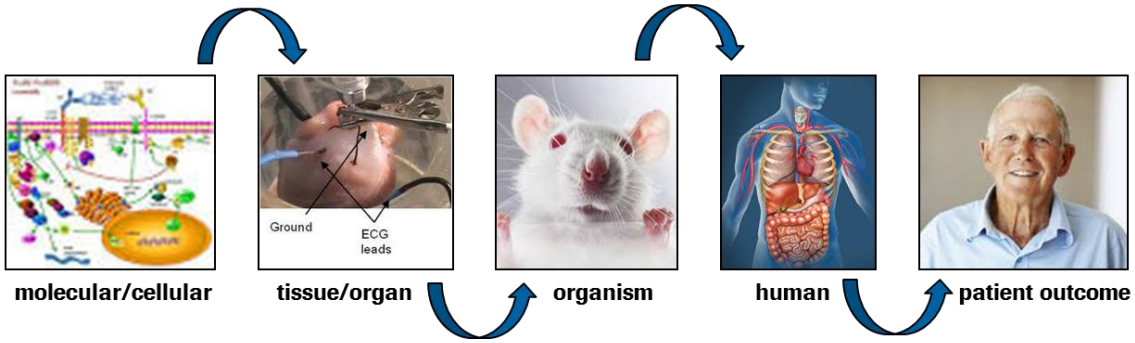


Model Based Approaches to Increase Predictability in Early Drug Development

Thierry Lavé

Head Project Leaders and M&S

Roche Pharmaceutical Research and Early Development

Roche Innovation Center Basel

Leveraging Modeling and Simulation

to increase predictability in early drug development

- **From Idea to Medicine**: How can M&S increase predictability in early drug development?
- **Advancing Confidence** in Compounds, Safety, Patients and Prediction Tools
- **Regulatory perspective**
- **Future perspectives**

Needs and expectations

Patient

- Effective & tailored medicines
- Medicines for children & elderly & all ethnicities
- Favorable risk / benefit

Society

- No animal testing
- Less medical burden due to AEs

Pharma Research and Development

- Development of drugs for unmet medical need
- Predictive research, Low attrition and Cost-effective development
- Embrace innovation
- Develop compounds that cannot be developed with traditional approaches

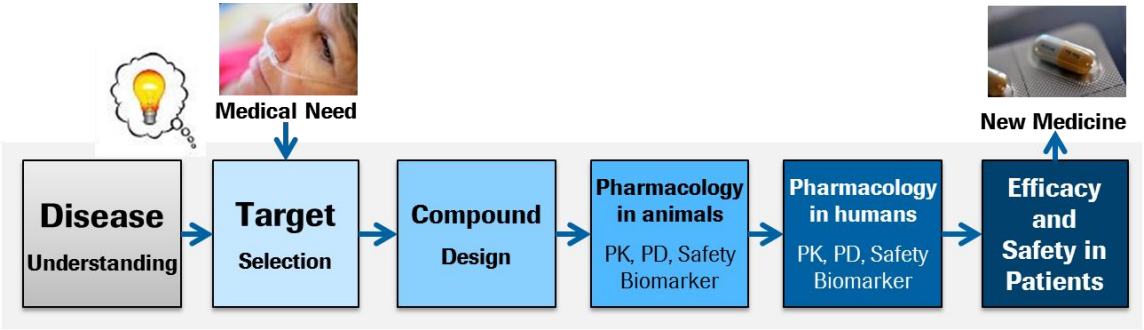
Leveraging Modeling and Simulation

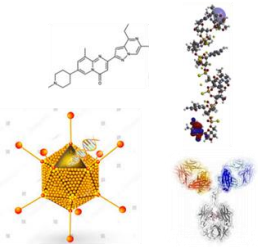
to increase predictability in early drug development

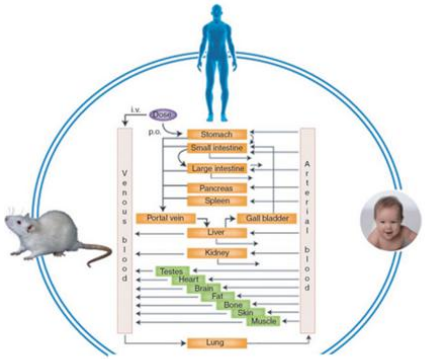
- **From Idea to Medicine**: How can M&S increase predictability in early drug development?
- **Advancing Confidence** in Compounds, Safety, Patients and Prediction Tools
- Regulatory perspective
- Future perspectives

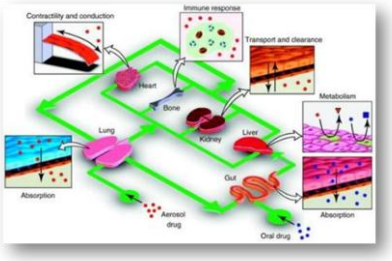
Confidence in Compounds, Safety, Patients

Need to be addressed early in development

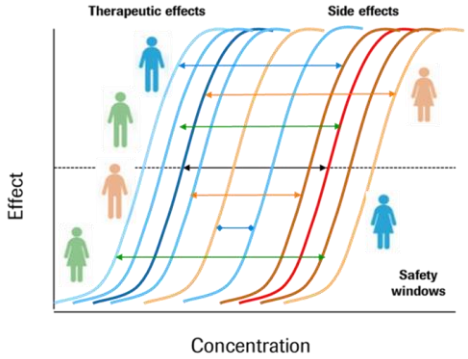








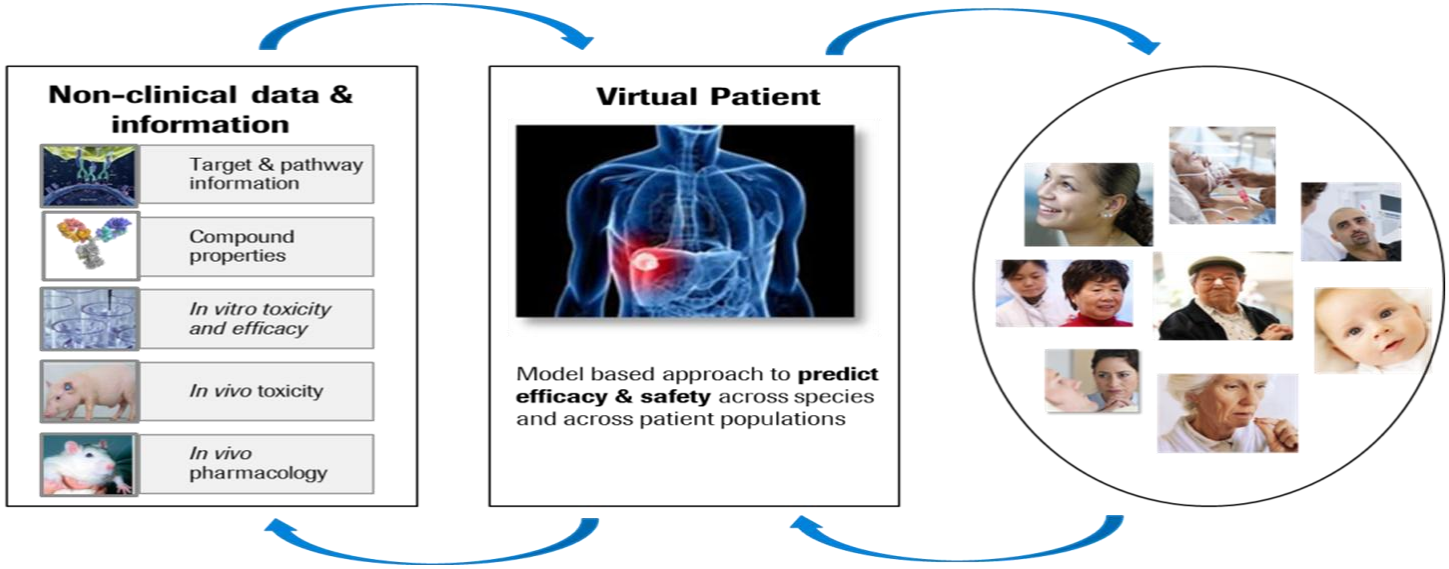
From population-based to individual-based view



M&S and "Virtual Patients"

Predict PK, safety and efficacy in humans based on in vitro and in vivo data

- Integration of drug specific information
- Construction of virtual patient
- Simulation of Drug responses
- In silico testing dosages
- Adjusting for Children, Elderly, Disease..



No match: new experiments to improve model

Matches: Confidence in model prediction

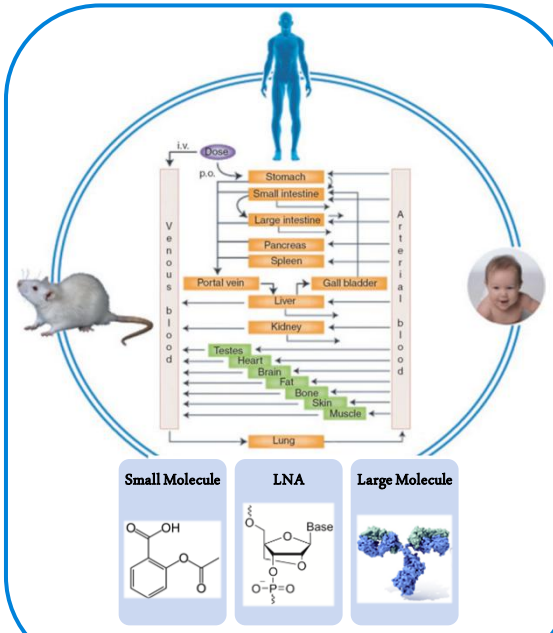
Verifying prediction early in vivo

M&S and "Virtual Patients"

3 Pillars: PK, Safety, Efficacy modeling

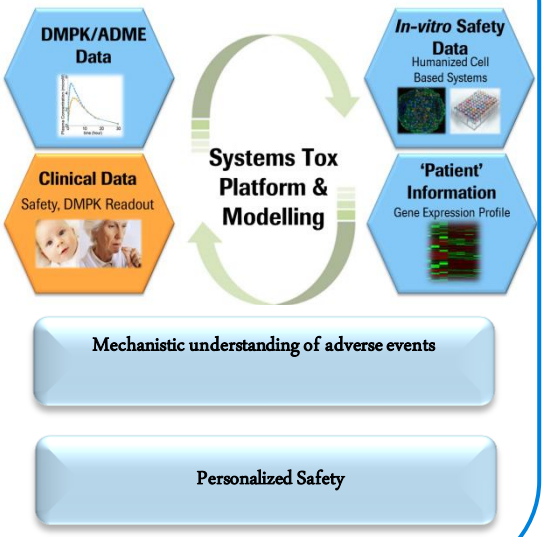
PBPK & Mechanistic PK

Target exposures

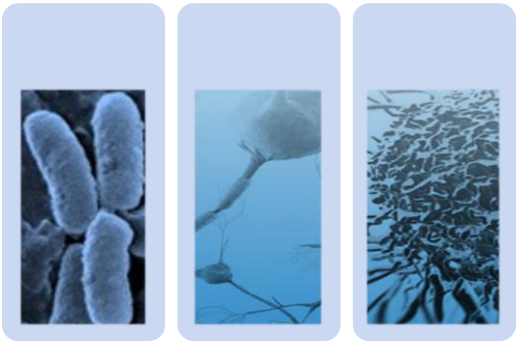


Safety prediction

Mechanistic safety



Efficacy prediction



"Virtual Human" for Pharmacokinetics

Simulating in plasma, tissues and target organs not accessible through measurements

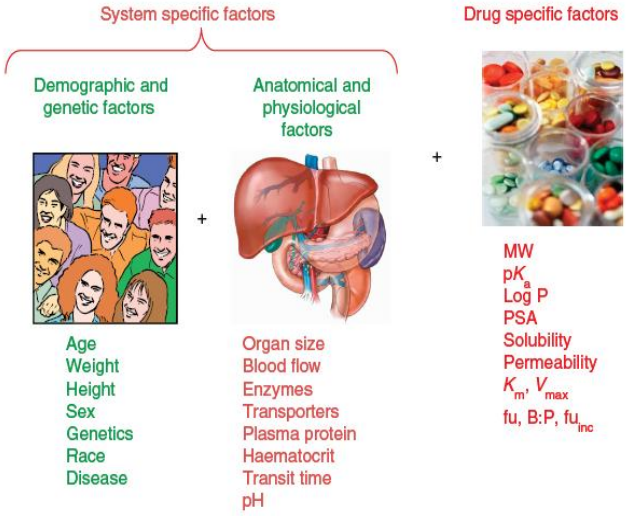
Problem Statement

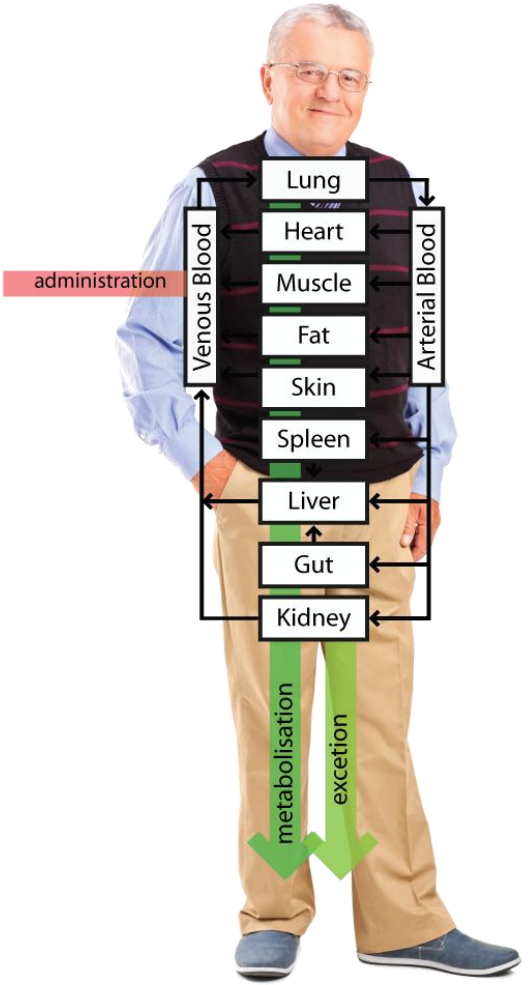
Rational Prediction of PKPD in man

Simulating in special patient populations

Assess DDI potential

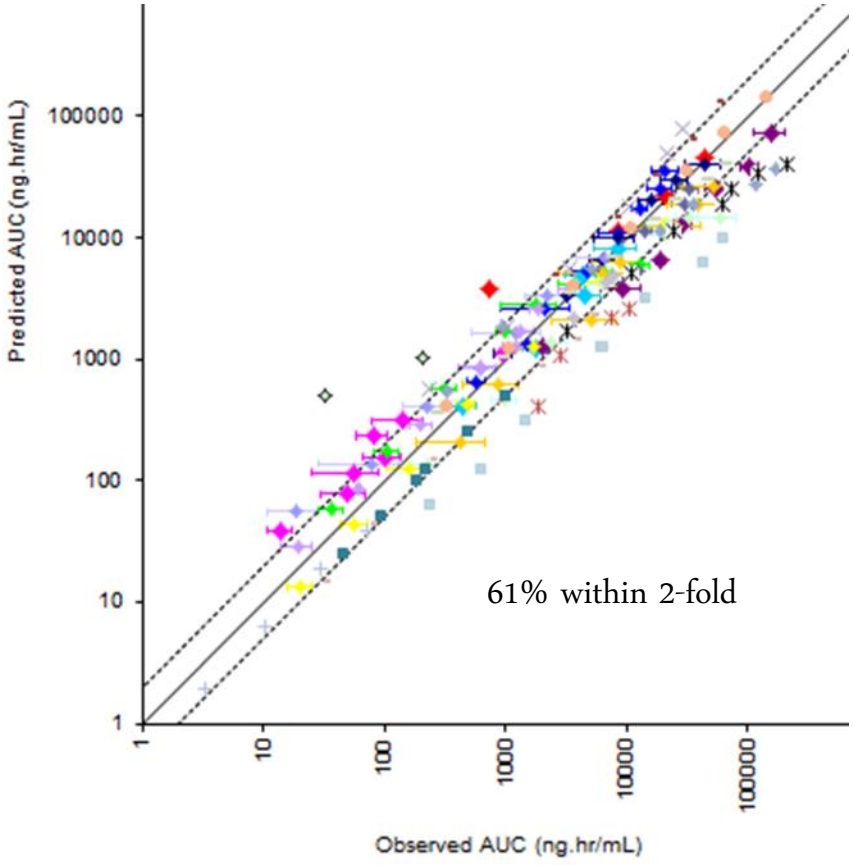
Assess impact of formulation on PK/PD profile



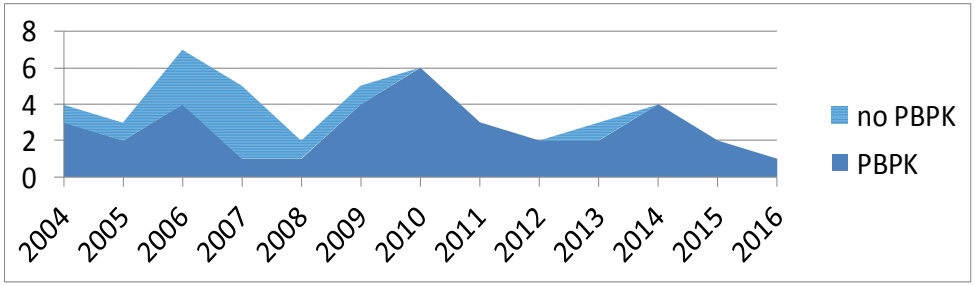


First time in human doses guided by "Virtual Human" for Pharmacokinetics

Prospective predictions for 33 compounds



Since 2010, systematic use of PBPK predictions at EIH

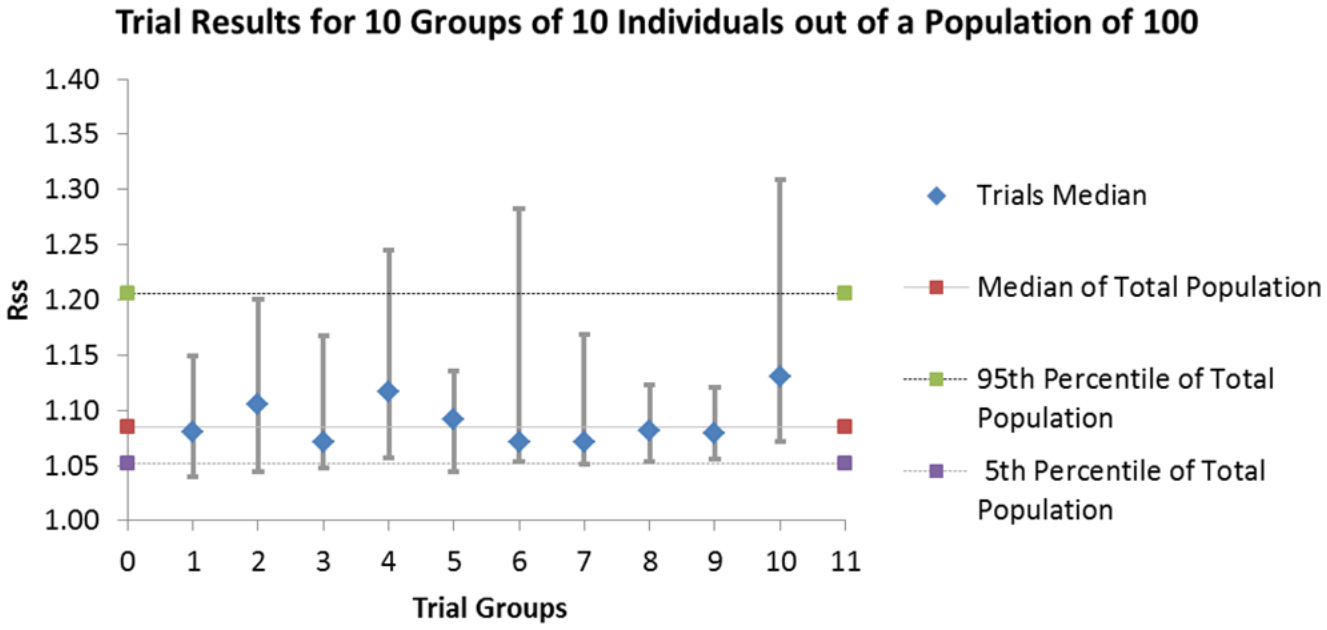


→ Safe starting doses in man

ALECENSA®

Roche

Saving unnecessary (DDI) clinical studies



Modeling by Neil Parrott

PBPK modeling used to demonstrate that at clinically relevant concentrations, alectinib does not have the potential to increase plasma concentrations of co-administered substrates of CYP2C8

Avoidance of a DDI clinical study – costing ~ 1 million CHF

Modeling & Simulation to predict across species and patient populations

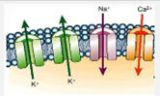
Towards personalized cardiac safety

- Integration of drug specific information

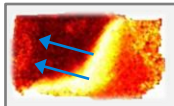
- Construction of virtual heart
- Simulation of drug responses

- Sub-population based prediction
- Optimal trial design

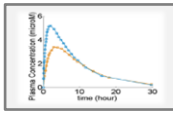
Pre-clinical data & information



Ion channel effect

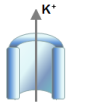


Impact on conduction

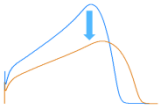


ADME Profile

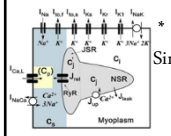
In-silico Virtual Heart



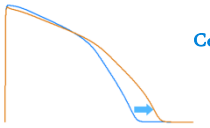
Single Channel



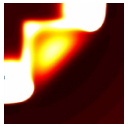
Ion channel response

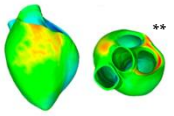


Single Cell



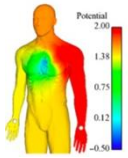
Cellular level change

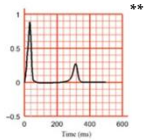




Tissue Organ

Multi-cellular effect





Pseudo ECG

Predicted clinical signal

Subpopulation Prediction

Fluoxetine: identify subpopulation at risk

Poor Metabolizer CYP2D6

Moderate risk

LQT2 hERG Mutation

High baseline risk

Poor Metabolizer with LQT2

Arrhythmia

Healthy Individual

Safe

* Mahanjan *et al.* 2008, Biophys J

** Zemzemi *et al.* 2013, BJP

Personalized Cardiac Safety Prediction

Patient specific risk can be predicted

Fluoxetine

Subpopulation Based Safety Prediction

Healthy individual	Minor QT prolongation: safe
Sub-population of poor metabolizer *None/low CYP2D6 activity*	Moderate QT increase: minor adjustment of dosing
Diseased population LQT2 *hERG mutation*	High baseline risk: subpopulation to be avoided if possible
Poor metabolizer with LQT2 *hERG mutation with non/low CYP 2D6 activity*	Arrhythmia events predicted: subpopulation to be excluded

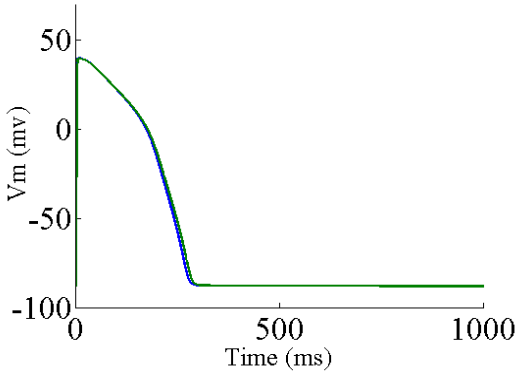
Personalized Cardiac Safety Prediction

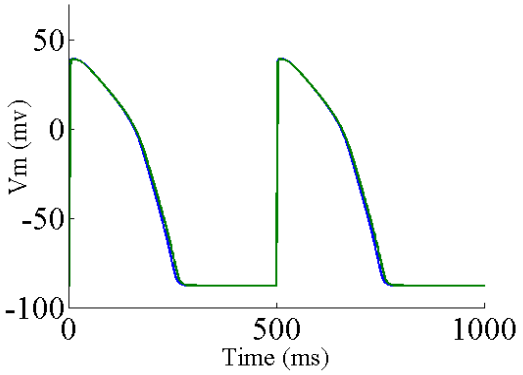
Subpopulation Specific Risk Manifested During Exercise

At rest 60 beats/min

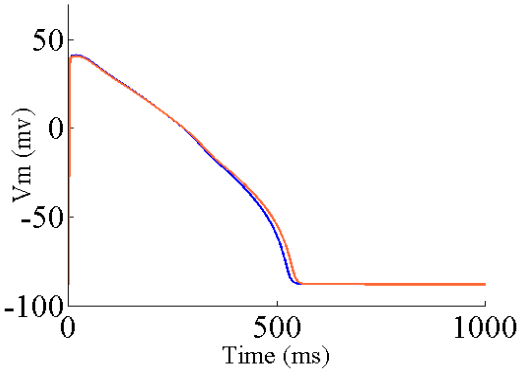
Exercising 120 beats/min

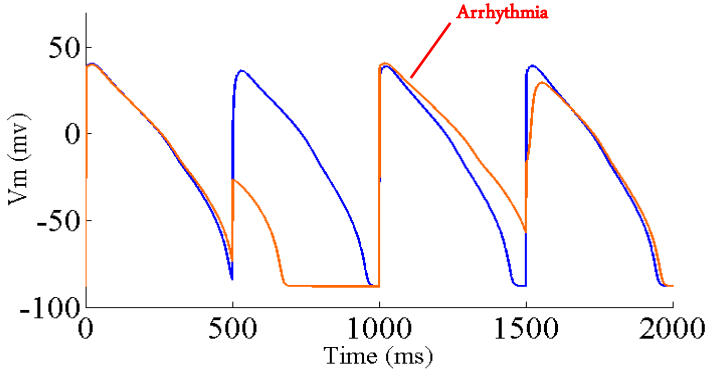
Healthy individual





Poor metabolizer with LQT2





This approach can be also used to explore **therapeutic indication** for subpopulation: e.g. Verapamil

Leveraging Modeling and Simulation

to increase predictability in early drug development

- **From Idea to Medicine**: How can M&S increase predictability in early drug development?
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Example 1, Oncology drug

Is the back up compound differentiated from our front runner?

Problem Statement

Thrombocytopenia is dose limiting toxicity for the lead compound

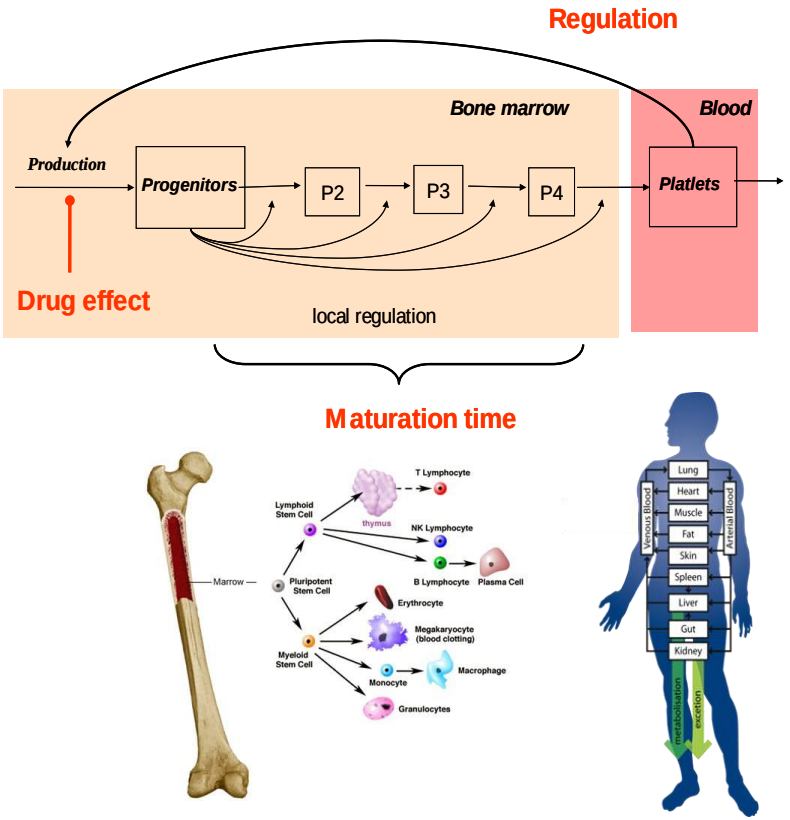
Question: Can we achieve better separation between thrombocytopenia and efficacy for backup vs front runner?

Data Input

- Human PK predictions based on PBPK (BU)
- PKPD study in monkey (BU)
- PKPD study in xenograft mice (BU & FR)
- Human PKPD data of FR (thrombocytopenia)

Model

Semi-mechanistic dose-effect model that reflects key processes of thrombocyte production and regulations.

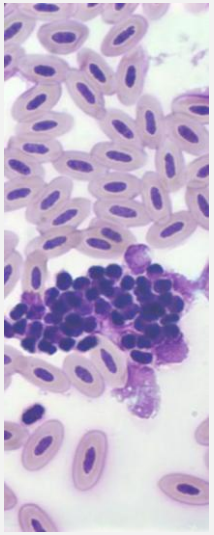


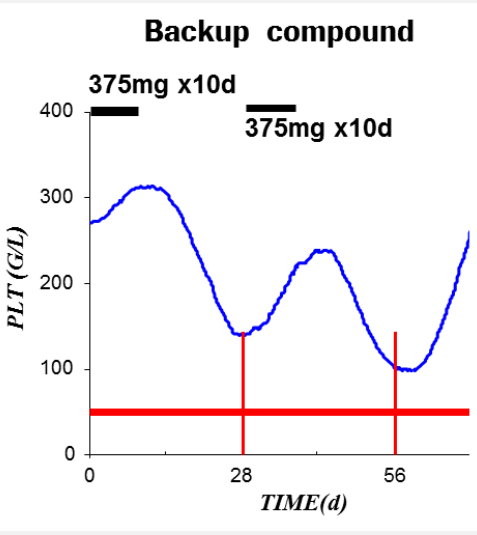
Example 1, Oncology drug

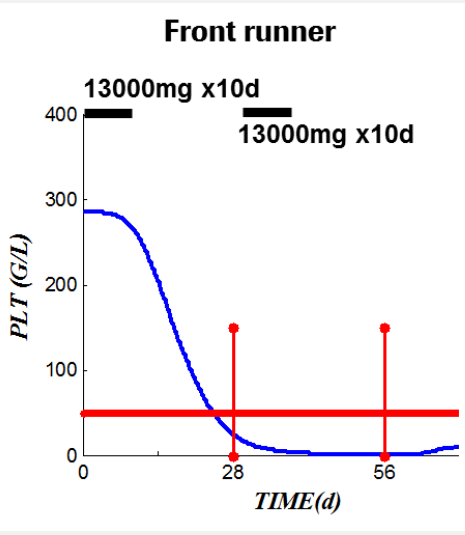
Is the back up compound differentiated from our front runner?

Results

Targeting the same efficacy, backup compound shows a clear advantage compared to front runner in terms of safety (thrombocytopenia)







Impact

The quantitative pharmacology approach raised confidence in the backup compound, which was advanced further in development.

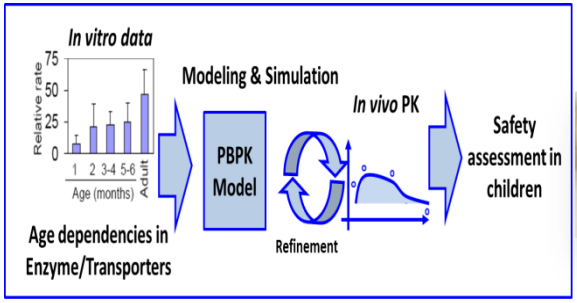
Example 2, Tamiflu line extension

PBPK modeling to support FDA approval of Tamiflu line extension for the treatment of influenza in infants

Problem Statement

- EMEA requested an IV compassionate use program in Europe
- Nonclinical data support the IV compassionate use application for adults and children >1 year
- For children <1 year EMEA requested a repeated dose IV toxicology study in juvenile marmosets
- Strategy: short PK study in newborn monkey plus comparative PBPK modelling and simulation in very young monkeys and infants

Model

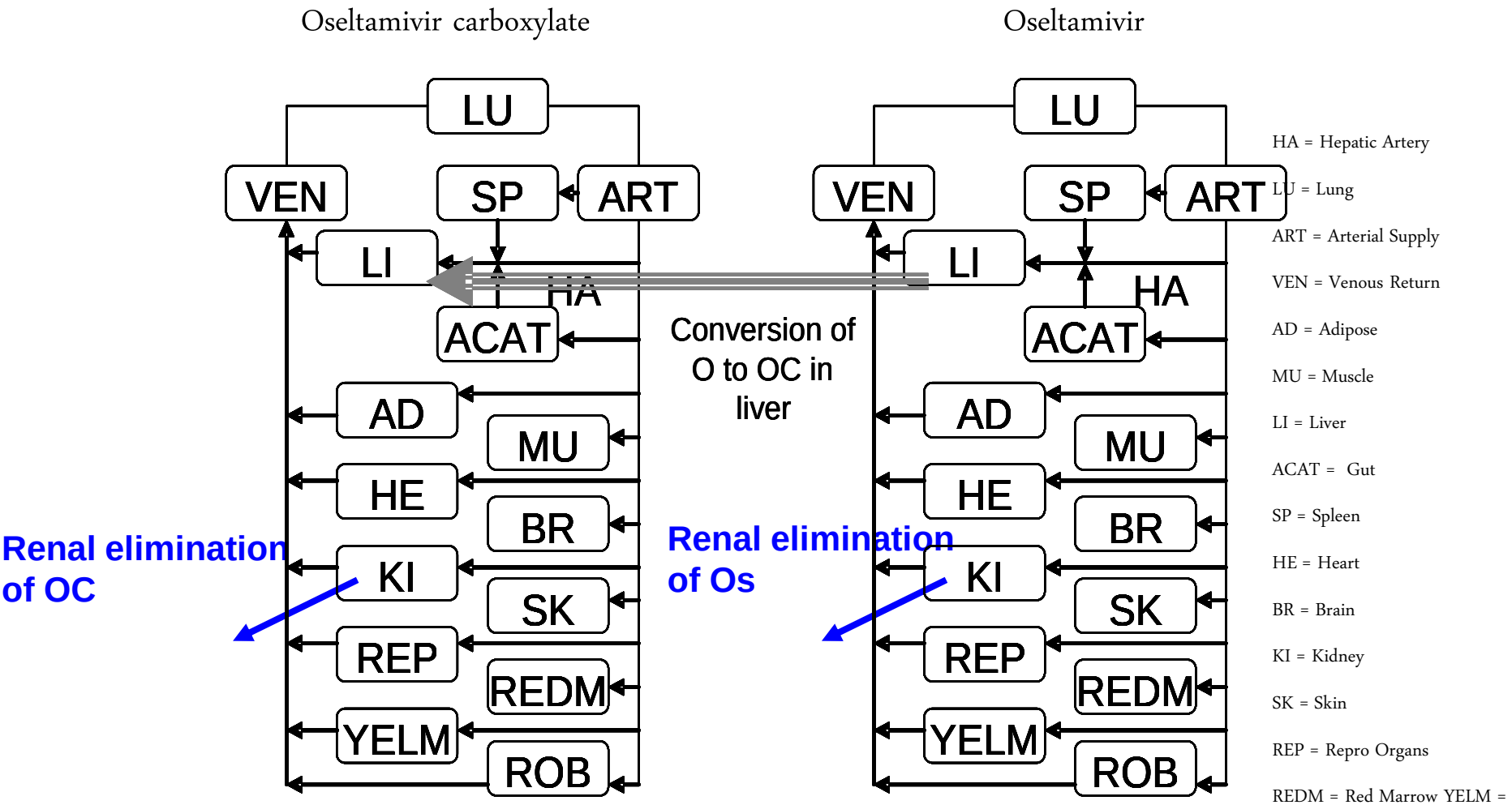


Development of a Physiologically Based Model for Oseltamivir and Simulation of Pharmacokinetics in Neonates and Infants

Neil Parrott,[1] *Brian Davies,*[2] *Gerhard Hoffmann,*[1] *Annette Koerner,*[1] *Thierry Lave,*[1] *Eric Prinssen,*[3] *Elizabeth Theogaraj*[4] and *Thomas Singer*[1]

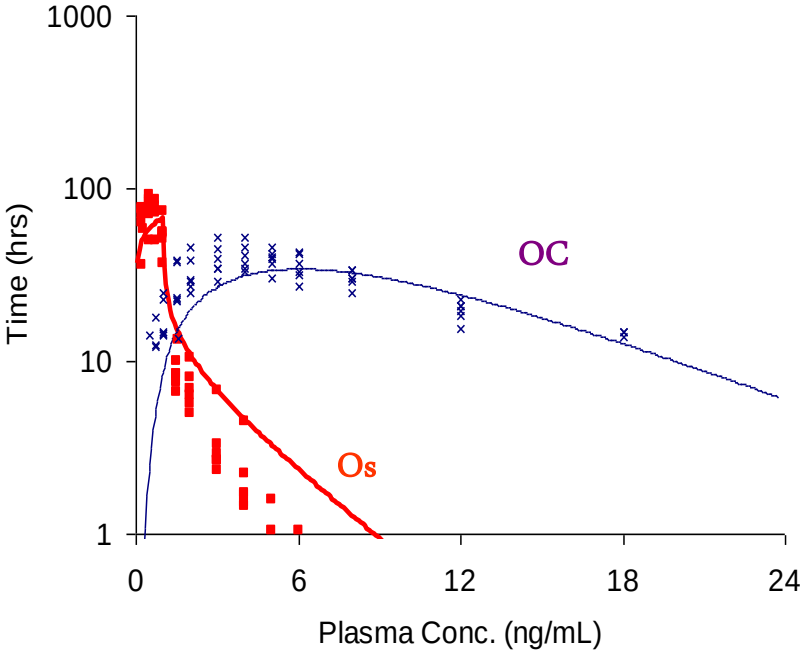
1 Non-Clinical Safety, Pharmaceuticals Division, F. Hoffmann-La Roche Ltd., Basel, Switzerland
2 Clinical Pharmacology, Pharmaceuticals Division, F. Hoffmann-La Roche Ltd., Basel, Switzerland
3 Discovery Neuroscience, Pharmaceuticals Division, F. Hoffmann-La Roche Ltd., Basel, Switzerland
4 Drug Regulatory, Pharmaceuticals Division, F. Hoffmann-La Roche Ltd., Basel, Switzerland

PBPK models for pro-drug and metabolite

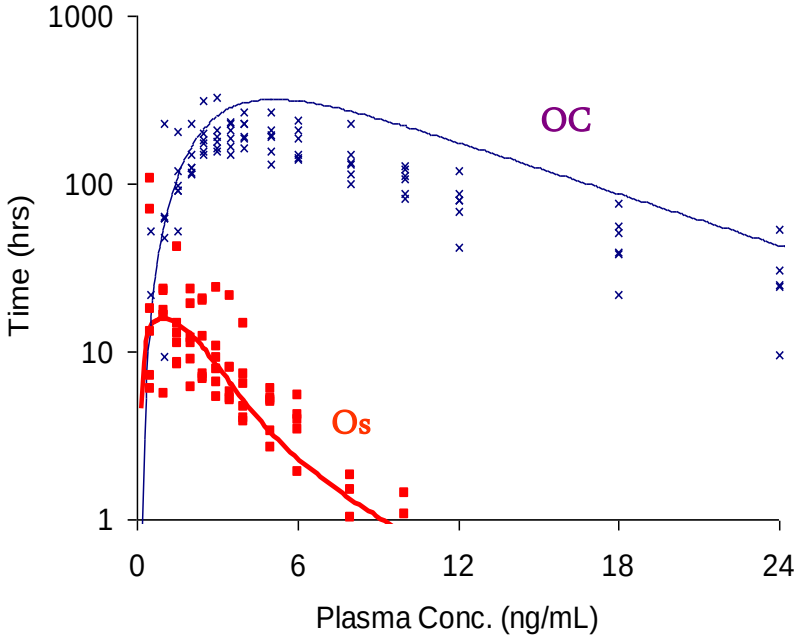


Verification of simulations in human adults

15 mg infused over 1 hour



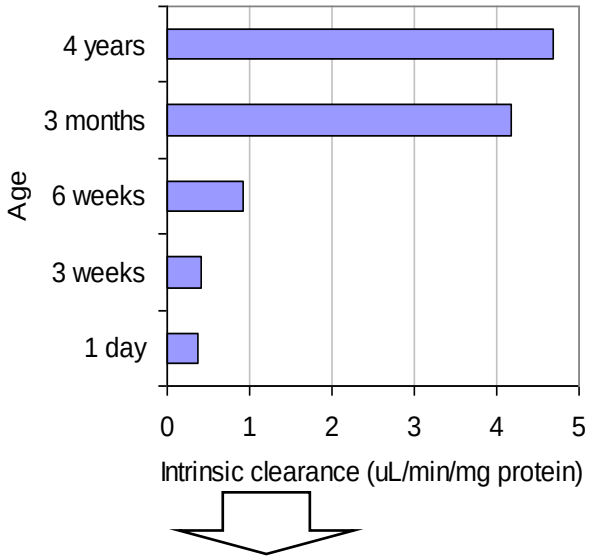
100 mg oral dose



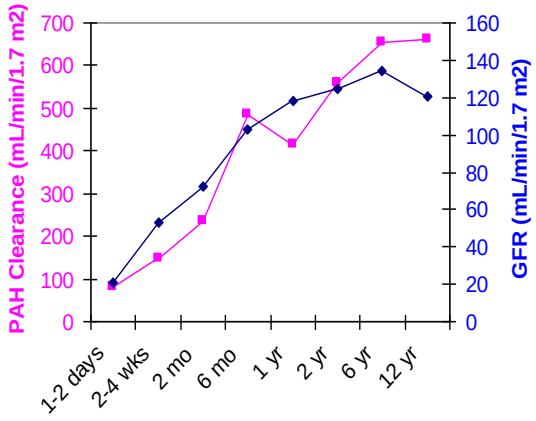
Integration of literature and in vitro data on age dependencies

Development of body and organ size with age

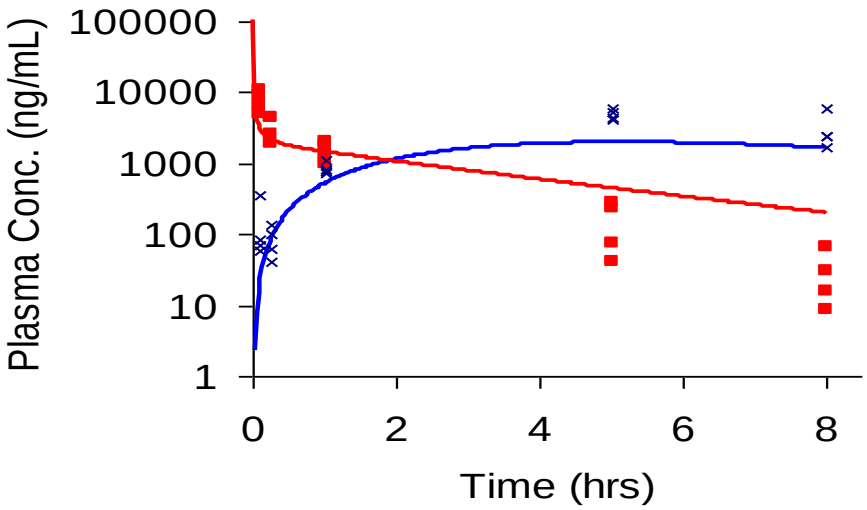
Development of metabolism with age



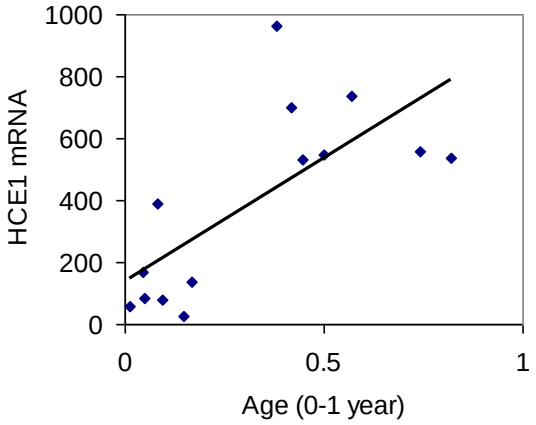
Maturation of renal function



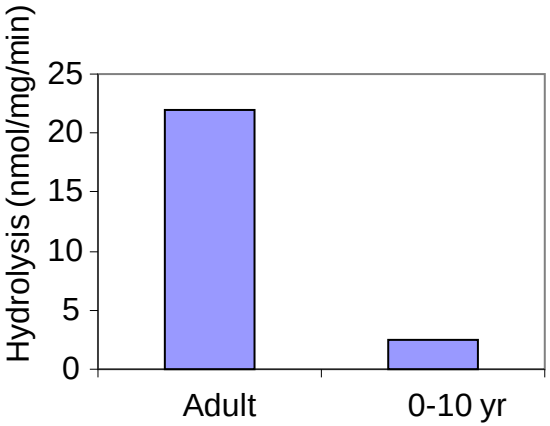
Simulation/Verification in newborn marmoset



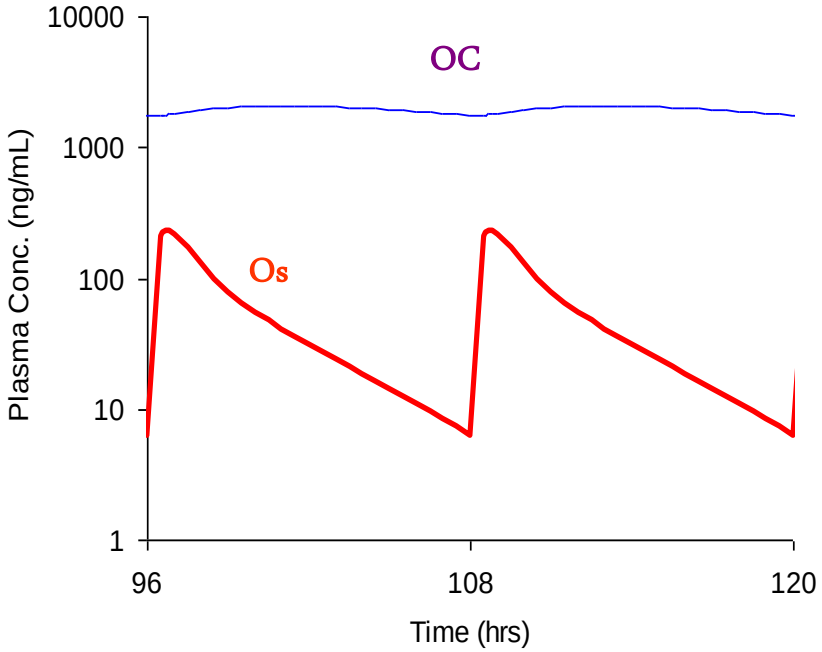
Simulation results of Tamiflu in newborns



Consistent with the mRNA and protein expression levels, adult microsomes are approx 10 times as active as microsomes from newborns



1.73 mg/kg b.i.d. given to premature neonates



Metabolic turn-over in newborns is sufficient at therapeutic doses to produce therapeutic levels of active metabolite

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to increase predictability in early drug development

- **From Idea to Medicine**: How can M&S increase predictability in early drug development?
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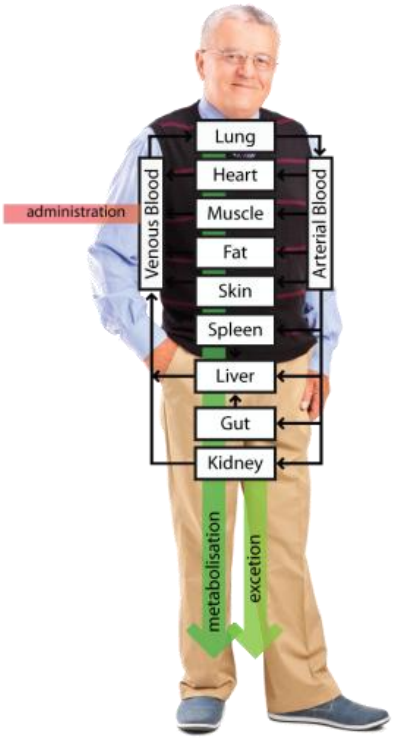
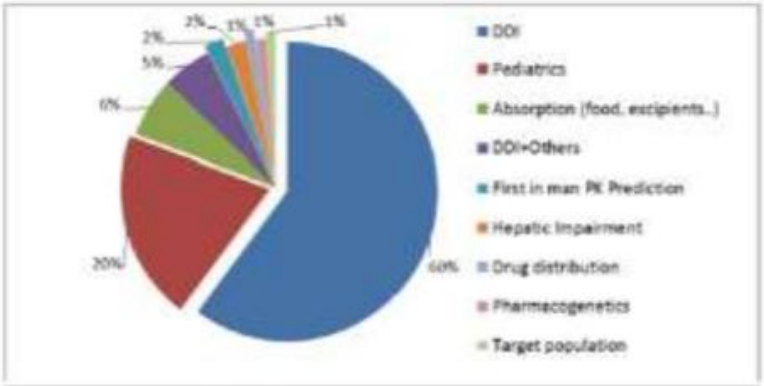
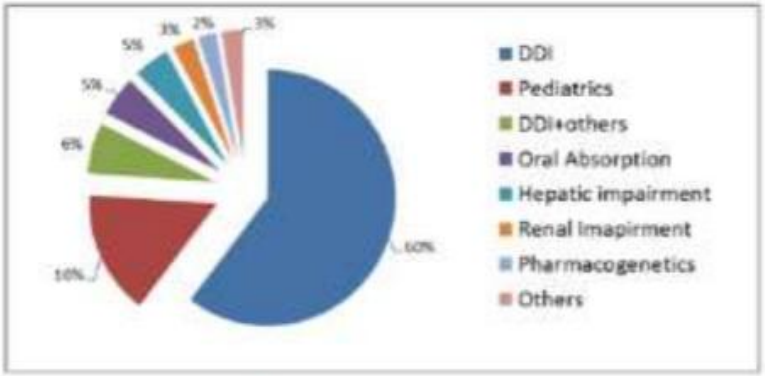
FDA submissions using PBPK modelling





Cumulative as of June 18, 2014 (n=96)

Sinha, MHRA PBPK Workshop 2014, London, UK



Cumulative as of Aug 1, 2016 (n=217)

New guidance documents for first in human dose selection emphasize importance of modeling

FDA

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Pmda

CFDA

Pharmaceuticals and Medical Devices Agency, Japan

- Regulators have mentioned PBPK modeling in multiple guidance documents
- In 2016 EMA and FDA bring out PBPK guidance documents

Recent examples of PBPK in drug labels

A recent FDA drug approval : PBPK modelling replaced clinical DDI studies and in the drug label

http://www.imbruvica.com/downloads/Prescribing_Information.pdf

Drug Interactions

Coadministration of Ibrutinib with CYP3A Inhibitors

In a sequential design trial of 18 healthy volunteers, a single dose of 120 mg of IMBRUVICA was administered alone on Day 1 and a single dose of 40 mg of IMBRUVICA was administered on Day 7 in combination with 400 mg of ketoconazole (given daily on Days 4 - 9). Ketoconazole increased ibrutinib dose-normalized C_{max} and AUC 29-fold and 24-fold, respectively. Simulations using physiologically-based pharmacokinetic (PBPK) models suggested that moderate CYP3A inhibitors (diltiazem and erythromycin) may increase the AUC of ibrutinib 6 to 9-fold in fasted condition.

Coadministration of Ibrutinib with CYP3A Inducers

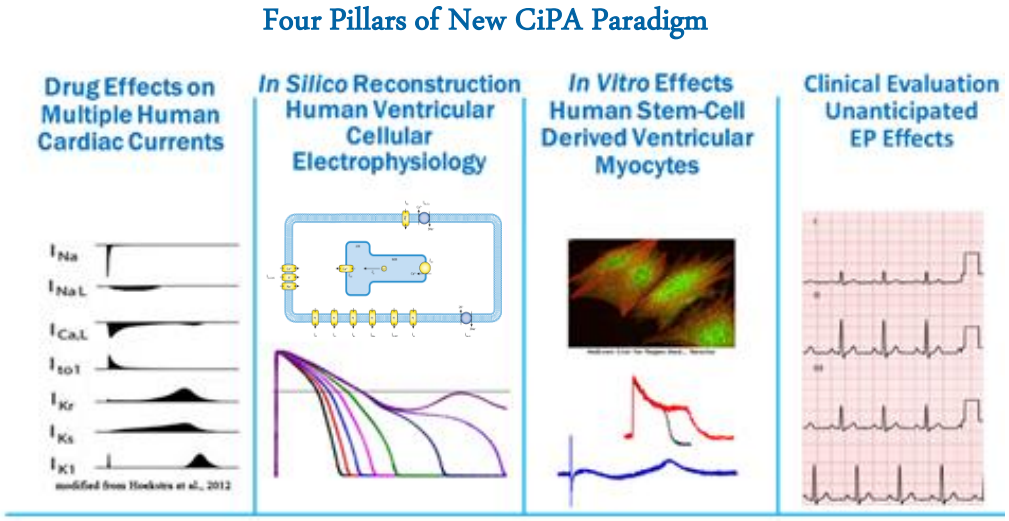
Preliminary PK data from an ongoing dedicated drug interaction trial and simulations using PBPK indicate that rifampin (a strong CYP3A inducer) can decrease ibrutinib C_{max} and AUC by more than 10-fold. Simulations using PBPK suggested that a moderate CYP3A inducer (efavirenz) may decrease the AUC of ibrutinib up to 3-fold.

Approved drugs where M&S informed the drug label (FDA, EMA and PMDA)

#	Drug	Company	Active ingredient
1	Revatio	Pfizer	Sildenafil citrate
2	Xarelto	Janssen	Rivaroxaban
3	Iclusig	Ariad	Ponatinib hydrochloride
4	Olysio	Janssen	Simeprevir sodium
5	Imbruvica	Pharmacyclics	Ibrutinib
6	Opsumit	Actelion	Macitentan
7	Movantik	Astrazeneca	Naloxegol oxalate
8	Cerdelga	Genzyme	Eliglustat tartrate
9	Jakafi	Incyte	Ruxolitinib phosphate
10	Zykadia	Novartis	Ceritinib
11	Lynparza	Astrazeneca	Olaparib
12	Lenvima	Eisai	Lenvatinib mesylate
13	Farydak	Novartis	Panobinostat lactate
14	Edurant	Janssen	Rilpivirine hydrochloride
15	Aristada	Alkermes	Aripiprazole lauroxil
16	**Cotellic**	**Roche/ Genentech**	**Cobimetinib fumarate**
17	Odomzo	Novartis	Sonidegib phosphate
18	**Alecensa**	**Roche/Genentech**	**Alectinib hydrochloride**
19	Tagrisso	Astrazeneca	Osimertinib mesylate

Recent Advances in Development and Application of Physiologically-Based Pharmacokinetic (PBPK) Models: a Transition from Academic Curiosity to Regulatory Acceptance, Masoud Jamei et al. Curr Pharmacol Rep April 2016

Increased regulatory requirements for the use of combined modeling & in vitro assessments



*

FDA CiPA

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

pmda Health Canada
Pharmaceuticals and Medical Devices Agency, Japan

ILSI Health and Environmental Sciences Institute
NIHS

- **Upcoming regulatory changes** in cardiac safety: replacement of hERG centric *in vitro* strategy **
- **Comprehensive *in vitro in silico* proarrhythmia assessment** pipeline to be implemented for **replacement of TQT study**
- Strategy applies to **most of small molecule projects**

* CiPA initiative: http://cipaproject.org/about-cipa/#2

** Kelly Servick, Science 2016 November

Leveraging Modeling and Simulation

to increase predictability in early drug development

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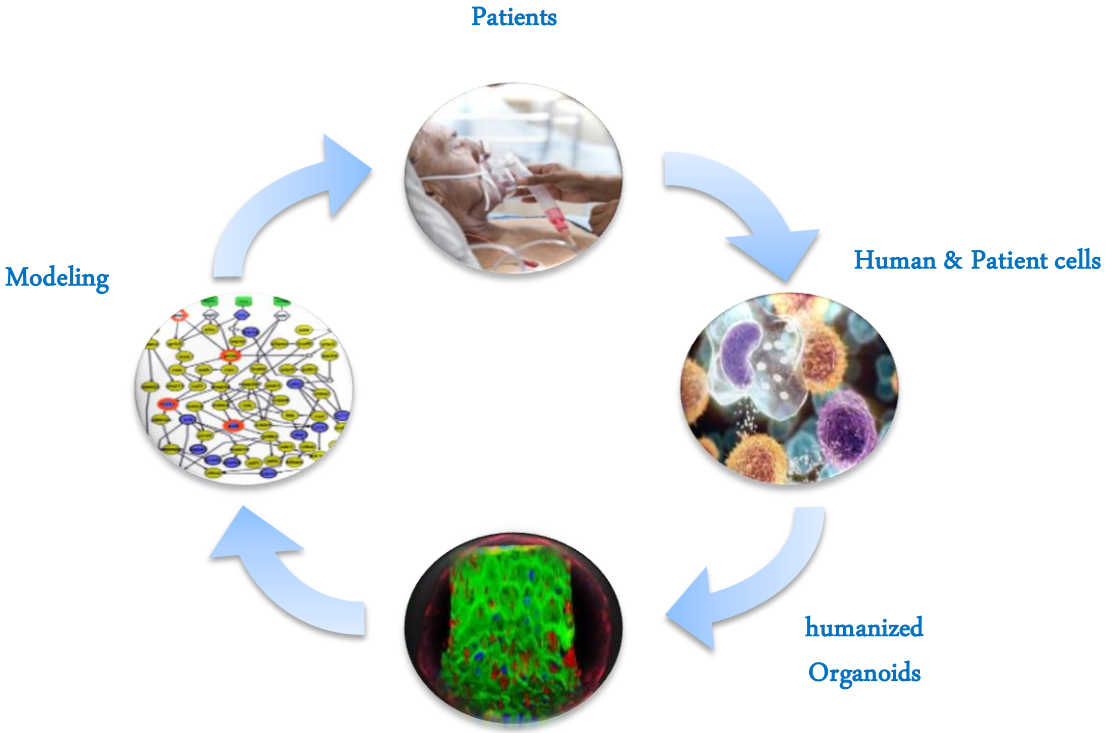
From Animal to Human Models

A paradigm shift for pharmaceutical industry

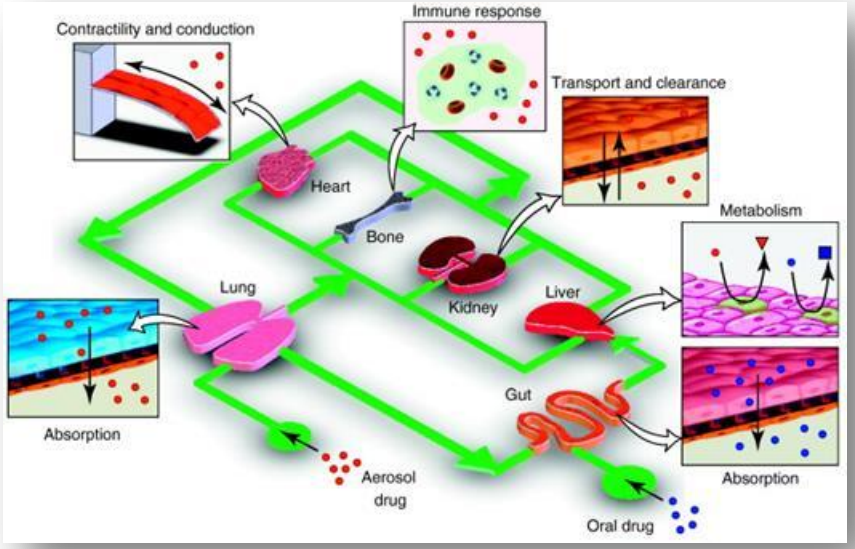
Humanized & Personalized assessments

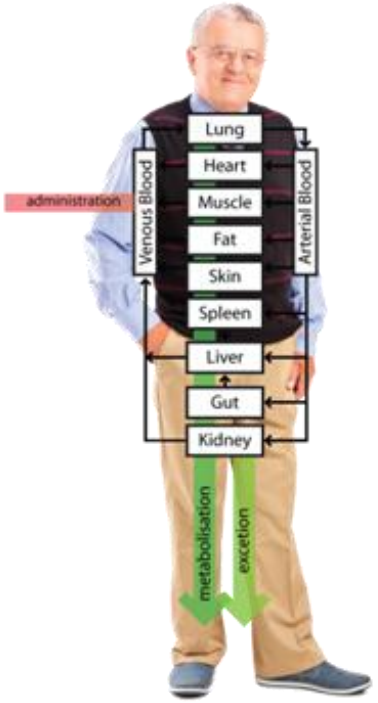


- Introduce human cell based assays and move away from animal models
- Introduce early detection of biomarkers including both safety & efficacy markers
- Introduce patient variability *in vitro*
- Mechanistic safety assessment for human risk mitigation

Organ-on-a-chip to mimic systemic response

Holds promise for more predictive safety testing by combining 3D cell culture & microfluidics





Advanced Drug Delivery Reviews 69–70 (2014) 179–189

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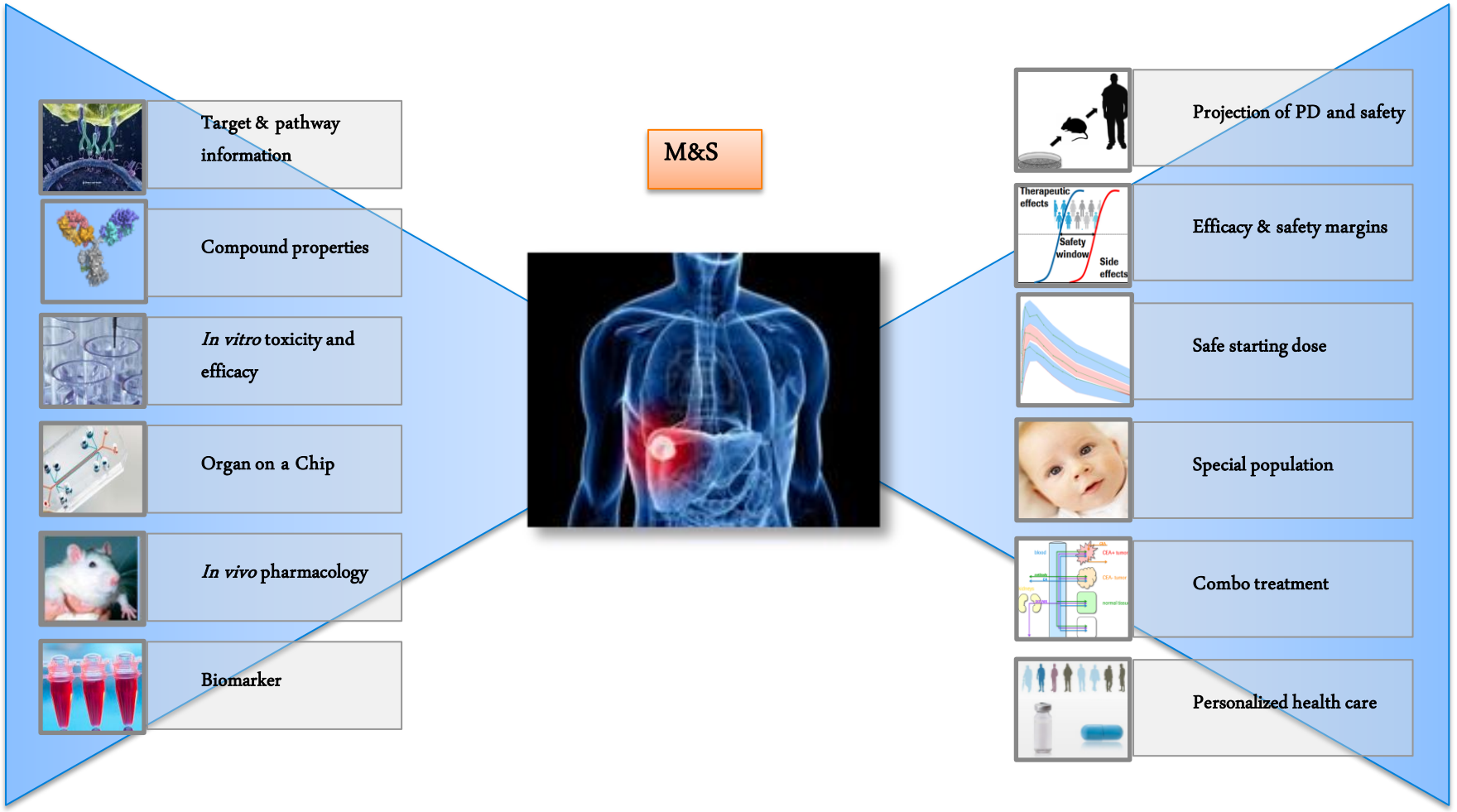
journal homepage: www.elsevier.com/locate/addr

The application of 3D cell models to support drug safety assessment: Opportunities & challenges☆

Adrian Roth *, Thomas Singer

F. Hoffmann-La Roche Ltd., Pharma Research, 4070 Basel, Switzerland

Adv Drug Del Rev 69 (2014)

Our scope to deliver future opportunities

We use a "patient centric" vision to predict human PK, safety and efficacy