Virtual Twins™ Based on PBPK Models for Precision Dosing in Drug Development and Beyond
PMDA Pharmacometrics Workshop, 3rd July 2019

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Disclosures

- I am a paid employee of Certara and South Australian Health.
- I am a consultant for CMAX Clinical Research, Sonic Genetics and Bellberry Ltd.
- I have an honorary academic affiliation with Monash University.
- Any views expressed in these slides are my personal thoughts and do not necessarily represent those of my employers or consultancy partners.
Summary

• Between patient variability in drug response is an important cause of **FAILED** drug development and **FAILED** drug therapy in clinical medicine.

• M&S is **EXPECTED** in drug development but is **RARE** in clinical medicine.

• **PRECISION DOSING** of subjects is possible in clinical trials and clinical medicine using quantitative M&S.

• Integration of patient specific information into PBPK models allows for the generation of **VIRTUAL TWINS** of clinical trial subjects and real-world patients.

• A virtual twin approach is likely to improve the clinical trial **SUCCESS** of drugs that are difficult to dose and to then become **DYNAMIC PRESCRIBING INFORMATION**.
Definitions

Precision dosing is dose selection by a prescriber for a given patient at a given time.

Polasek et al. 2018 Expert Review of Clinical Pharmacology, 11(8) 743-746

Model-informed precision (MIPD) dosing is biosimulation to predict the drug dose for a given patient based on their individual characteristics that is most likely to improve efficacy and/or lower toxicity compared with traditional dosing.

Polasek et al. 2019 Clinical Pharmacology in Drug Development, 8(4) 418-425
Model-informed precision dosing

Precision dosing vs Model-informed precision dosing

Things prescribers know:
- Age
- Weight
- Renal function
- LFTs
- Frailty
- BSA
- Some DDIs

+ EXPERIENCE

= in cerebro biosimulation informs prescribing

Things prescribers know + MUCH MORE:
- DMET genotype ± phenotype
- Organ sizes & blood flows
- Inflammatory status
- Many DDIs
- All these together!

+ NEW TECHNOLOGY SKILLS
+ EXPERIENCE

= in silico biosimulation informs prescribing
Extra work is required for MIPD

Does dose matter that much?

YES

Best use of data

Modelling and simulation (M&S)

NO
Pediatric/Rare Disease Examples

- Gaucher disease
- Tay-Sachs disease
- Tuberous sclerosis complex
- Paediatric oncology and hematology
  - Solid tumors with NTRK e.g., infantile fibrosarcoma, papillary thyroid cancer
  - Fanconi anemia
- Venous thromboembolism in children

Darwich et al. 2017 Clinical Pharmacology & Therapeutics, 101(5) 546-656
Between subject variability in drug response

Environment → Disease

Genetics
(possibly 2D6 poor metaboliser!?!)

Slide Courtesy of Geoff Tucker, University of Sheffield
How to tackle the problem of BSV in drug response

**Drug development**
- Understand covariates
- Select drugs with less variability
- Homogenize clinical trials
- Sometimes -> Dose recommendations for special populations in prescribing information

**Clinical medicine**
- Ignore it
- Select drugs with fewer adverse effects or less severe adverse effects
- Select drugs with less variability
- Precision dosing (and rarely MIPD) for individual patients
Model-informed drug development

• Quantitative M&S is **ROUTINE** in drug development to understand dose-exposure-response relationships.

• Approaches include:
  o Population pharmacokinetic ± pharmacodynamic M&S
  o Physiologically-based pharmacokinetic M&S
  o Quantitative systems pharmacology/toxicology
  o Clinical trial simulation
  o Model-informed meta-analysis

*Kimko & Pinheiro 2015 British Journal of Clinical Pharmacology, 79(1) 108-116*
Model-informed drug development saves time and money and is expected by regulators.

Impact of Modeling and Simulation: Myth or Fact?

With the challenges to reduce the cost of drug development and increase knowledge, there is great interest in the patient who is knowledgeable, and industry and regulators are increasingly leveraging modeling and simulation (M&S) approaches. The question now becomes whether M&S has influenced drug discovery and development as we had hoped, is it an impact on the fact of the matter or fact that industry, in reducing costs while delivering innovation, is planning to deliver added benefits by using simulation and increasing computational capability and decision science to quantitatively answer critical questions that lower the costs of new drug development.

The new approaches and tools have led to the expansion of a specialized field, M&S, sometimes called quantitative pharmacology (QPPV) or pharmacometrics. M&S is an integrative science that combines clinical, preclinical, and exploratory drug characterization and individual variability to leverage existing knowledge and guide future research. It helps define the questions and assumptions that can drive informed decision-making. It is important to note that, due to the complexity and uncertainty inherent in the process, the experts in the field must understand variability and uncertainty in clinical endpoints.

A critical test for the model is the ability to predict new experiments or new patients. The research-driven models are most useful when the model is predictive. The impact of the model on the process is orders of magnitude greater than the model itself.

Model-informed drug development

Saves time and money

Expected by regulators

I want to highlight one example of these steps, which we’re investing in, and will be expanding on, as part of our broader Innovation Initiative. **It’s the use of in silico tools in clinical trials for improving drug development and making regulation more efficient.**

FDA’s Center for Drug Evaluation and Research (CDER) is currently using **modeling and simulation** to predict clinical outcomes, inform clinical trial designs, support evidence of effectiveness, optimize dosing, predict product safety, and evaluate potential adverse event mechanisms.

Virtual twins – the next level of MIPD based on individualization

Mechanistic in nature

Risk Assessment
• Simulate typical clinical scenarios
• Simulate complex, rare and/or extreme clinical scenarios
Virtual twins are based on PBPK models

Outputs
- PK parameters – CL, VD, half-life etc.
- Concentration-time profiles in plasma, whole blood, tissues etc.
## Impact of PBPK modeling – many clinical studies are avoided

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug Name</th>
<th>Indication</th>
<th>No Clinical Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson &amp; Johnson</td>
<td>Xarelto (Rivaroxaban)</td>
<td>Deep Vein Thrombosis - Pulmonary Embolism – hip/knee replacement and surgery</td>
<td>4</td>
</tr>
<tr>
<td>Actelion</td>
<td>Cpsumit (Macitentan)</td>
<td>Pulmonary Arterial Hypertension</td>
<td>2</td>
</tr>
<tr>
<td>Gilead Sciences</td>
<td>Edurant (Rilpivirine)</td>
<td>HIV infection</td>
<td>1</td>
</tr>
<tr>
<td>Jenssen</td>
<td>Olysio (Simeprevir)</td>
<td>Hepatitis C</td>
<td>7</td>
</tr>
<tr>
<td>Novartis</td>
<td>Imbruvica (Ibrutinib)</td>
<td>Mantle cell lymphoma &amp; chronic lymphocytic leukemia</td>
<td>24</td>
</tr>
<tr>
<td>AstraZeneca</td>
<td>Movantik (Naloxegol)</td>
<td>Opioid induced constipation</td>
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</tr>
<tr>
<td>Genzyme</td>
<td>Cerdelga (Elaglumab)</td>
<td>Gaucher Disease</td>
<td>12</td>
</tr>
<tr>
<td>Novartis</td>
<td>Zykadia (Ceritinib)</td>
<td>Metastatic Non-Small Cell Lung Cancer</td>
<td>2</td>
</tr>
<tr>
<td>Sanofi</td>
<td>Jevtana (Cabazitaxel)</td>
<td>Metastatic hormone refractory prostate cancer</td>
<td>1</td>
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<tr>
<td>AMGEN</td>
<td>Blincyto (Blinatumomab)</td>
<td>Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)</td>
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</tr>
<tr>
<td>Novartis</td>
<td>Farydak (Pancobinostat)</td>
<td>Myeloma</td>
<td>2</td>
</tr>
<tr>
<td>EMER</td>
<td>Lenvima (Lenvatinib)</td>
<td>Metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer</td>
<td>1</td>
</tr>
<tr>
<td>Novartis</td>
<td>Odonzos (onidegib)</td>
<td>Adult patients with locally advanced basal cell carcinoma (BCC)</td>
<td>3</td>
</tr>
<tr>
<td>Genentech</td>
<td>Alecensa (Alecinitib)</td>
<td>Non Small Cell Lung Cancer</td>
<td>1</td>
</tr>
<tr>
<td>Alkermes</td>
<td>Aristata ((Aripiprazole)</td>
<td>Schizophrenia</td>
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</tr>
<tr>
<td>Genentech</td>
<td>Cotelic (Cobimetinib)</td>
<td>Metastatic Melanoma</td>
<td>16</td>
</tr>
</tbody>
</table>

*SlideCourtesy of Patrick Smith, Certara*
Separate systems and drug data
Separate systems and drug data

Age
Weight
Tissue Volumes
Tissue Composition
Cardiac Output
Tissue Blood Flows
[Plasma Protein]
DMET genotypes
Separate systems and drug data

**Systems Data**
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**Trial Design**

**Drug Data**
- MW
- LogP
- pKa
- Protein binding
- BP ratio
- *In vitro* Metabolism
- Permeability
- Solubility
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- Populations
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**Mechanistic IVIVE linked PBPK models**

**Prediction of drug PK (PD) in population of interest**
Separate systems and drug data

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**Mechanistic IVIVE linked PBPK models**

**Prediction of drug PK (PD) in population of interest**
Virtual twins for model-informed precision dosing

Systems data in PBPK models are individualized

**Traditional data required:**
- Age
- Body size - weight, BSA
- Renal function
- Liver function

**New data required:**
- DMET genotype ± phenotype
- Organ sizes
- Organ/tissue blood flows
- Hematological parameters - Hct, albumin conc.
- Inflammatory status
- Drug-drug interactions

**Virtual twin considers ALL these data TOGETHER to predict dose for the individual subject**
Applications of virtual twins in drug development

(1) ‘Classic’ PBPK applications
   o Reducing the need for clinical studies
   o Ethnicity, DDIs, renal and hepatic impairment, pregnancy, pediatrics etc.

(2) Phase 1
   o Superior determination of FIH doses
   o Individualized SAD and MAD escalation e.g., CYP2D6 genotype specific

(3) Phase 2 and 3 studies
   o Precision dosing in a heterogeneous patient population that is more representative of the market population (exposure targeted)
   o Select individuals more likely to be responders (enriched trial population)
Applications of virtual twins in drug development – Example 1

...cohorts 1 and 2 were assigned doses predicted by modelling to achieve an AUC equivalent to the adult doses...
Applications of virtual twins in drug development – Example 2

...verified PBPK model will be used to select the rivaroxaban dose for the treatment of VTE in EINSTEINE-Jr phase II and phase III studies ...
Applications of virtual twins in clinical medicine

• There are many examples of suitable clinical cases. Some include:
  o Treatment resistant schizophrenia – clozapine initiation
  o Rate control in paroxysmal AF – CCB/β-blocker titration
  o Treatment of oncology and hematological malignancies – protein kinase inhibitor initiation and titration
  o Prevention of seizures with everolimus in Tuberous sclerosis complex

Correct dose

= decreased ADRs
= decreased admissions to hospital
= decreased length of stay
= decreased specialist visits
= decreased GP visits
Applications of virtual twins in clinical medicine – Example 1

PHARMACOKINETICS

Prediction of olanzapine exposure in individual patients using physiologically based pharmacokinetic modelling and simulation

Correspondence Dr Thomas Polasek, Department of Clinical Pharmacology, Flinders Medical Centre, Bedford Park, Adelaide 5042, South Australia. Tel.: +61 8 8204 3999; Fax: +61 8 8204 5114; E-mail: tom.polasek@flinders.edu.au

Received 25 July 2017; Revised 21 November 2017; Accepted 22 November 2017

Thomas M. Polasek1,2, Geoffrey T. Tucker3, Michael J. Sorich1,4, Michael D. Wiese5, Titus Mohan6, Amin Rostami-Hodjegan7,8, Pomtipa Korprasertthaworn9, Vidya Perera10 and Andrew Rowland1,2

...olanzapine exposure was predicted in patients based on CYP1A2 activity and other important covariates....
Applications of virtual twins in clinical medicine – Example 1

A Without CYP2C8 Genotype

B With CYP2C8 Genotype

C

D
Applications of virtual twins in clinical medicine – Example 2

Real Patient and its Virtual Twin: Application of Quantitative Systems Toxicology Modelling in the Cardiac Safety Assessment of Citalopram

Nikunjkumar Patel,1,2 Barbara Wiśniosławska,2 Masoud Jamei,1 and Sebastian Potak1,2,3

Received 3 August 2017; accepted 16 October 2017

Abstract. A quantitative systems toxicology (QST) model for citalopram was established to simulate, in silico, a ‘virtual twin’ of a real patient to predict the occurrence of cardiotoxic events previously reported in patients under various clinical conditions. The QST model considers the effects of citalopram and its most notable electrophysiologically active primary (desmethylcitalopram) and secondary (didesmethylcitalopram) metabolites, on cardiac electrophysiology. The in vitro cardiac ion channel current inhibition data was coupled with the biophysically detailed model of human cardiac electrophysiology to investigate the impact of (i) the inhibition of multiple ion currents (I_{	ext{Na}}, I_{	ext{K}}, I_{	ext{Ca,L}}); (ii) the inclusion of metabolites in the QST model; and (iii) unbound or total plasma as the operating drug concentration, in predicting clinically observed QT prolongation. The inclusion of multiple ion channel current inhibition and metabolites in the simulation with unbound plasma citalopram concentration provided the lowest prediction error. The predictive performance of the model was verified with three additional therapeutic and supratherapeutic drug exposure clinical cases. The results indicate that considering only the hERG ion channel inhibition of only the parent drug is potentially misleading, and the inclusion of active metabolite data and the influence of other ion channel currents should be considered to improve the prediction of potential cardiac toxicity. Mechanistic modelling can help bridge the gaps existing in the quantitative translation from preclinical cardiac safety assessment to clinical toxicology. Moreover, this study shows that the QST models, in combination with appropriate drug and systems parameters, can pave the way towards personalised safety assessment.

KEY WORDS: Citalopram, Cardiotoxicity; QT prolongation; Cardiac safety simulator; Simcyx; hERG; Personalised medicine; Quantitative systems toxicology; Virtual twin.

...QTc prolongation by citalopram was predicted in individual patients after adjusting base PBPK model for individual characteristics, and when considering citalopram metabolites...
The ‘wave’ of activity around MIPD...

Why Has Model-Informed Precision Dosing Not Yet Become Common Clinical Reality? Lessons From the Past and a Roadmap for the Future

AS Darwich1, K Ogungbenro2, AA Vinks2,3, JR Powell1, I-L Ren3,4, N Marossi5, Y Dahl1,2, D Fattman5, J Cook1, IJ Lesko1, JS McCune3, C Cumming6, AF Zuppa1, P Viciani1, I Arena1, TF Stigle, A. Fattman5, R. Dahl1,2, D. Fattman5, J. Lesko1, J. McCune3, C. Cumming6, A. Zuppa1, P. Viciani1, I. Arena1, TF. Stigle1, A. Fattman5, R. Dahl1,2, D. Fattman5, J. Lesko1, J. McCune3, C. Cumming6, A. Zuppa1, P. Viciani1, I. Arena1, TF. Stigle1

U.S. FOOD & DRUG ADMINISTRATION

Precision Dosing: Defining the Need and Approaches to Deliver Individualized Drug Dosing in the Real-World Setting
August 12, 2019
FDA White Oak Great Room

Workshop Co-chairs

Raj Madabushi, PhD
Yaning Wang, PhD
FDA, Office of Clinical Pharmacology

Robert Powell, PharmD
University of North Carolina at Chapel Hill

What Does it Take to Make Model-Informed Precision Dosing Common Practice? Report from the 1st Asian Symposium on Precision Dosing

Alexander A. Vinks1,2,11

From Molecule to Patient and Ways to Get the Dose Precisely Right

Thomas M. Polasek1,2,11 Amin Rostami-Hodjegan1,2, Dong-Seok Yim1, Masoud Jamei1, Howard Lee5,6, Holly Kimko7, Jae Kyong Kim7, Phuong Thi Thu Nguyen7, Adam S. Darwich4, and Jae-Gook Shin6

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• Professor Sepehr Shakib (Royal Adelaide Hospital and the University of Adelaide)

Polasek et al. 2019 Clinical Pharmacology in Drug Development, 8(4) 418-425