MODEL-BASED DOSE INDIVIDUALIZATION APPROACHES USING BIOMARKERS

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OUTLINE

- Introduction and Aims
- Key steps in the development of a model incorporating biomarkers
- Specific model-based examples
  - Sunitinib
  - Warfarin
  - Sitagliptin
  - Cyclooxygenase-2 inhibitors
- Conclusions

CONFLICTS OF INTEREST

I have nothing to declare related to this presentation
The views expressed are my own

INTRODUCTION

- Biomarker – "A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention" – Biomarkers Definitions Working Group – (BDWG)[1]

- In drug development biomarkers can
  - Contribute to knowledge of clinical pharmacology
  - Serve as proof-of-concept (POC)
  - Be used to guide dose selection

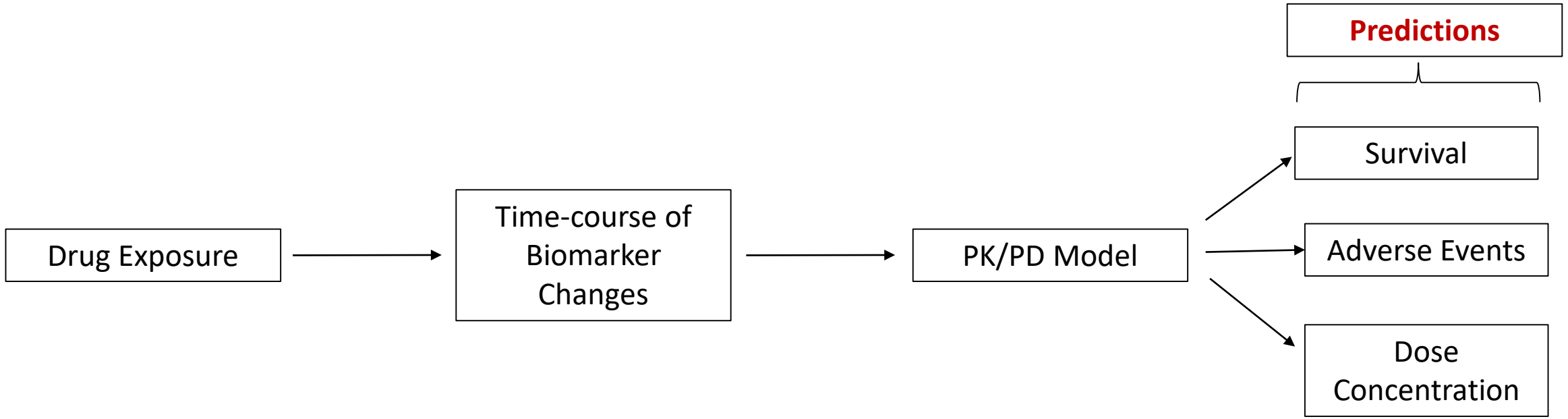
1) Biomarkers and surrogate endpoints. Clin Pharmacol Ther. 2001 Mar;69(3):89-95.

INTRODUCTION

- Biomarkers in pharmaceutical research

Biomarker	Drug/s	Therapeutic Category	Use of biomarker
Proprotein convertase subtilsin-kexin type 9 **(PCSK9)**	PCSK9 monoclonal antibodies (mAbs)	Atherosclerosis	Target engagement
Vascular endothelial growth factor **(VEGF)**	Anti-VEGF mAbs (Ramucirumab)	Hepatocellular carcinoma	Mechanism of action
Parathyroid hormone **(PTH),** bone formation and bone resorption markers	MK-5442	Osteoporosis	Disease biomarker, Proof-of-concept
Growth differentiation factor **(GDF-15)**	Apixaban	Atrial fibrillation	Risk factor

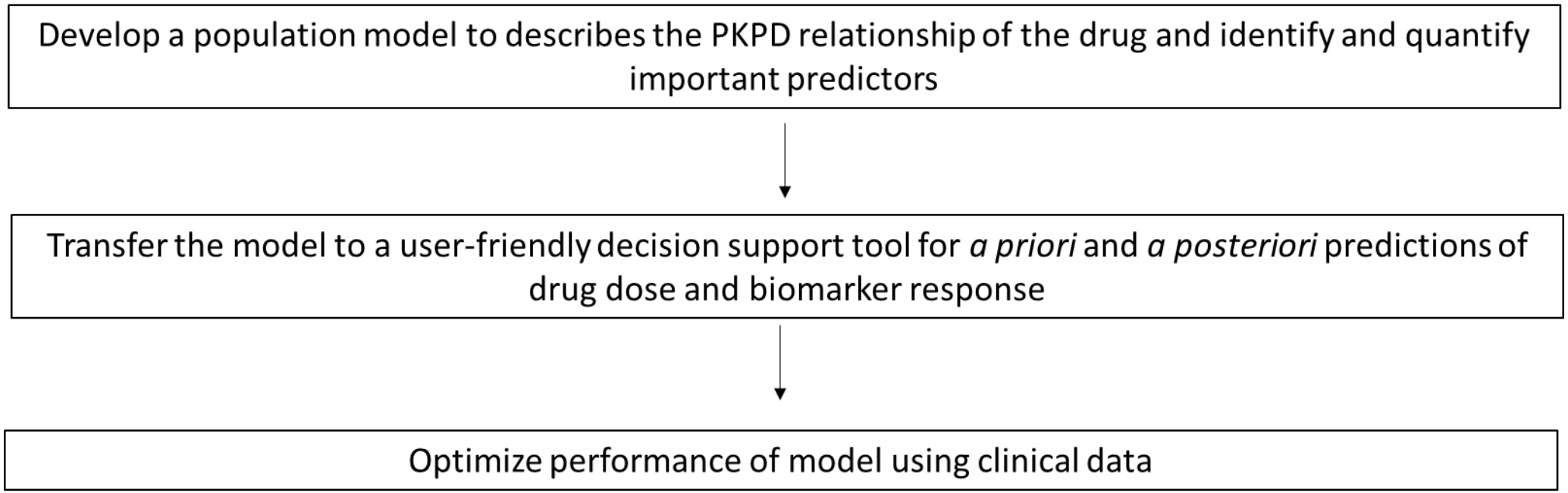
INTRODUCTION



AIMS

- To develop an understanding of how biomarkers can be incorporated into a PK/PD model
- Gain a brief understanding of the application of biomarkers in drug development

Key steps in the development of a model incorporating biomarkers



PK/PD MODELING OF SUNITINIB

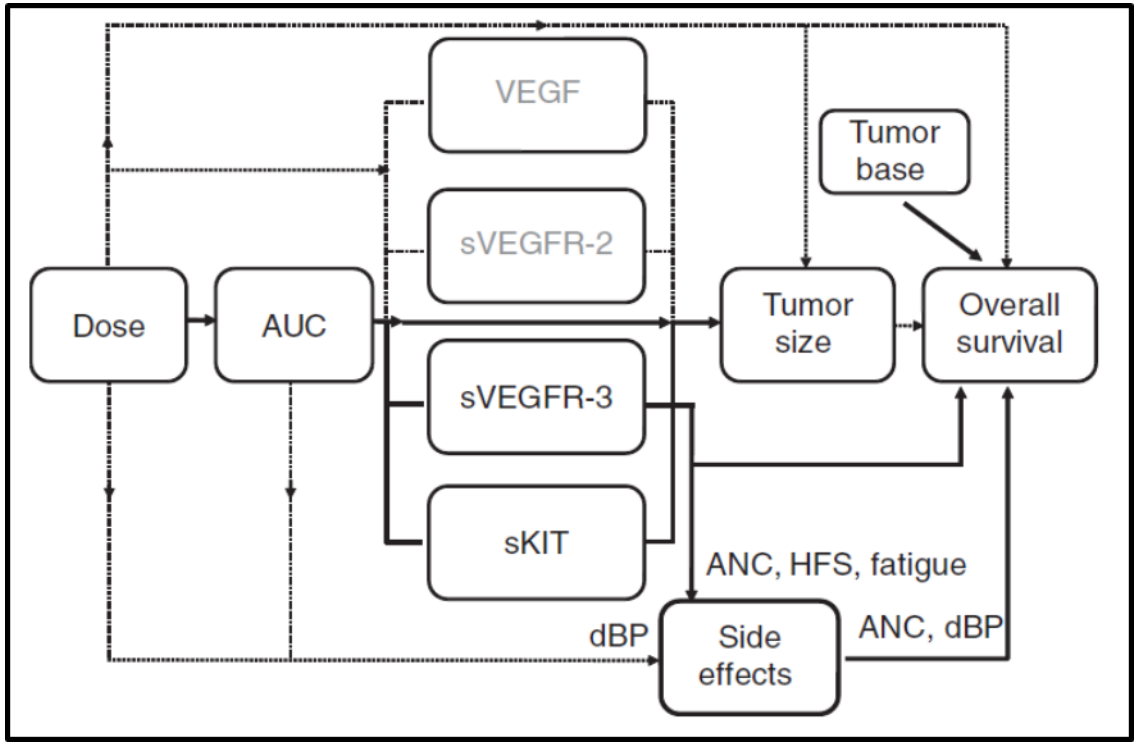
- A modeling framework relating exposure, **biomarkers (VEGF, soluble VEGF 2, 3 and soluble stem cell factor (sKIT), and tumor growth** to overall survival was developed and extended to include adverse effects (myelosuppression, hypertension, fatigue, and hand-foot syndrome (HFS))[2]

- **Longitudinal PK/PD models** – data from 303 patients with gastrointestinal stromal tumor

- Myelosuppression was characterized by semi-physiological model using the extent and time course of the change in absolute neutrophil count (ANC) following sunitinib treatment.

- Hypertension was characterized by indirect response model

- Proportional odds models with a first-order Markov model described the incidence and severity of fatigue and HFS



Solid lines - relationships included in the final models
Dashed lines - relationships investigated but not included in the final models

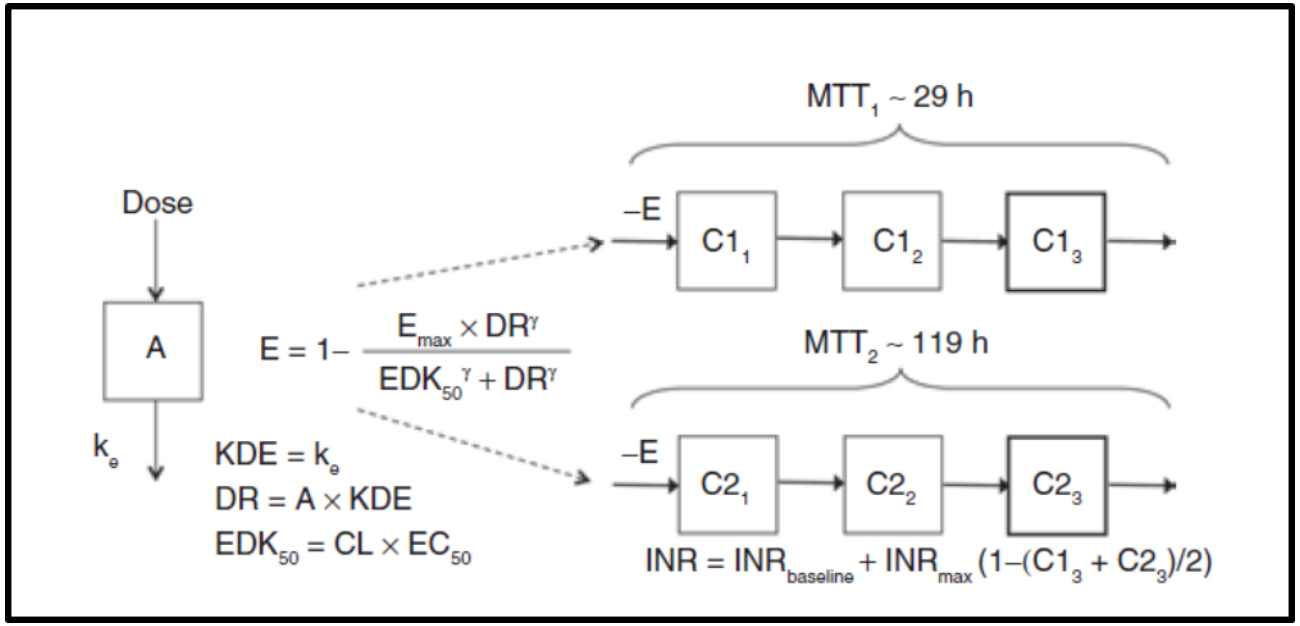
2) *Hansson et al, CPT: Phrmacometrics & Systems Pharmacology (2013) 2, e85*

CONCLUSIONS: PK/PD MODELING OF SUNITINIB

- Relative change in sVEGFR-3 was the most effective predictor of the occurrence and severity of myelosuppression, fatigue, and HFS
- Hypertension was best correlated with sunitinib exposure
- Baseline tumor size, time courses of neutropenia, and relative increase of diastolic blood pressure were identified as precursors of overall survival
- This framework has potential to be used for early monitoring of adverse effects and clinical response, thereby *facilitating dose individualization to maximize overall survival*

PK/PD MODELING OF WARFARIN – EXAMPLE 1

- A NONMEM model was developed to describe the relationship between warfarin dose and international normalized ratio (INR) response
- Furthermore, the effects of age and *CYP2C9* genotype on S-warfarin clearance were estimated from high-quality PK data
- A temporal dose-response (K-PD) model was developed from information on dose, INR, age, and *CYP2C9* and *VKORC1* genotype, with drug clearance as a covariate
- This reformulated K-PD model decreases dependence on PK data and enables robust assessment of INR response and dose predictions, even in individuals with rare genotype combinations



A schematic of the final K-PD model[3]

**However, this model has some limitations…therefore*

3) Hamberg AK, Clin Pharmacol Ther. 2010 Jun;87(6):727-34. doi: 10.1038/clpt.2010.37

LIMITATIONS

- The Hamberg et al., (2010) empirical model doesn't work well with doses higher than 7 mg/day[#]

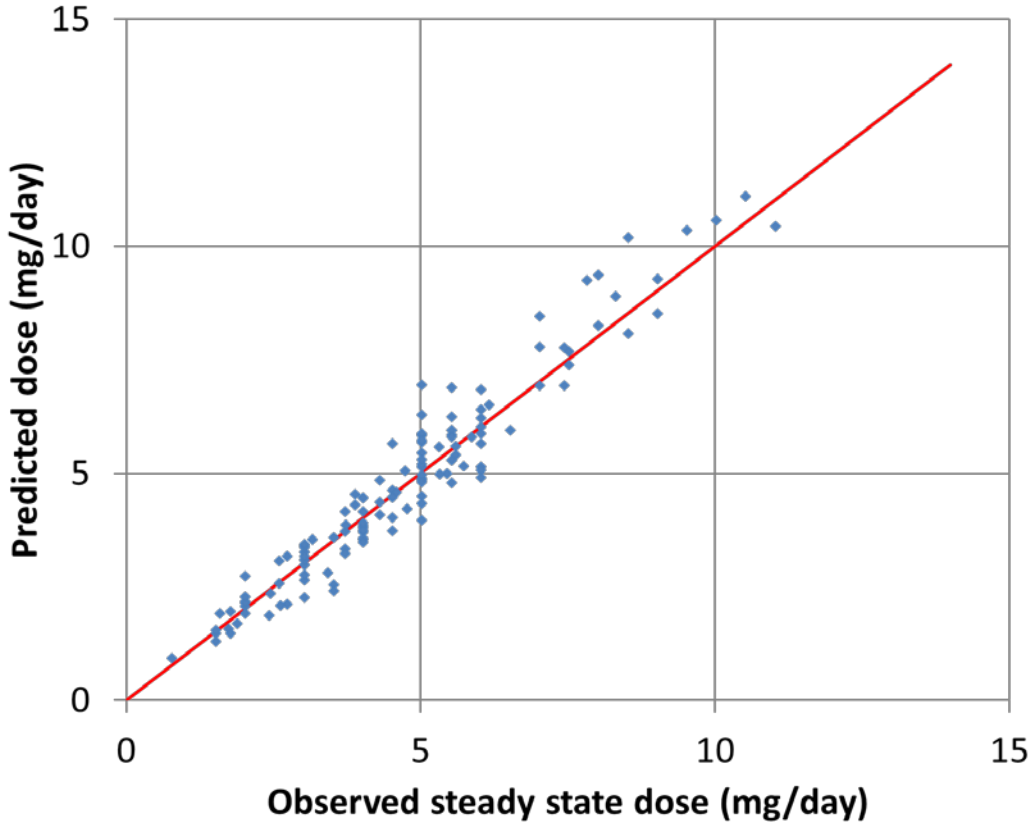
- However, the theory-based turnover model used by NextDose[4] succeeds with the same validation dataset that showed the Hamberg et al., (2010) model had limitations[#]

[#]Saffian et al., (2016) Ther Drug Monit, 38 (6) pg 677-683

4) https://www.nextdose.org

PK/PD MODELING OF WARFARIN – EXAMPLE 2

- Bayesian dose individualization methods used to evaluate warfarin, based on use of INR as a biomarker
- Warfarin dose individualization using INR with a theory based PKPD model[5] is unbiased and precise as shown by simulation and external evaluation
- Biomarker based *dose individualization* should be evaluated on a case by case basis



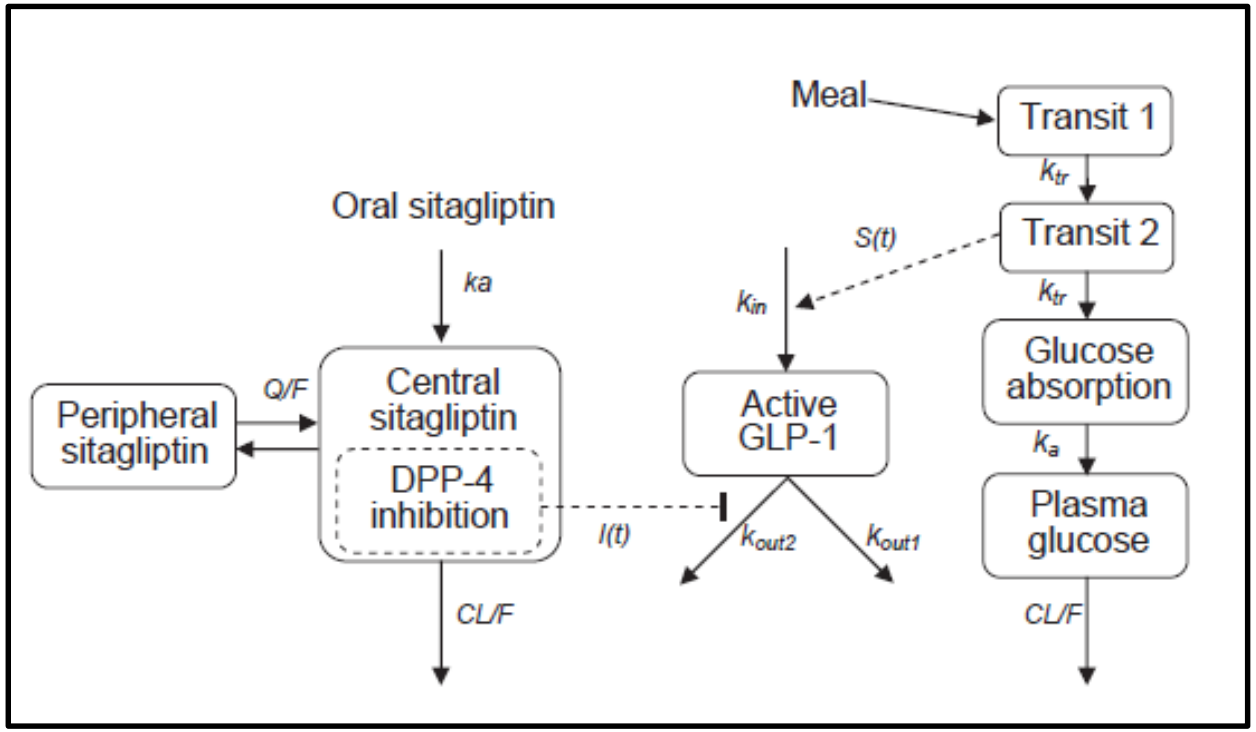
Theory based warfarin dose individualization method is more accurate than (Hamberg et al., (2010)) using the same observations of steady state INR and doses [5]

5) PAGE 27 (2018) Abstr 8562 [www.page-meeting.org/?abstract=8562]

PK/PD MODELING OF SITAGLIPTIN

- Sitagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor and is an anti-hyperglycemic agent
- PK/PD model using nonlinear mixed effects modeling was developed based on physiology of incretins
- Study was conducted in healthy volunteers
- Sitagliptin pharmacokinetics was modelled using a two-compartment model with first-order absorption
- Changes in DPP-4 inhibition were linked to the PK model using a sigmoid E_{max} model
- The active GLP-1 changes were explained using an indirect response model; this model incorporated glucose and DPP-4 inhibition models

A schematic of the PK/PD model of Sitagliptin[6]



Physiology of incretins (GIP and GLP-1). Incretin hormones are defined as intestinal hormones released in response to nutrient ingestion, which potentiate the glucose-induced insulin response

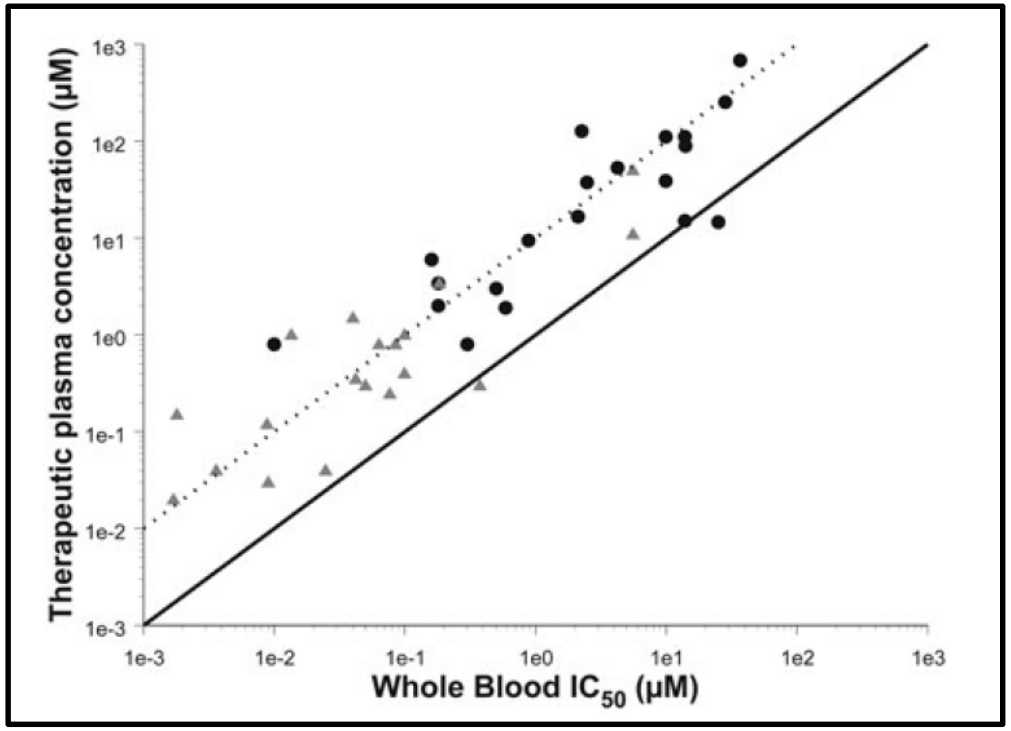
6) Kim BH, Basic Clin Pharmacol Toxicol. 2013 Aug;113(2):113-25. doi: 10.1111/bcpt.12068

CONCLUSIONS: PK/PD MODELING OF SITAGLIPTIN

- The model adequately described the changes in sitagliptin concentration, DPP-4 inhibition and active GLP-1 in healthy volunteers
- However, the sample size in the present study may be too low to generalize the model
- The developed PK/PD model can be a useful tool for developing other DPP-4 inhibitors
- With patient data, the model can be further refined to be more physiological and can be used for predicting clinical response in diabetic patients

PK/PD MODELING OF COX-2 INHIBITORS

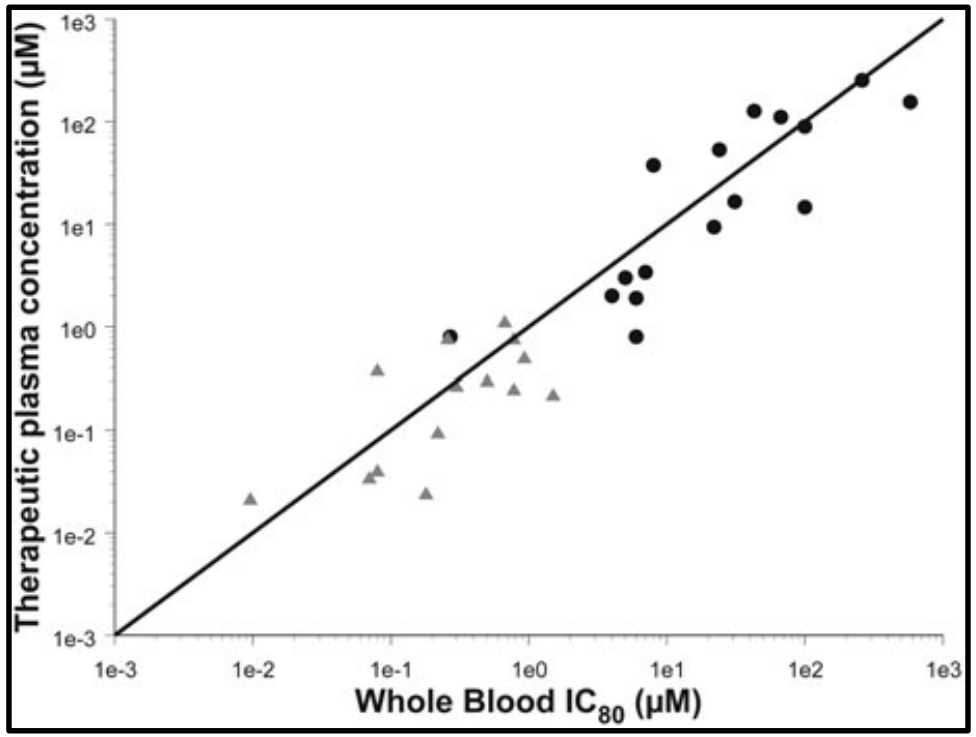
- Prostaglandin E2 (PGE_2) and Thromboxane B2 (TXB_2) were investigated as potential biomarkers for development of COX-r inhibitors [7]
- Systemic PGE_2 and TXB_2 production was measured using the human whole blood assay (hWBA)
- The plasma concentrations of COX inhibitors at which analgesic therapeutic effect was achieved were correlated to *in vitro* estimates for the inhibition of COX-2 in humans
- Initially, *in vitro* IC_{50} values of COX-2 inhibition of 22 different COX inhibitors were correlated with their analgesic therapeutic plasma concentrations



7) *Huntjens DR, Rheumatology (Oxford). 2005 Jul;44(7):846-59*

CONCLUSIONS: PK/PD MODELING OF COX-2 INHIBITORS

- Data from previous correlation show that more than 50% inhibition is required to achieve analgesia
- Therefore, the model was reparametrized to obtain IC_{80} estimates
- Analgesic therapeutic plasma concentration is directly correlated with IC_{80}. From this correlation it is evident that at least 80% inhibition of COX-2 is required to produce analgesia
- Therefore, this *in vitro*-derived parameter can be used to predict the exposure levels of COX inhibitors that yield an analgesic effect



CONCLUSIONS

- Biomarkers can be valuable for *dose individualization* and to act as indicators of safety
- The examples discussed show how model based analyses of biomarker data can support the drug development process
  - In conjunction with non-linear mixed-effect modelling, the relationship between biological marker, pain measurement and safety can be characterized
- Biomarker based *dose individualization* should be evaluated on a case by case basis

ACKNOWLEDGEMENTS

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Thank you for your attention