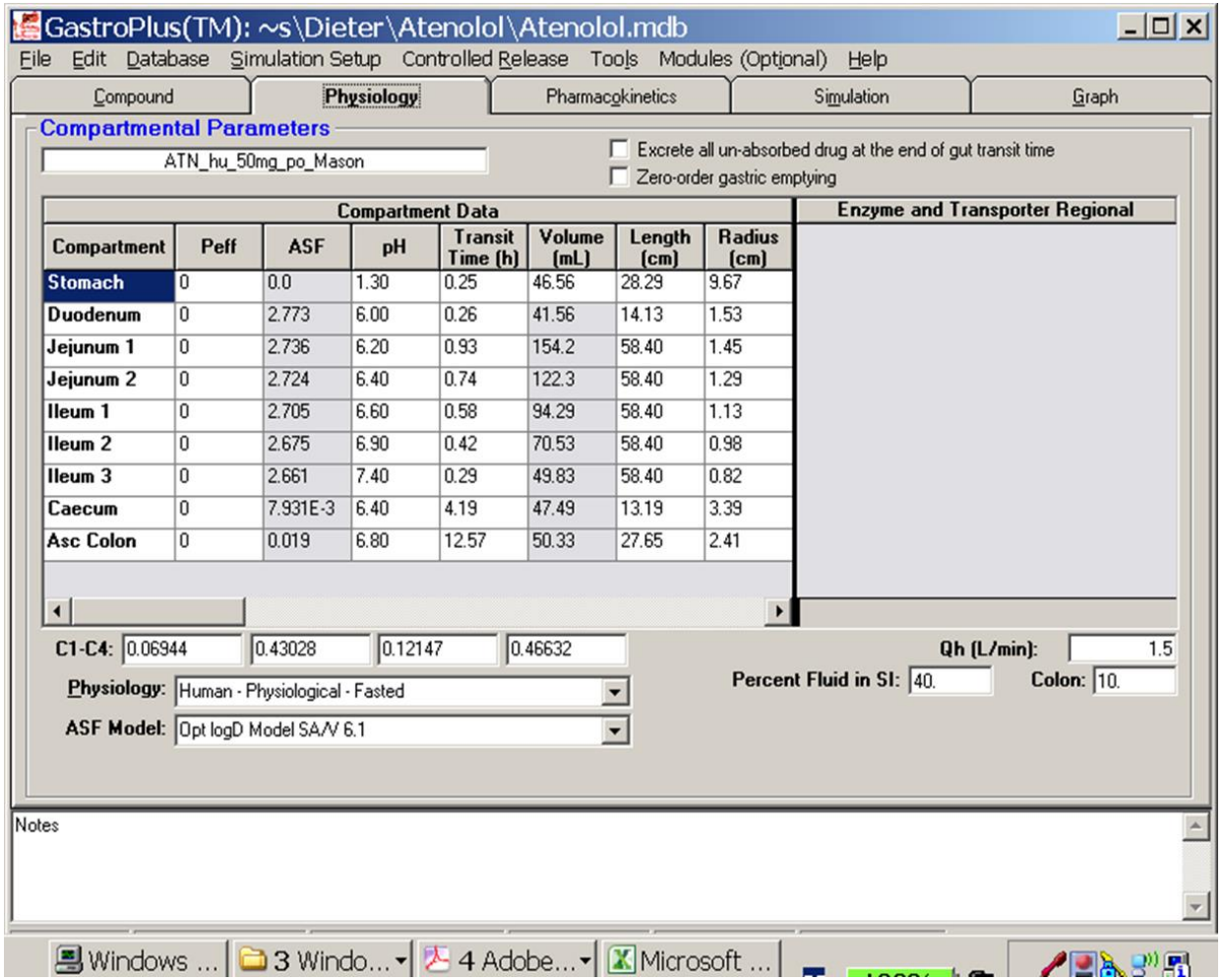
Example: Atenolol

Human – Physiological - Fasted



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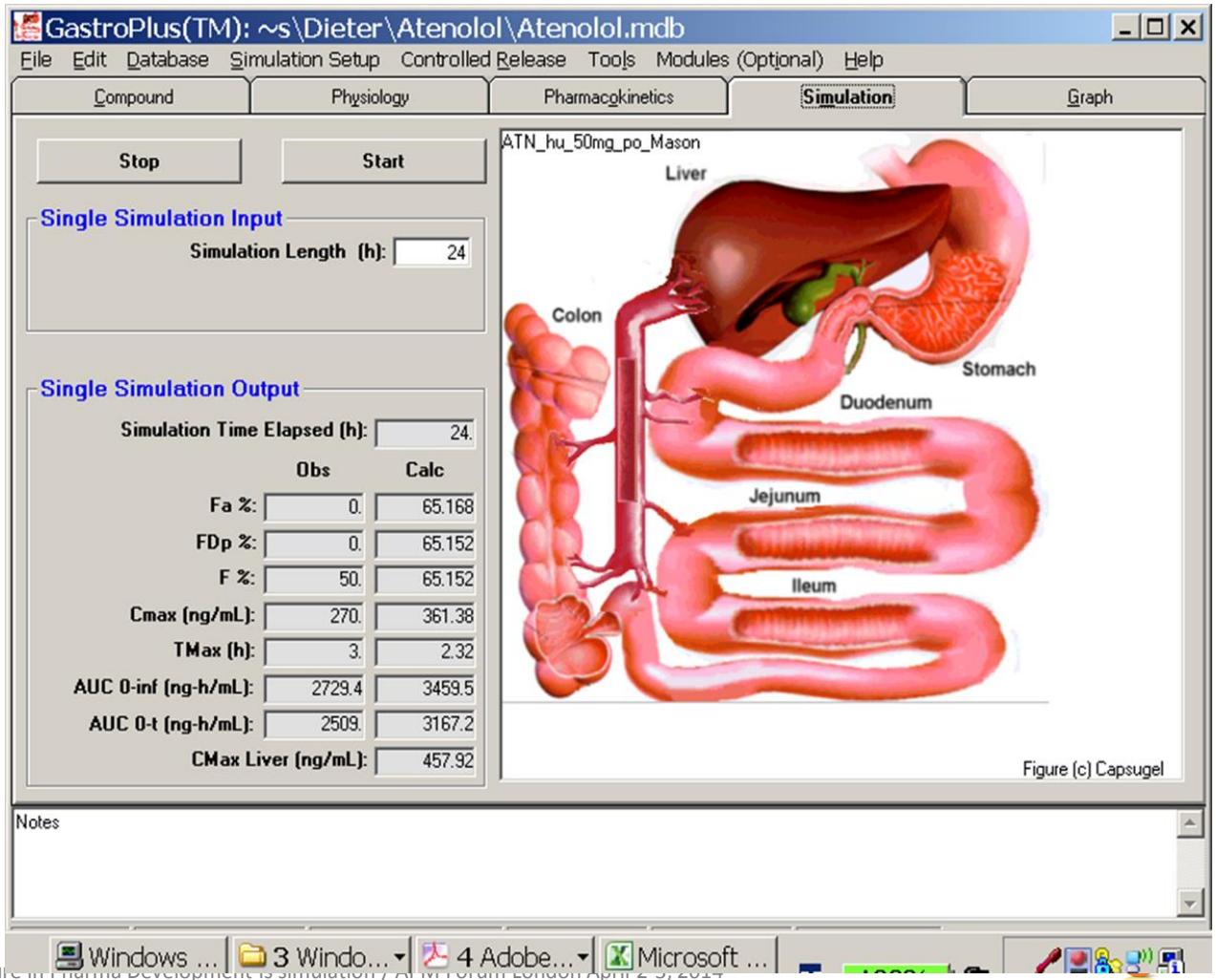
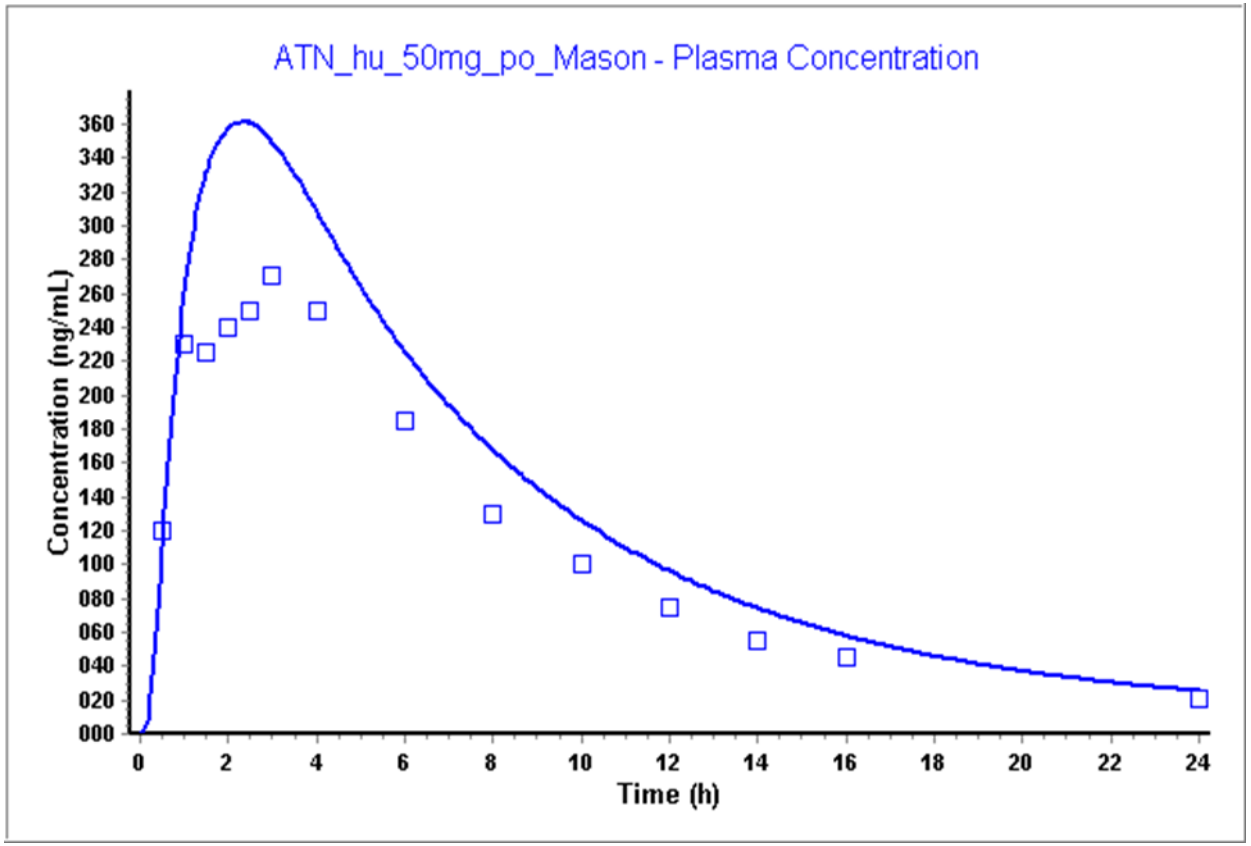
Example: Atenolol

Sim length	h	24
Calculated:		
Fa%		65.168
FDp%		65.168
F%		65.168
Cmax		361.38
Tmax		2.32
AUC 0-inf		3459.5
AUC 0-t		3167.2
Cmax liver		457.9



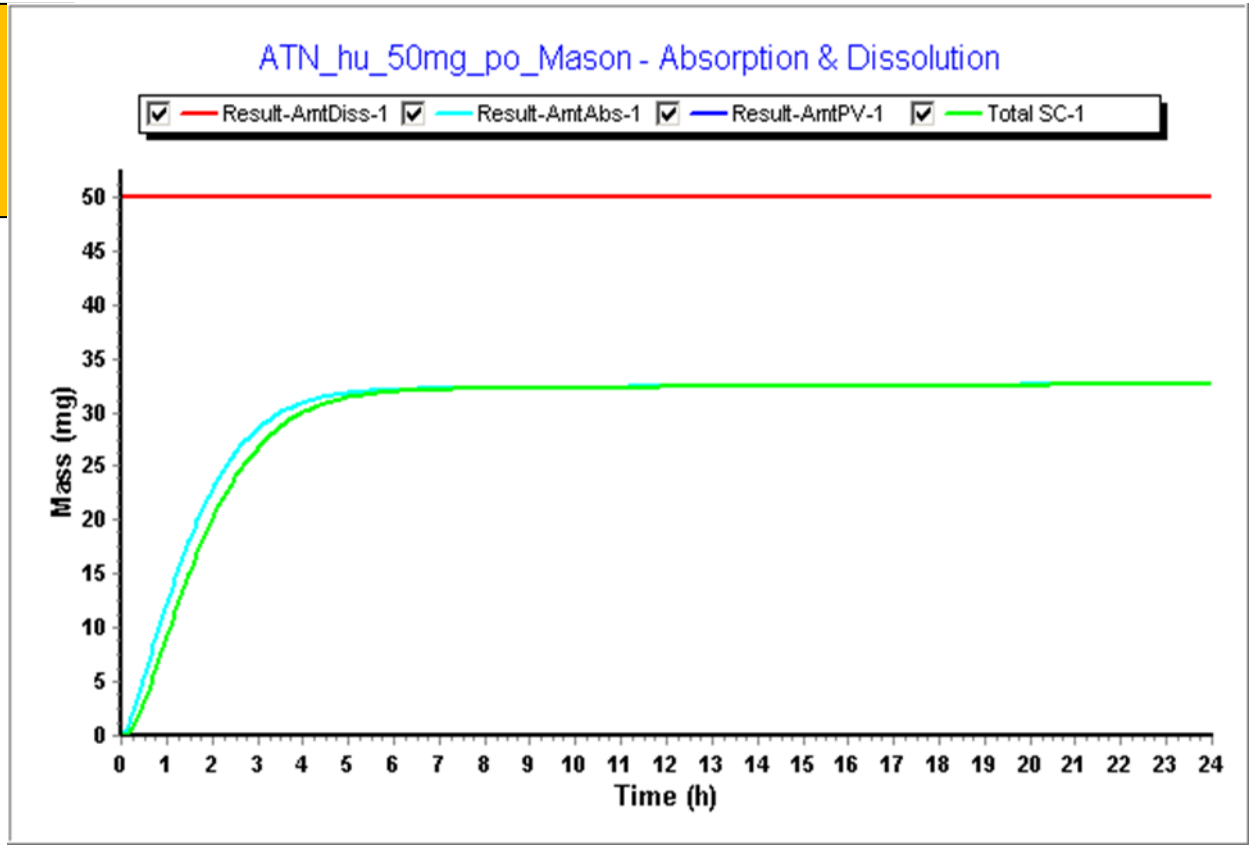
Example: Atenolol

Observed	□
Simulated	-



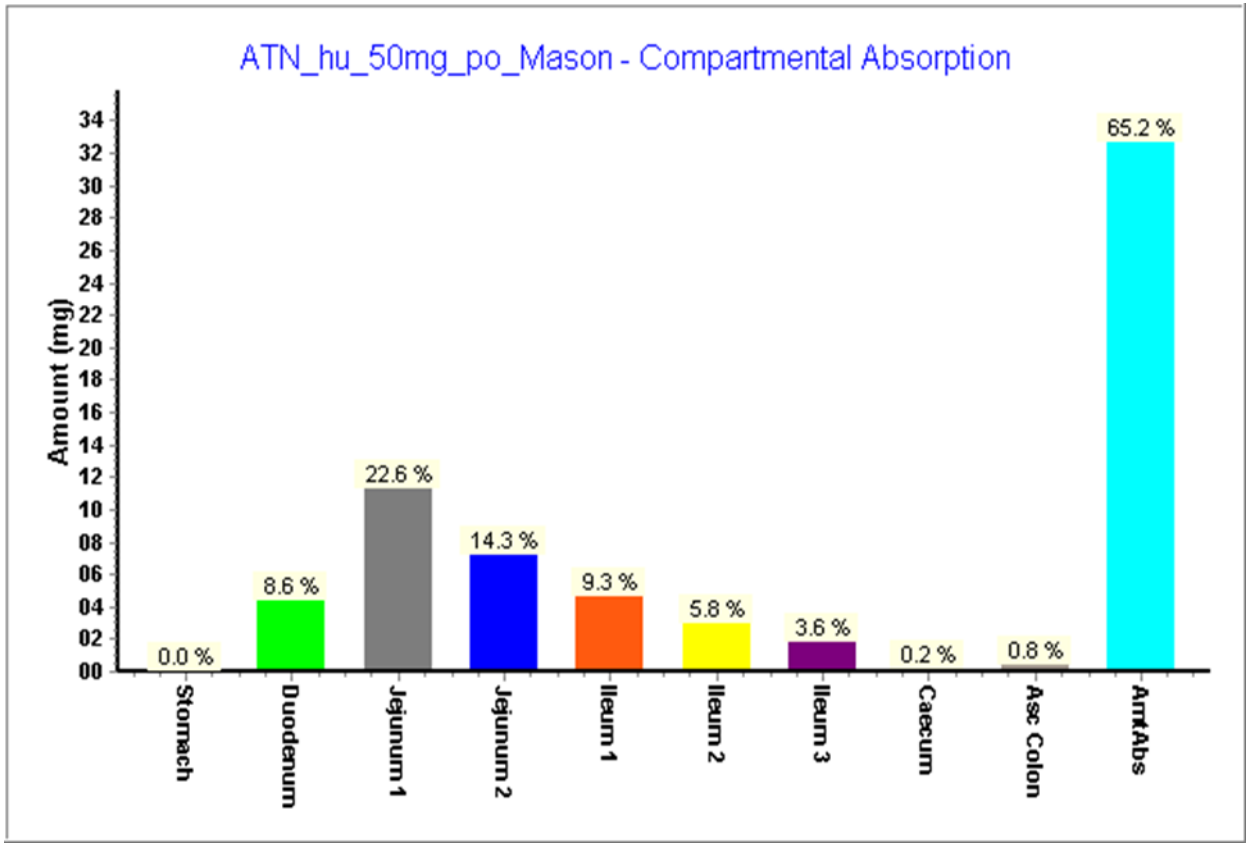
Example: Atenolol

Red Dissolved
Green Systemic Circulation



Example: Atenolol

Absorption of the drug Atenolol in the different segments of the gastro-intestinal tract



Example: Atenolol

- Entry of measured data in the above example = 51 values only!

Conclusion

- **Prize pressure on Pharmaceutical Products increase**
- **Pharma R&D cost very high**
- **Attrition rate 90% in Product Development**

➔ **Need to Cut Cost in R&D**

- Reduce staff (70% of R&D cost)
- Use simulation (gCOAS) to more accurately predict product performance in men thereby detect un-successful projects ***earlier*** in product development and use the saved capacity to faster drive the successful projects
- Foster successful product composition and process selection by predicting performance in humans ***earlier*** using simulation (gCOAS)
- Encourage inter-departmental know-how exchange by using the same key data that are already integrated in simulation (gCOAS) software

Annex

Classification of Pharmaceutical Formulations

Route of Administration	***Conventional Dosage Forms***
Oral	Tablets, capsules, solutions
Parenteral	Sterile s.c., i.m., i.v. injectables
Inhalation	Pressurized multidose inhalers
Topical	Creams, ointments, gels
Transdermal	Passive patches