PBPK to guide dose selection in early development
and meet regulatory requirements

Thierry Lavé and Neil Parrott
Head Project Leaders and M&S

Roche Pharmaceutical Research and Early Development
Roche Innovation Center Basel
Translating PK in the early 90s

- Resource intensive and empirical
- Response >>>> PK
- High attrition due to poor PK in man
- Expensive failures in clinic
- Dosing schedules suboptimal
- Information obtained of limited relevance for the patient
Today: PBPK continuum in discovery and development

- Great use of mechanistically based modelling in all phases of drug discovery and development.
- Continuum across discovery and clinical PBPK/PD
- Great use of M&S (PBPK, PK/PD) to support decision making
- Important role in regulatory reviews
- PBPK in support to PHC

Outstanding success rate in Health Authority interactions

Proven track record for contributions to approval of innovative and differentiated medicines

Best Company for Translational Safety according to McKinsey Survey 2013

Low Phase 1 attrition rate
*Drug discovery/development becomes more predictive*
Outline

• What enabled development and increased application of PBPK?
• Why is PBPK important?
• Current status with the application of PBPK
• Future perspectives
Key drivers for development and increased application of PBPK

- Improved understanding of the elimination, distribution and absorption
- Physiologic models incorporating physicochemical and in vitro human drug data to predict elimination, distribution and absorption
- User-friendly, commercially available PBPK software platforms, incorporating all physiological, biochemical and other data.
- Building confidence through extensive validation, published examples and successful contribution to projects
- Acceptance and required by regulators
- 3Rs
Old Paradigm

Use in vivo animal model as the predictor of human behavior (eg. allometric scaling)
New Paradigm

Use predictive, relevant in vitro data that will feed the model for predicting in vivo behavior.
Implementation and support to entire small molecule portfolio: PBPK strategy at Roche

MoA, ADME descriptors; in vitro and in silico data ADME / PD / Tox

Simulation

PBPK animal

Model refinements

Confirmation

Simulation

PBPK Man

in vivo preclinical data

Any mismatch suggests violation of model assumptions. Additional processes to be considered.

A Novel Strategy for Physiologically Based Predictions of Human Pharmacokinetics

Hannah M. Jones, Neil Parrott, Karin Jorge and Thierry Lavy

1 Drug Metabolism and Pharmacokinetics, F. Hoffmann-La Roche Ltd, Basel, Switzerland
2 Clinical Pharmacology, F. Hoffmann-La Roche Ltd, Basel, Switzerland
PBPK strategy at Roche results in improved prediction accuracy

PBPK accuracy 76%

Significantly better predictions with PBPK

Empirical accuracy 37%

A Novel Strategy for Physiologically Based Predictions of Human Pharmacokinetics

Hannah M. Jones,1 Neil Parrott,1 Karin Jorgi2 and Thierry Lazić2

1 Drug Metabolism and Pharmacokinetics, F. Hoffmann-La Roche Ltd, Basel, Switzerland
2 Clinical Pharmacology, F. Hoffmann-La Roche Ltd, Basel, Switzerland

229 citations
Outline

• What enabled development and increased application of PBPK?
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Why is PBPK important?

• Connecting response to the unbound drug concentrations at the site of action
• Simulating beyond systemic exposures in target organs not accessible through measurements
• Increased acceptance and requirements for PBPK to address regulatory questions
Beyond simulations of plasma exposures
Connecting response to the unbound drug concentrations at the site of action
Transport is needed to get to the target

Liver: In vitro models translated in vivo

Poirier et al., DRUG METABOLISM AND DISPOSITION, 2008, 36(12), 2434-2444
Showing that the drug reaches the target tissue and causes the desired pharmacological action

*Setting the stage for high probability of success*

**Pfizer: The 3 Pillars correlate with Phase II success**

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<tr>
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<th>Pillar 1, 2&amp;3</th>
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<td>• Exposure at Target</td>
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<td>• Interaction with target</td>
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**None or Partial**

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<tr>
<td><strong>0%</strong></td>
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% progression to Phase III (n=44, 2005-2009)
PBPK Informs FDA Interactions

136 submissions to FDA where PBPK modelling has been applied (Grillo, 2014)
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<sub>max</sub> 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<sub>max</sub> 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 have informed the drug label (FDA, EMA and PMDA)**

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<td>Osimertinib mesylate</td>
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</table>

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
Regulators have mentioned PBPK modeling in multiple guidance documents.

In 2016, EMA and FDA bring out PBPK guidance documents for first-in-human dose selection, emphasizing the importance of modeling.
PBPK in support to 3Rs principles

Physiologically-based Kinetic Modelling (PBK Modelling): Meeting the 3Rs Agenda

The Report and Recommendations of ECVAM Workshop 63a

Michel Bouvier d’Yvoire,1 Pilar Prieto,1 Bas J. Blaauwboer,2 Frederic Y. Bois,3 Alan Boobis,4 Céline Brochet,5 Sandra Cooeke,1 Andreas Freidig,3 Ursula Gundert-Remy,6 Thomas Hartung,1 Miriam N. Jacobs,1 Thierry Lavé,7 David E. Leahy,8 Hans Lennernäs,9 George D. Loizou,10 Bette Meek,11 Camilla Pease,12 Malcolm Rowland,13 Martin Spendiff,10 Jiansong Yang14 and Marco Zeilmaker15

Human clearance prediction: shifting the paradigm

Thierry Lavé, Kathryn Chapman, Paul Goldsmith & Malcolm Rowland

1E. Hoffmann-La Roche Ltd, Grenzacherstrasse 124, CH-4070 Basel, Switzerland
Outline

• What enabled development and increased application of PBPK?
• Why is PBPK important?
• Current status with the application of PBPK
• Future perspectives
Questions addressed across the entire value chain

- **Medical Need**
  - Disease Understanding
  - Target Selection
  - Compound Design
  - Pharmacology in animals
    - PK, PD, Safety Biomarker
  - Pharmacology in humans
    - PK, PD, Safety Biomarker
  - Efficacy and Safety in Patients

- **Compound properties**
  - Prediction of Human PK, Safety, efficacy
  - Simulating in special patient populations

- **Drugability of target**
  - Prediction of Human Efficacious Dose

- **Safety Margins**
  - Formulation impact

- **Candidate selection**
  - Selection of useful biomarkers

- **Safety Margins**
  - DDI impact
Outline

• What enabled development and increased application of PBPK?

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• Current status with the application of PBPK
  – Dose selection in EIH studies: Learnings from a retrospective survey on EIH studies with small molecules conducted between 2004 and 2016
  – Case study: PBPK to support use tamiflu in infants

• Future perspectives

Neil Parrott, Marie-Laure Delporte, Thierry Lave, Richard Peck, Benedicte Ricci

Pharma Research & Development, F. Hoffmann-La Roche, Inc., Roche Innovation Centre Basel, Switzerland
Preceding surveys at Roche revealed use of empirical methods for starting dose selection

Four methods

- **Dose by Factor**
  - From NOAEL, apply sensitivity factor
- **Similar Drug**
  - \( SD_i = \frac{SD_s}{NOAEL_i} \times NOAEL_{ii} \)
- **PK-Guided**
  - All with CL by allometric scaling
- **Comparative**
  - Combination of at least 2

New survey: 47 FIH pRED sponsored studies with small molecules since 2004, 42 in HVs

- **Small molecules N=47**
  - **NORD N=19**
    - Includes one IV administration only under eIND
  - **CVM N=12**
  - **ONC N=7**
  - **ID N=5**
  - **INF N=4**
    - Includes one IV administration only
  - **Patients N=5**
  - **HVs N=2**
New since last survey
PBPK approach in 74% of EIH overall

Since 2010, systematic use of PBPK predictions at EIH
PBPK strategy for FIM predictions

Molecular descriptors; *in vitro* and *in silico* data ADME / PD / Tox

Simulation

PBPK
animal

Model
refinements

Confirmation

Simulation

PBPK
Man

in vivo preclinical data

Any mismatch suggests violation of model assumptions. Additional processes to be considered.

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2 Clinical Pharmacology, F. Hoffmann-La Roche Ltd, Basel, Switzerland
Prospective predictions
Accuracy confirmed for 2003 - 2015

N=33
Ave. fold error 2.1
69% within 2-fold
Learning from our experiences

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All predictions performed with GastroPlus software. 10 different PS scientists following the pRED strategy

**Are there common features of the less accurate predictions?**

* Very long t1/2 >10-fold under predicted. AUCinf not reliable AUC24 reasonably predicted
Common pitfalls and how to address them

- Minimum set of in vitro input data defined
- Poor human prediction seen when pre-clinical verification not achieved
- Need to clearly communicate the impact of uncertainty on clinical dose estimates and safety margins
- Qualitative different PK process in human vs animals plus IVIVC failed in human e.g. Taar1 – polymorphic UGT2B10 pathway, MAOB–target binding
- Unexpected long half-life. Strategy developed in 2016 with input from external experts
- Need additional human relevant tools e.g. for transporters & non-CYP enzymes
  - Work closely with PS experts on refined tools to fill gaps
Compound properties, predictability and learnings

Hydrophilic & poorly permeable molecules have rarely been selected in the past.

New disease areas and tissue targeting approaches are likely to increase this property for future candidates.
Key learnings

• An analysis of small molecule entry in human studies has been performed including assessment of PK predictions and dose selection.

• There is a successful uptake of model-based approaches for selection of starting dose.

• PBPK delivered good PK predictions with 69% of them “on target” and some common features for poor prediction have been identified and actions taken to improve in the future.

• Actual selected starting doses were lower than MRSD in 70% EIH studies. In some cases superior safety to MRSD is very clear.

• The first doses were well tolerated in all studies. Starting doses were generally not too cautious.

• All EIH studies in HVs were safe.

• Overall, pharmacodynamics was characterized in nearly half of the studies.
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  - Case study: PBPK to support use tamiflu in infants
- Future perspectives
Example, 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
Tamiflu

Oseltamivir (Os) → oseltamivir carboxylate (OC)
PBPK models for pro-drug and metabolite

Oseltamivir carboxylate

Oseltamivir

Renal elimination of OC

Conversion of O to OC in liver

Renal elimination of Os

HA = Hepatic Artery
LU = Lung
ART = Arterial Supply
VEN = Venous Return
AD = Adipose
MU = Muscle
LI = Liver
ACAT = Gut
SP = Spleen
HE = Heart
BR = Brain
KI = Kidney
SK = Skin
REP = Repro Organs
REDM = Red Marrow
YELM = Yellow Marrow
ROB = Rest Of Body
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

Maturation of renal function

Development of metabolism with age

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.

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

- Strengthen the safety assessment of IV Tamiflu in infants < 1 year of age
- Acceptance by EMA of use of existing data and M&S as sufficient to support safety of IV Tamiflu
- Reduce animal usage by convincing European health authorities that an IV tox. study is not needed
- FDA approval of Tamiflu line extension for the treatment of influenza in infants
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Ensure continuum through discovery and development
including ethnicities, special populations
Including variability
Support for personalized healthcare

Classical view:
- no variability on the therapeutic and side effect
- the safety window is clearly defined

Modern view:
- variability on the therapeutic and side effect
- the safety window is individual for each patient
Acknowledgements

• Neil Parrott
• Marie-Laure Delporte
• Benedicte Ricci
• Richard Peck
• Thomas Singer
Doing now what patients need next