

Vivo Drug Delivery
Pharma Consulting

The future in Pharma Development is simulation

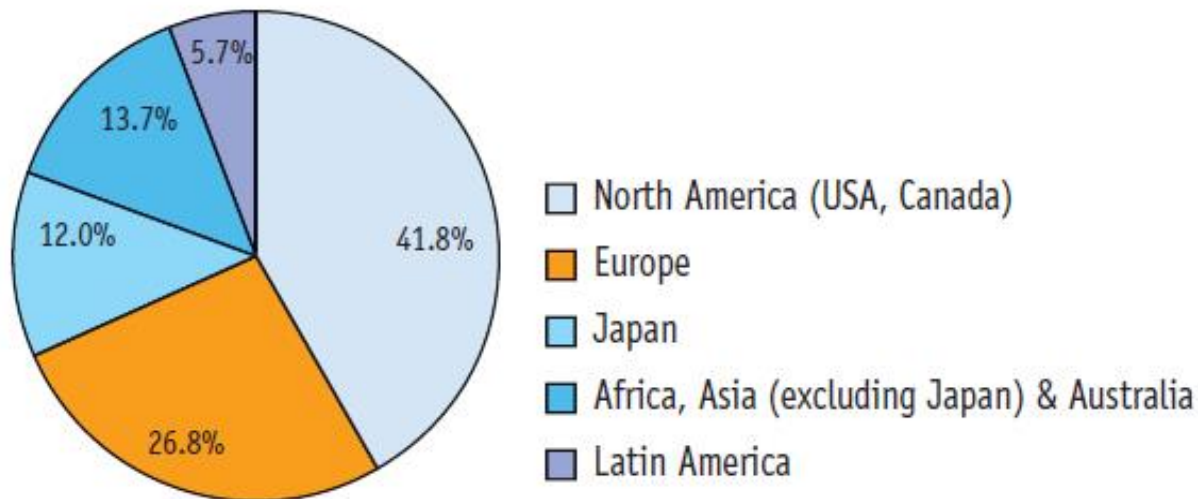
APM Forum,
April 2-3, 2014
London, Royal Garden Hotel
Dr. Dieter Becker

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)

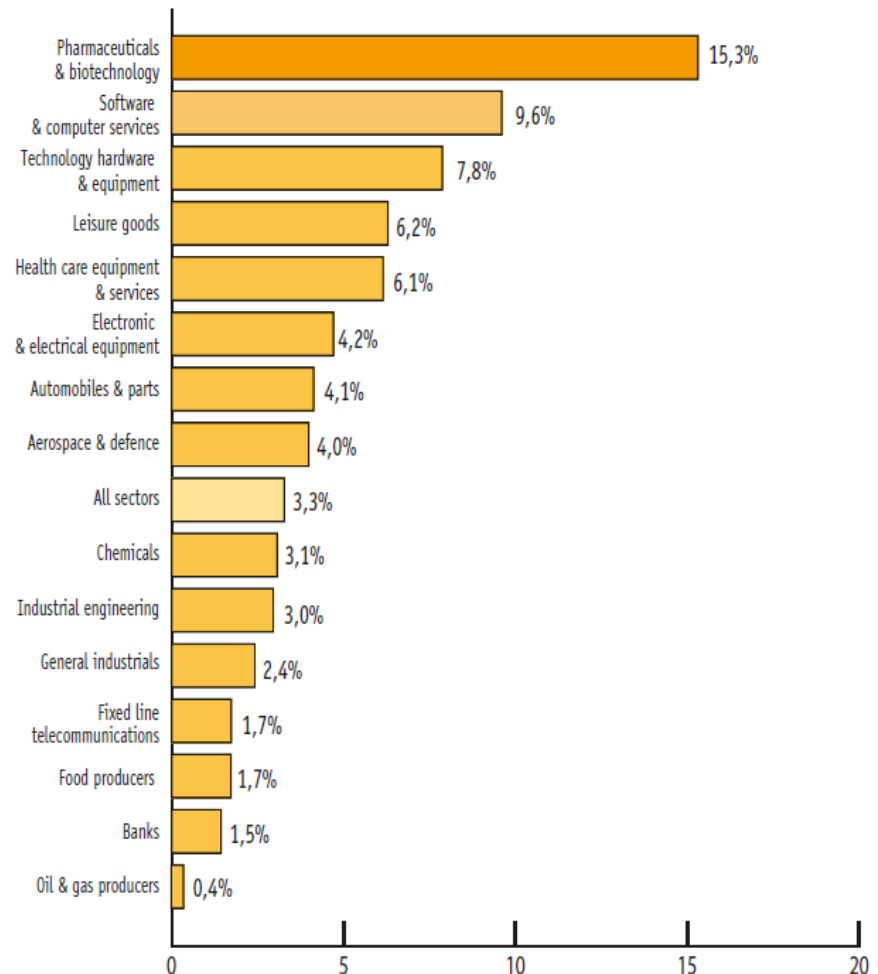
EFPIA report 2012: The pharmaceutical industry in figures

R&D spending in industry

Pharma 15.3 %

Automobile 4.1 %

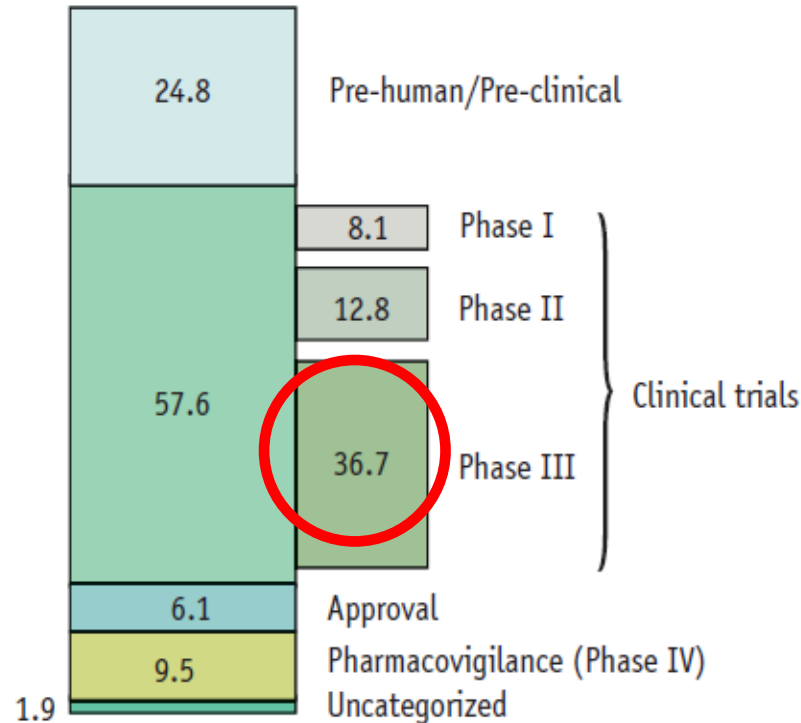
Oil & Gas 0.4%



EFPIA report 2012: The pharmaceutical industry in figures

Pharma Market

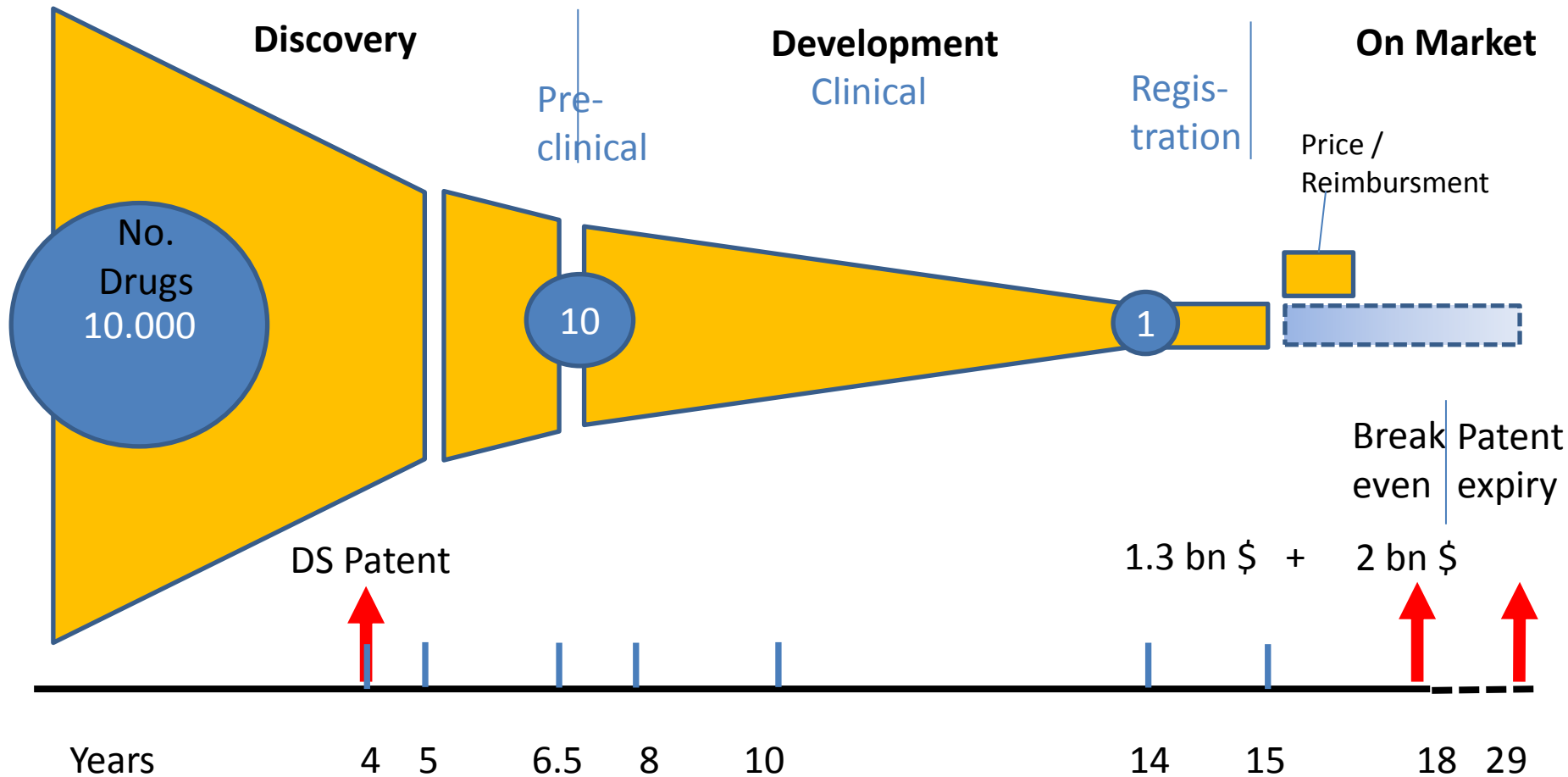
ALLOCATION OF R&D INVESTMENTS BY FUNCTION (%)



- 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

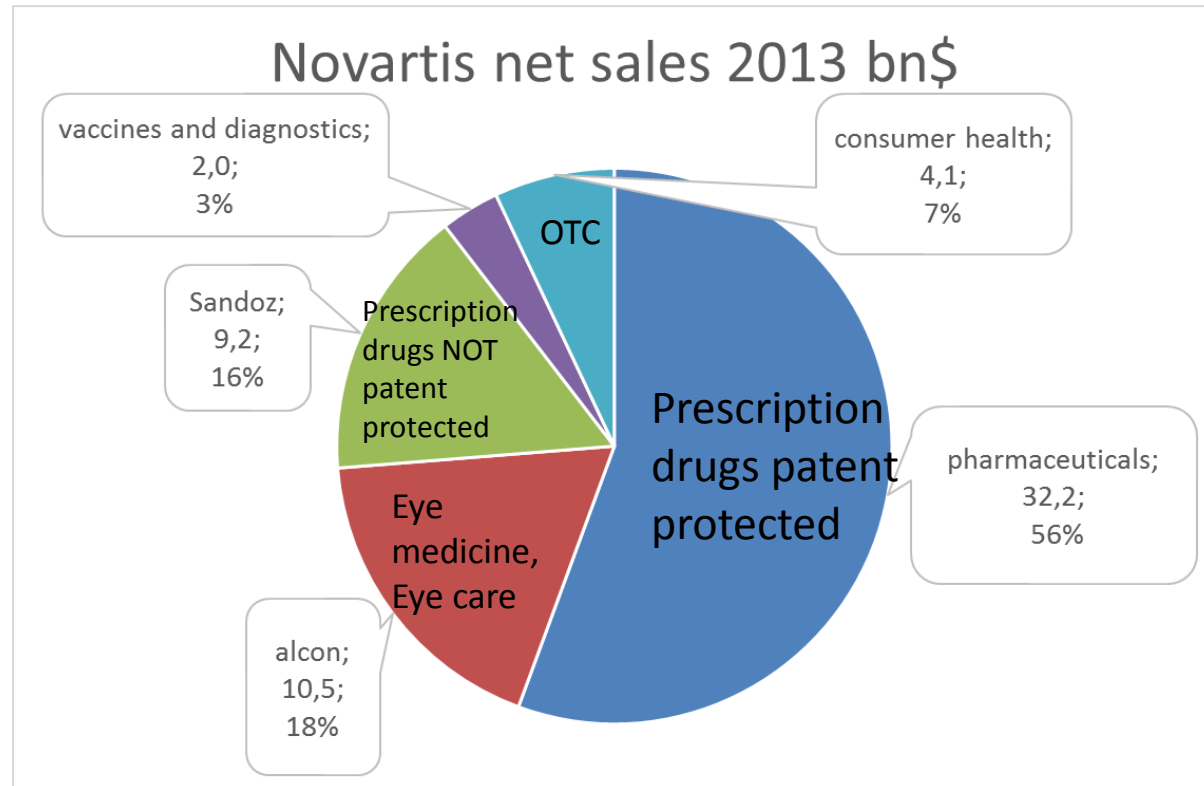
Drug Development Overview



EFPIA report 2012: The pharmaceutical industry in figures

Big Pharma - Novartis

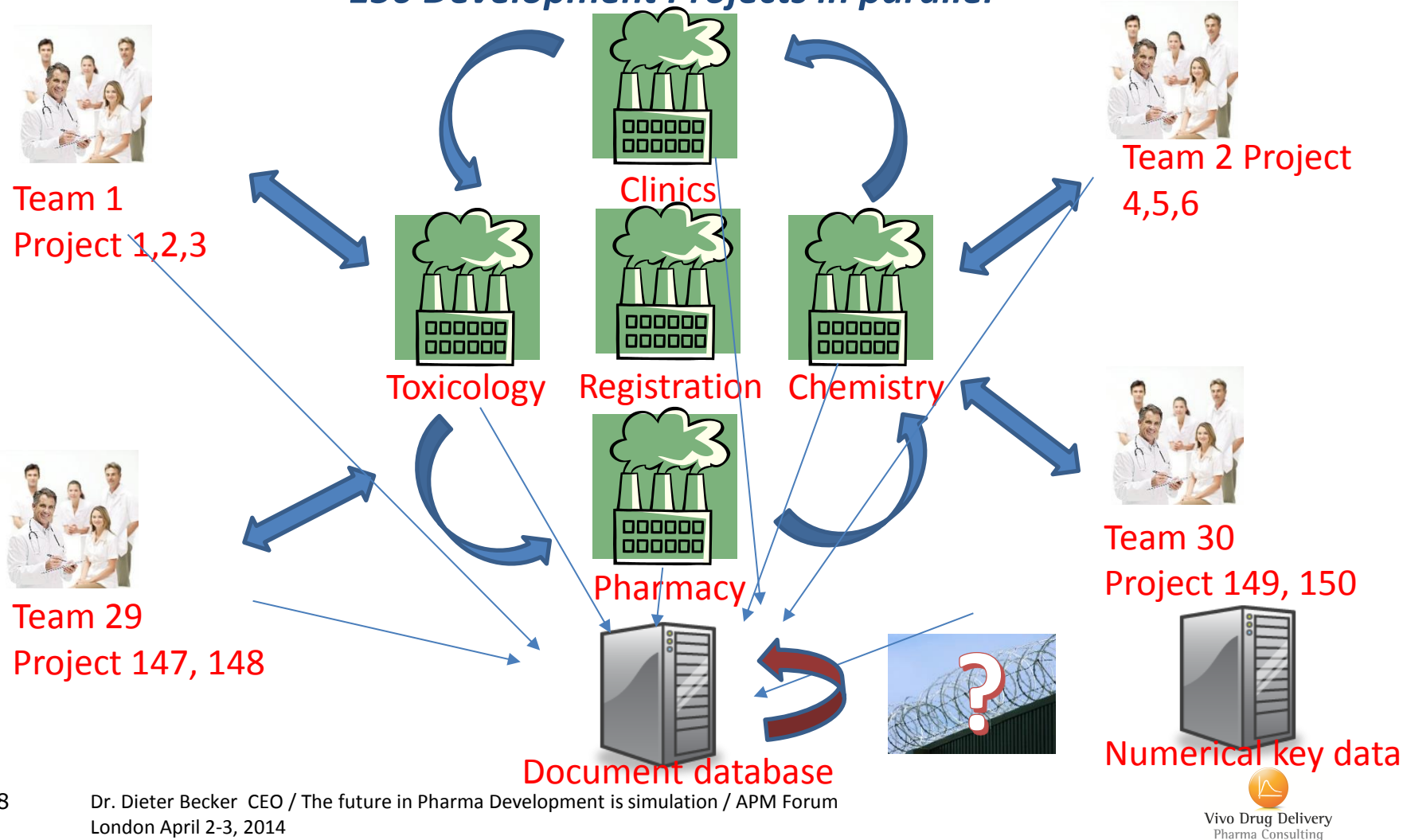
- 57.9 bn\$ Sales
- ~120'000 Co workers
- ~350 drug substances in marketed products (only pharmaceuticals)
- ~ 150 Products in Development (only pharmaceuticals)



OTC = Over The Counter (non-prescription drugs)

Product development Pharma Novartis

150 Development Projects in parallel



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

GastroPlus(TM): ~\Dieter\Atenolol\Atenolol.mdb

File Edit Database Simulation Setup Controlled Release Tools Modules (Optional) Help

Compound Physiology Pharmacokinetics Simulation Graph

Selected Compound

ATN_hu_50mg_po_Mason

Current=9; Total=9

Chemical Structure: CC(C)NCC(O)COc1ccc(cc1)C(=O)N

Molecular Formula: C₁₄H₂₂N₂O₃
Molecular Weight (g/mol): 266.3
logP (neutral): 0.23 @pH: -1

pKa Table
Enzyme Table
Transporter Table

ver. 7.0.0017

SI Trans Time (h) = 3.209 Mean Abs Time (h) = 3.439
Longest Diss. Time (h) is @ pH 1.0 = 0.006 hours
Max Abs Dose (S+) = 2.429E+4 mg Max Abs Dose (lit) = 1.867E+4 mg

Support Files
ATN_hu_50mg_po_Mason.ipd ATN_hu_50mg_po_Mason.opd

Dosage Form: IR: Solution

Initial Dose (mg): 50
Subsequent Doses (mg): 0
Dosing Interval (h): 0
Dose volume (mL): 250

pH for Reference Solubility: 7
Solubility (mg/mL @pH=7): 13.5
Mean Precipitation time (sec): 900
Diff. Coeff. (cm²/s x 10⁻⁵): 0.8187
Drug Particle Density (g/mL): 1.2

Particle Size: R=25.00, D=50.00

Effective Permeability

Source: Human

Peff (cm/s x 10⁻⁴): 0.466
Sim Peff x10⁻⁴ (Human): 0.466

Convert from User Data

Biorelevant Solubilities

Dose No. = 0.0228

Absorption No. = 0.933

Dissolution No. = 5.094E+2

Notes

Windows ... 3 Windo... 4 Adobe... Microsoft ...

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

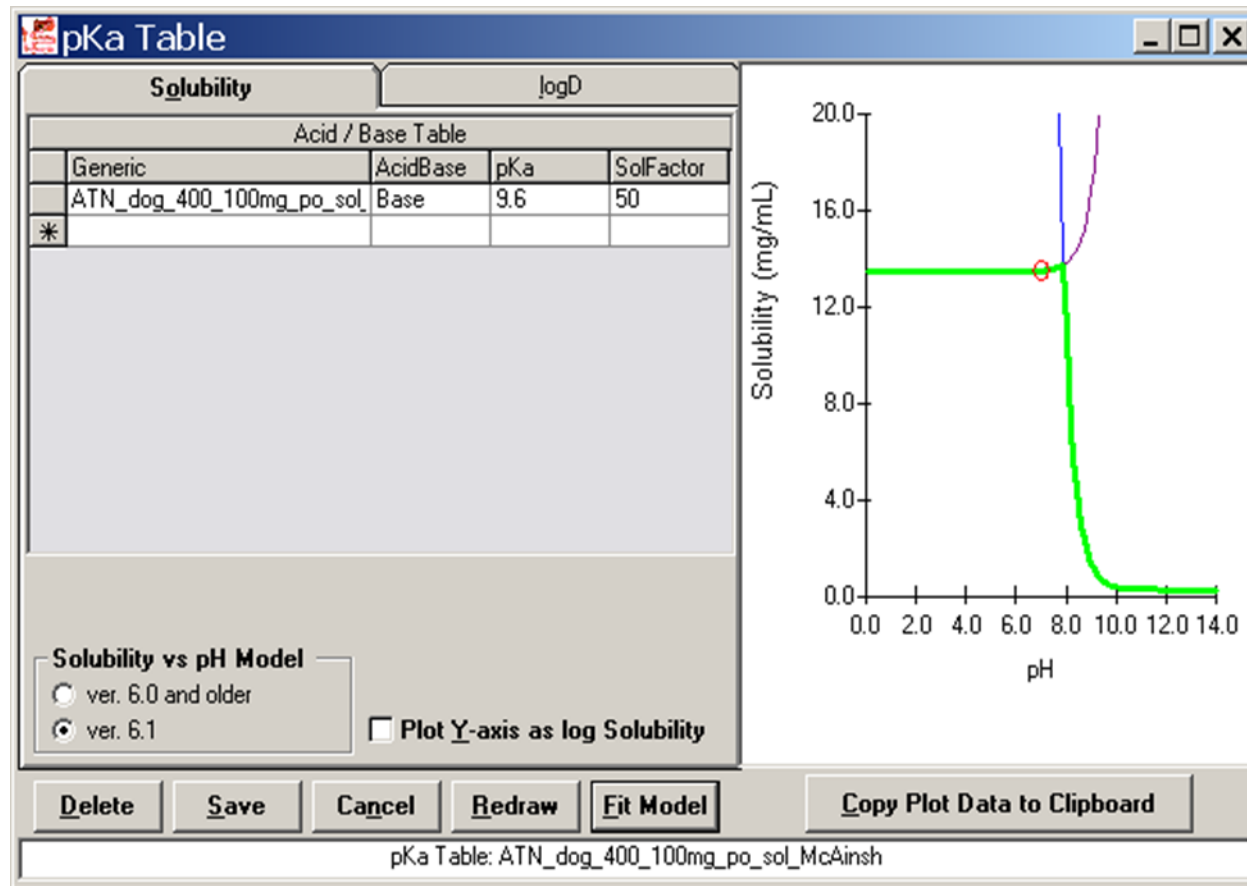
Diff Coef 0.818

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.

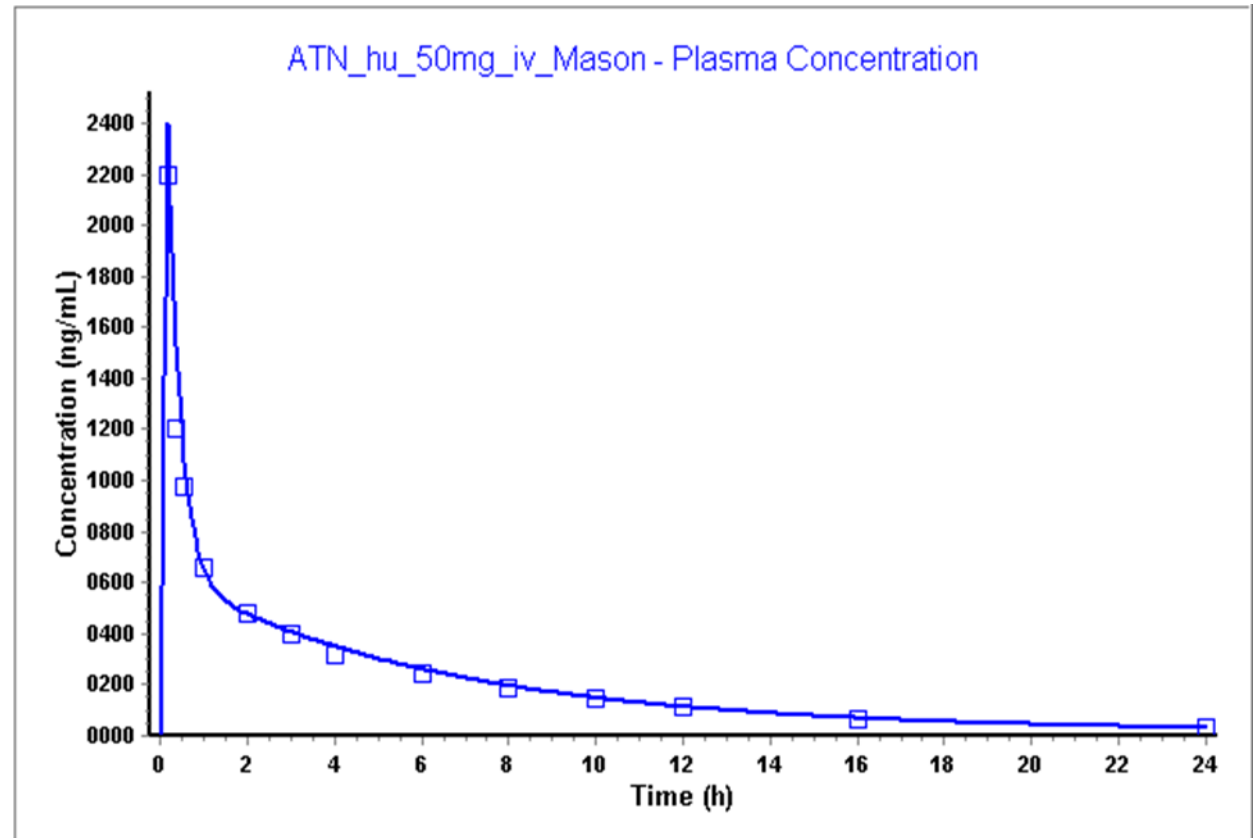
Example: Atenolol pKa

Base
pKa 9.6



Example: Atenolol iv human

$R^2=0.972$



Example: Atenolol

3-compartment
model calcu-
lated 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

GastroPlus(TM): ~s\Dieter\Atenolol\Atenolol.mdb

File Edit Database Simulation Setup Controlled Release Tools Modules (Optional) Help

Compound Physiology **Pharmacokinetics** Simulation Graph

PK Parameters

PK Model: Compartmental

Body Weight (kg): 70

FPE (if fixed) [%]:

Oral: 0 Intestinal: 0 Liver: 0.85

Blood/plasma concentration ratio: 1

☒ Use Exp Plasma Fup [%]: 5

☐ Use Adj Plasma Fup [%]: 5

Renal Clearance CL_r(L/h/kg): 0

CL (L/h): 8.4772 or (L/h/kg): 0.1211

V_c(L/kg): 0.186

T 1/2 (h): 34.15

K_{12} (1/h): 2.7111 K_{13} (1/h): 0.15234

K_{21} (1/h): 0.84467 K_{31} (1/h): 0.02578

V_2 (L/kg): 0.597 V_3 (L/kg): 1.0991

Observed Values

Fa %: 0 C_{Max} (µg/mL): 0

FDp %: 0 T_{Max} (h): 0

F %: 100 AUC (ng·h/mL): 4730

Hepatic Clearance (L/h): 0

ATN_hu_50mg_iv_Mason

Metabolism/Transporter Scale Factors

Enzymes

	Gut	Liver
V _{max} SF:	1.	1.
K _m SF:	1.	1.

Gut Transporters

	Apical	Basolateral
Influx V _{max} SF:	1.	1.
Influx K _m SF:	1.	1.
Efflux V _{max} SF:	1.	1.
Efflux K _m SF:	1.	1.

Transfer SFs to Enz/Trans tables

Liver Enzyme Turnover Rates

Notes

Mason iv 50mg inf time 2 min

Sol Model: 6.1 logD Model: Emp-6.1 Diss Model: Johnson Sol-PartSize: OFF Sol-BileSalt: OFF Diff-BileSalt: OFF

Example: Atenolol

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

Obs. Values:

Cmax 0.282
Tmax 3.3
AUC 2650

GastroPlus(TM): ~s\Dieter\Atenolol\Atenolol.mdb

File Edit Database Simulation Setup Controlled Release Tools Modules (Optional) Help

Compound Physiology **Pharmacokinetics** Simulation Graph

PK Parameters

PK Model: Compartmental

Body Weight (kg): 70

FPE (if fixed) [%]

Oral: 0 Intestinal: 0 Liver: 0

Blood/plasma concentration ratio: 1

☒ Use Exp Plasma Fup [%]: 5

☐ Use Adj Plasma Fup [%]: 5

Renal Clearance CLr(L/h/kg): 0

CL (L/h): 8.4772 or (L/h/kg): 0.1211

Vc(L/kg): 0.186

T 1/2 (h): 34.15

K12(1/h): 2.7111 K13(1/h): 0.15234

K21(1/h): 0.84467 K31(1/h): 0.02578

V2 (L/kg): 0.597 V3 (L/kg): 1.0991

Observed Values

Fa %: 0 CMax (µg/mL): 0.282

FDp %: 0 Tmax (h): 3.3

F %: 50 AUC (ng-h/mL): 2650

Hepatic Clearance (L/h): 0

ATN_hu_50mg_po_Mason

Metabolism/Transporter Scale Factors

Enzymes

	Gut	Liver
Vmax SF:	1.	1.
Km SF:	1.	1.

Gut Transporters

	Apical	Basolateral
Influx Vmax SF:	1.	1.
Influx Km SF:	1.	1.
Efflux Vmax SF:	1.	1.
Efflux Km SF:	1.	1.

Transfer SFs to Enz/Trans tables

Liver Enzyme Turnover Rates

Notes

Example: Atenolol

Human –
Physiological -
Fasted

GastroPlus(TM): ~s\Dieter\Atenolol\Atenolol.mdb

File Edit Database Simulation Setup Controlled Release Tools Modules (Optional) Help

Compound Physiology Pharmacokinetics Simulation Graph

Compartmental Parameters

ATN_hu_50mg_po_Mason

☐ Excrete all un-absorbed drug at the end of gut transit time
☐ Zero-order gastric emptying

Compartment Data								Enzyme and Transporter Regional
Compartment	Peff	ASF	pH	Transit Time (h)	Volume (mL)	Length (cm)	Radius (cm)	
Stomach	0	0.0	1.30	0.25	46.56	28.29	9.67	
Duodenum	0	2.773	6.00	0.26	41.56	14.13	1.53	
Jejunum 1	0	2.736	6.20	0.93	154.2	58.40	1.45	
Jejunum 2	0	2.724	6.40	0.74	122.3	58.40	1.29	
Ileum 1	0	2.705	6.60	0.58	94.29	58.40	1.13	
Ileum 2	0	2.675	6.90	0.42	70.53	58.40	0.98	
Ileum 3	0	2.661	7.40	0.29	49.83	58.40	0.82	
Caecum	0	7.931E-3	6.40	4.19	47.49	13.19	3.39	
Asc Colon	0	0.019	6.80	12.57	50.33	27.65	2.41	

C1-C4: 0.06944 0.43028 0.12147 0.46632

Physiology: Human - Physiological - Fasted

ASF Model: Opt logD Model SA/V 6.1

Qh (L/min): 1.5

Percent Fluid in SI: 40. Colon: 10.

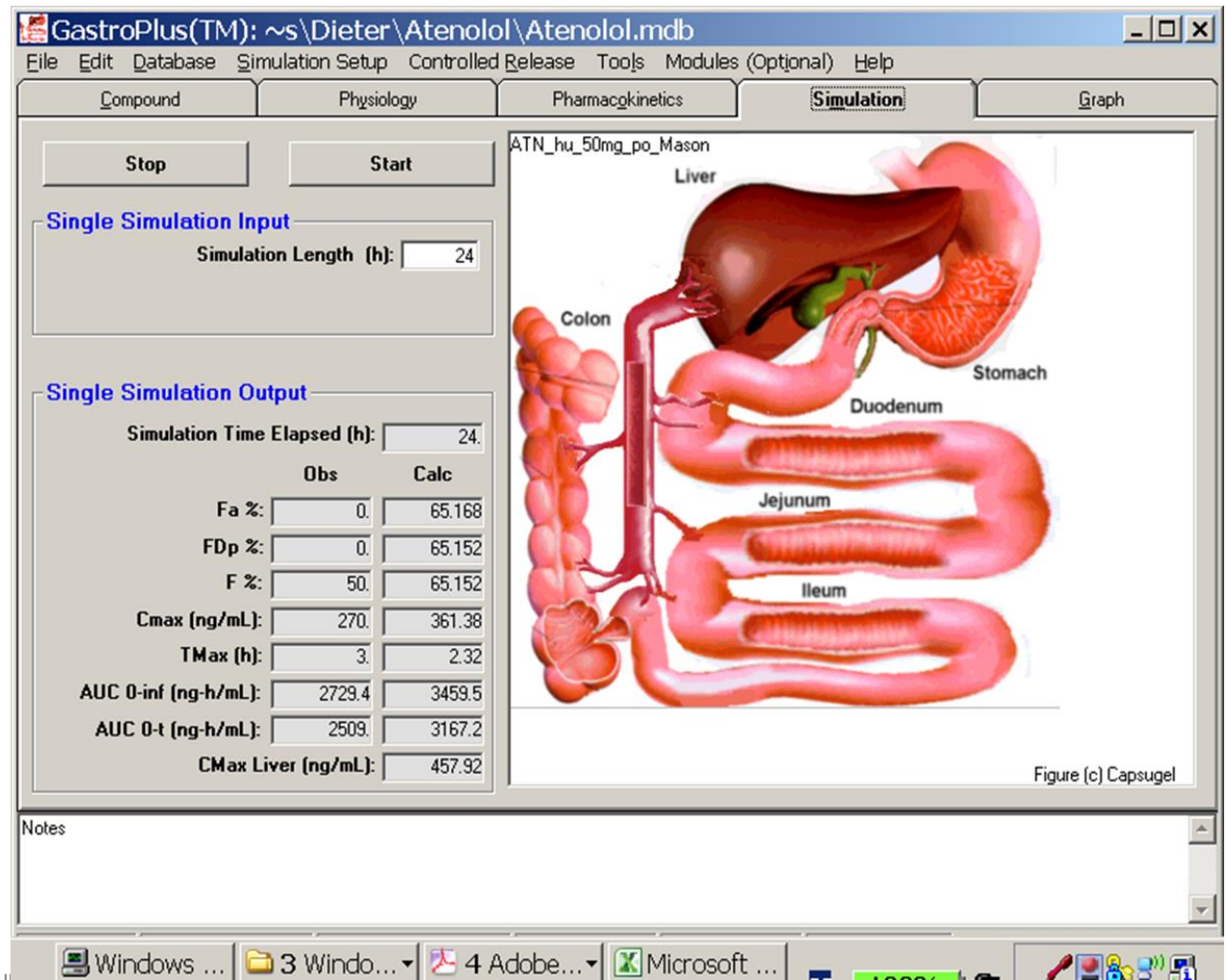
Notes

Example: Atenolol

Sim length h 24

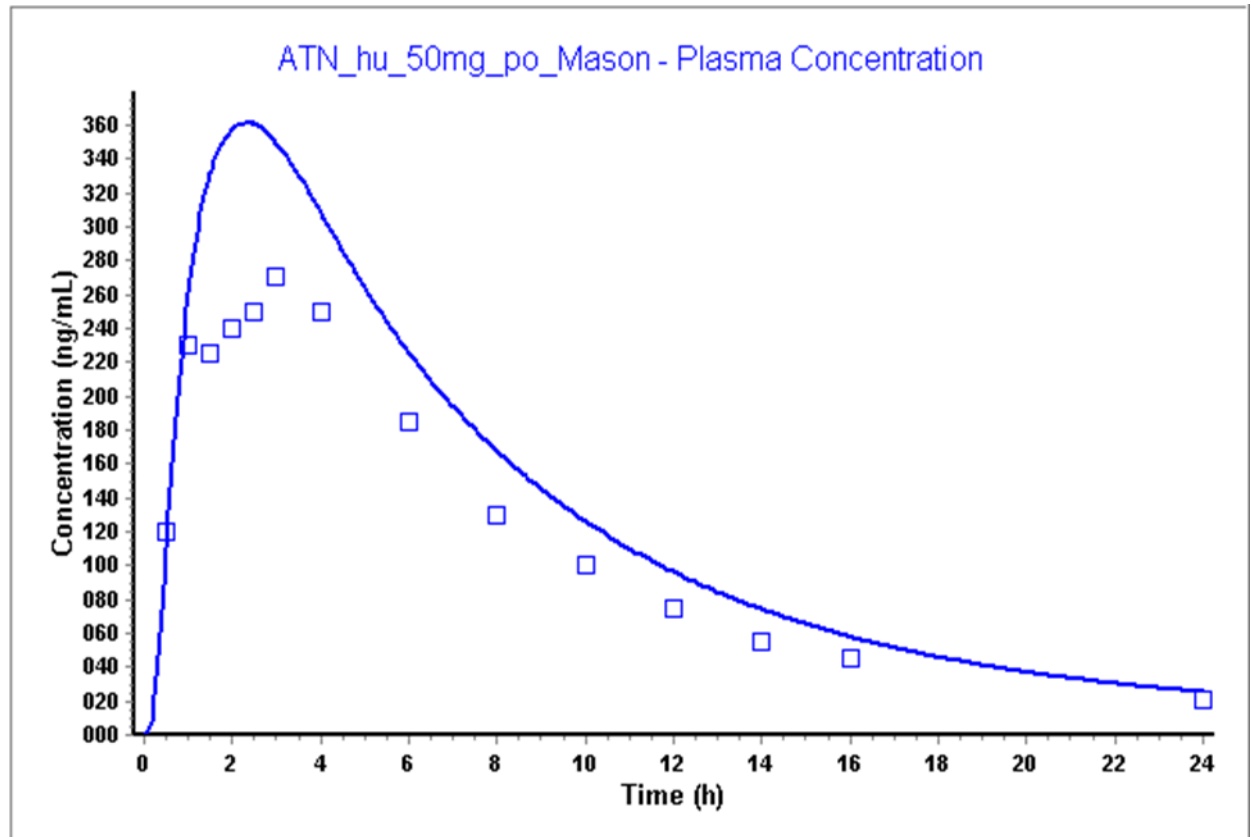
Calculated:

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



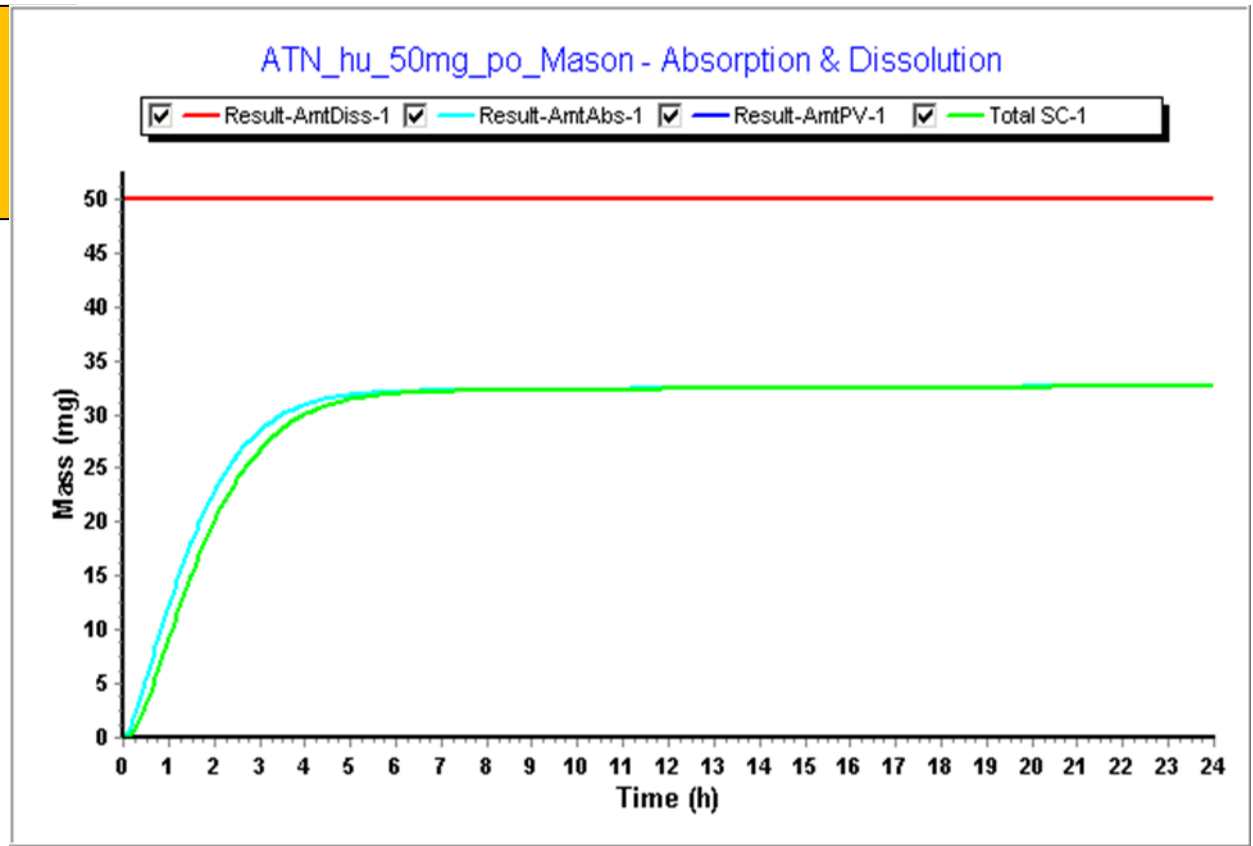
Example: Atenolol

Observed 
Simulated -



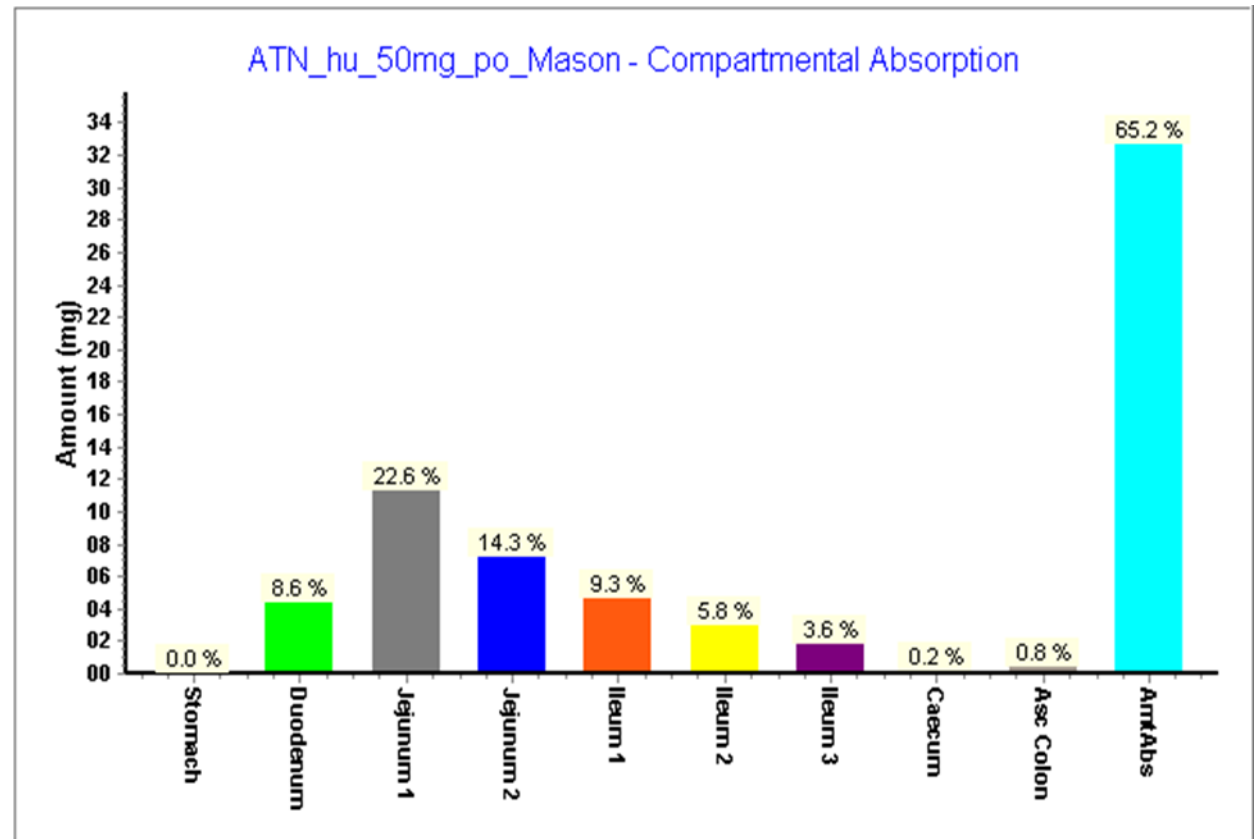
Example: Atenolol

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