Towards Regulatory Qualification of a PBPK model for use in TB Drug Development

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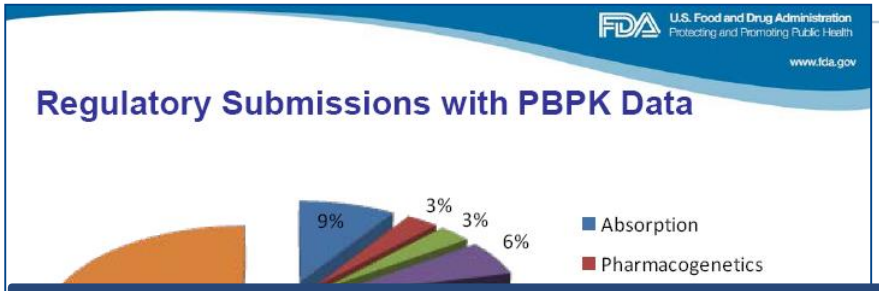
Critical Path to TB Drug Regimens

Outline

- Regulatory uses of PBPK models
- Components of the PBPK model for TB drug development
  - Populations
  - Compound files
  - Structure of the PBPK Model
- Strategy for model qualification
  - Context of use

Regulatory Acceptance of PBPK



e.g. DDI Predictions over the last decade:

- Increased knowledge/understanding
- Increased model complexity (static to dynamic),
- Validation/best practice
- Regulatory acceptance
- Routine use across industry
- Labelling

Proof of concept

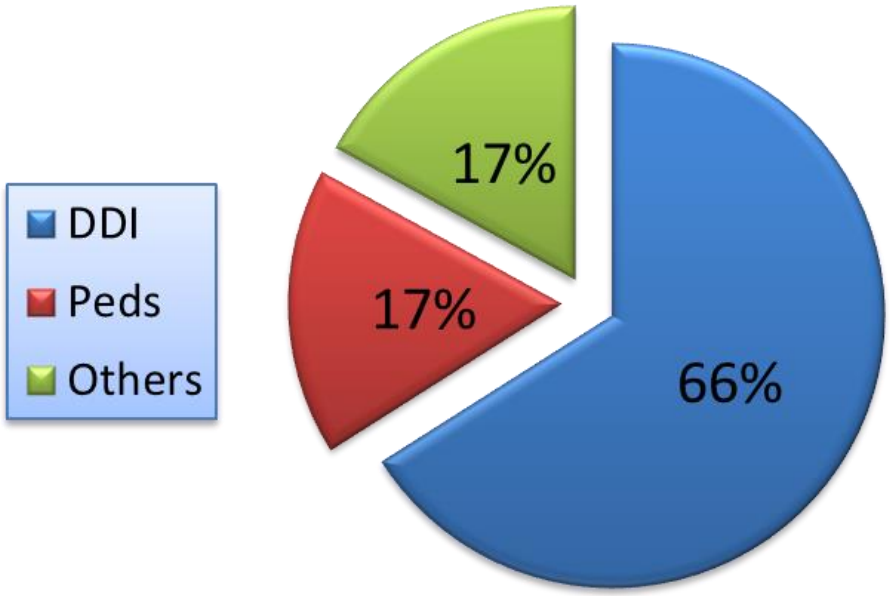
impact on clinical use (label wording)

- ibrutinib (Janssen)
- macitentan (Actelion)
- simprenavir (Janssen)

Sinha *et al.*, 2014

PBPK areas of application (FDA) - Updated

Based on the PBPK review knowledgebase of the Office of Clinical Pharmacology (of FDA), there are ***180*** records between ***2008 and 2015*** addressing various clinical pharmacology issues.



66% of these records fall into the category of predicting DDI potential, with the remaining 34% equally distributed between pediatric PK prediction and other applications (e.g., drug absorption, pharmacogenetics, and organ impairment).

Mehrotra et al., DMD, 2016

PBPK Impact on New Drug Approvals

Regulatory agencies have issued draft guidance on PBPK modelling and reporting

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 July 2016
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the qualification and reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

Draft

- Draft guidance issued July 2016; Public meeting in November 2016

Physiologically Based Pharmacokinetic Analyses — Format and Content

Guidance for Industry

- FDA draft guidance issued December 2016

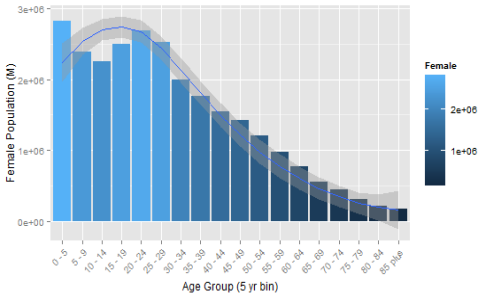
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM531207.pdf

PBPK model for TB drug development

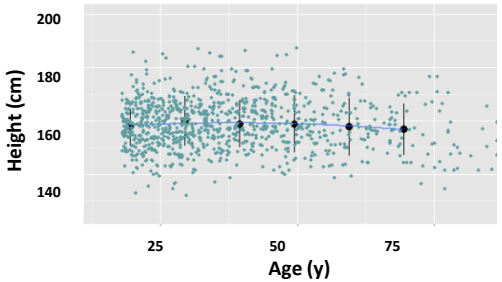
- Uses Simcyp Simulator PBPK platform
  - Full body PBPK models for up to 4 parent compounds and 4 metabolites
  - All of the moieties mutually interact through competitive and mechanism-based inhibition and induction processes
- Consists of
  - Population files
    - Virtual South African Population which also accounts for alterations in physiological parameters for some components that are known to change with TB infection
  - Compound files
    - SOC, Moxifloxacin, Bedaquiline, Pretomanid, Delaminid
  - Multi-compartment permeability limited model of the lung
  - Multi-compartment permeability limited model of TB granuloma
  - Pharmacodynamic models

South African Population

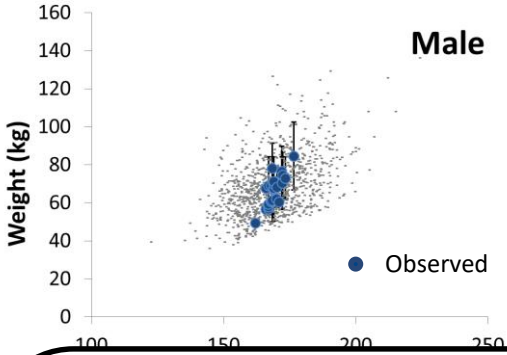
Age-Distribution



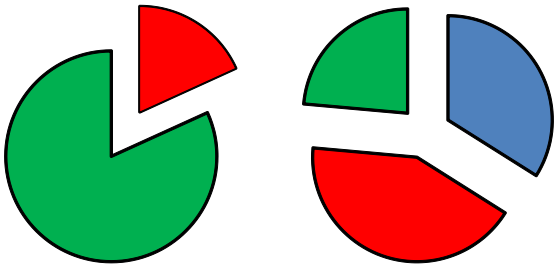
Age-Height



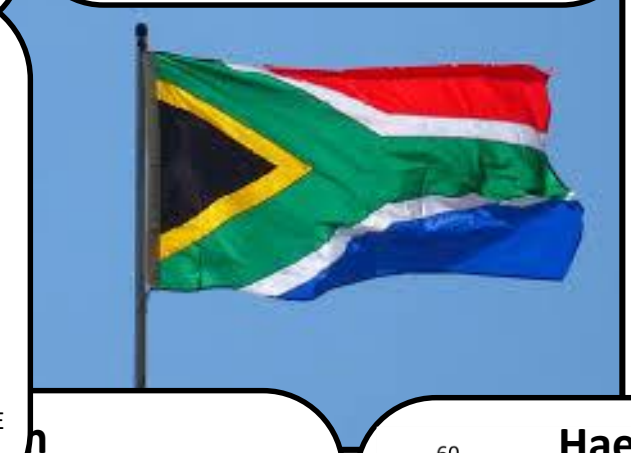
Height-Weight



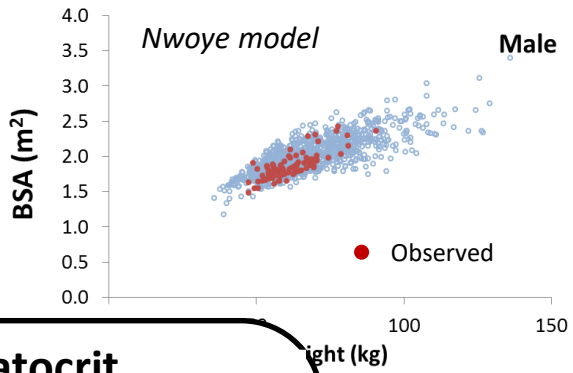
CYP3A5 / NAT-2



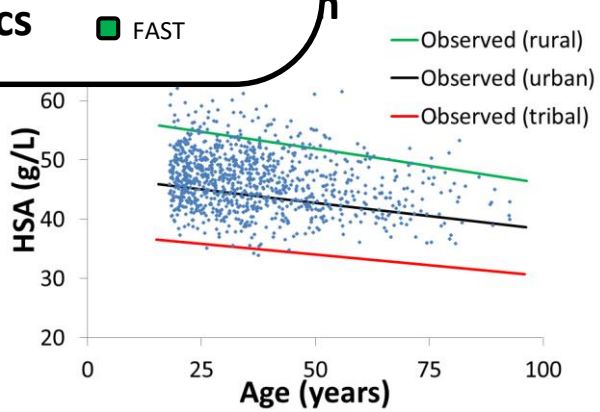
Genetics



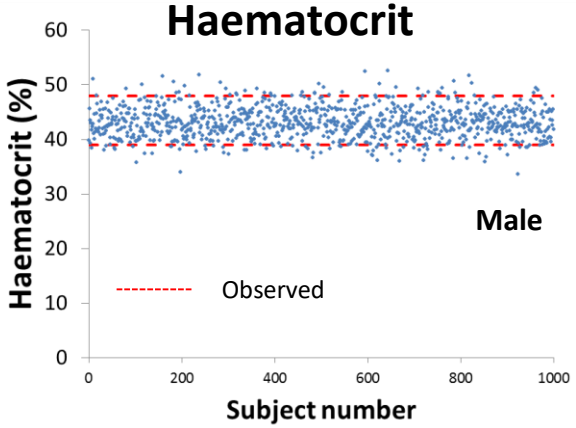
Body Surface Area



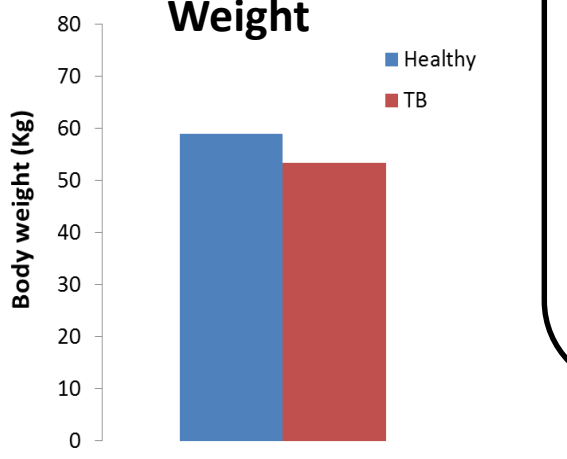
HSA

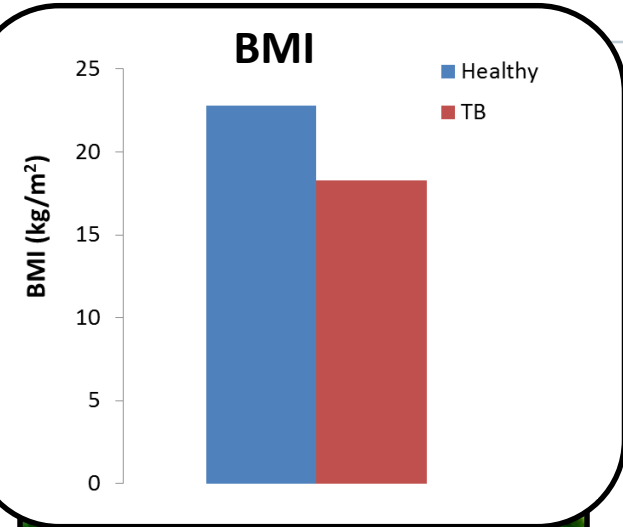


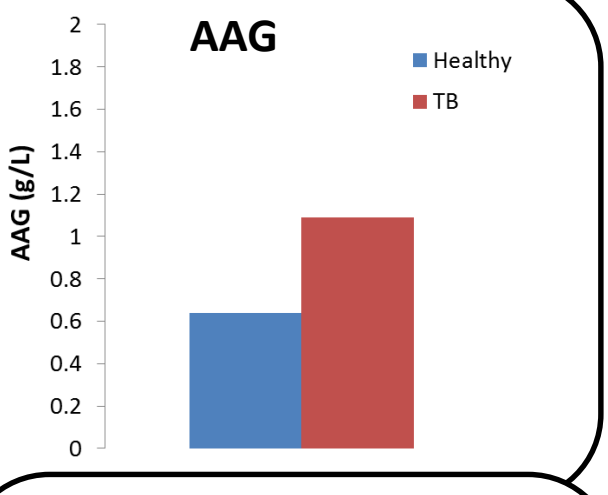
Haematocrit

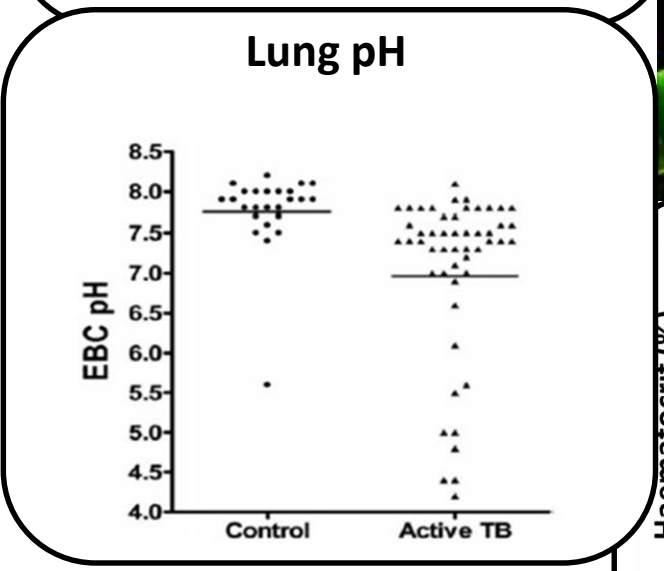


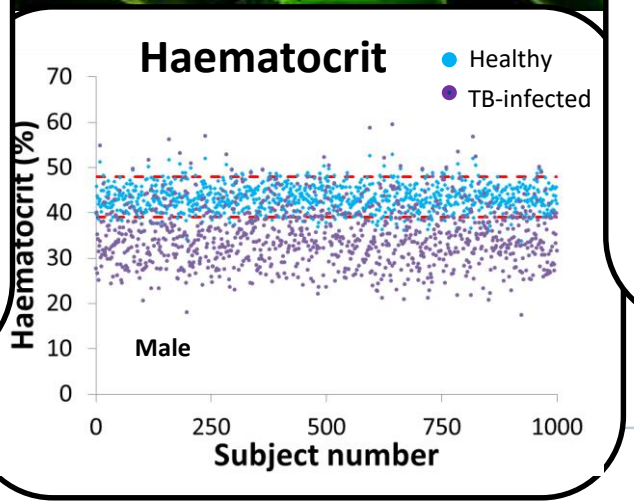
Physiology changes in TB

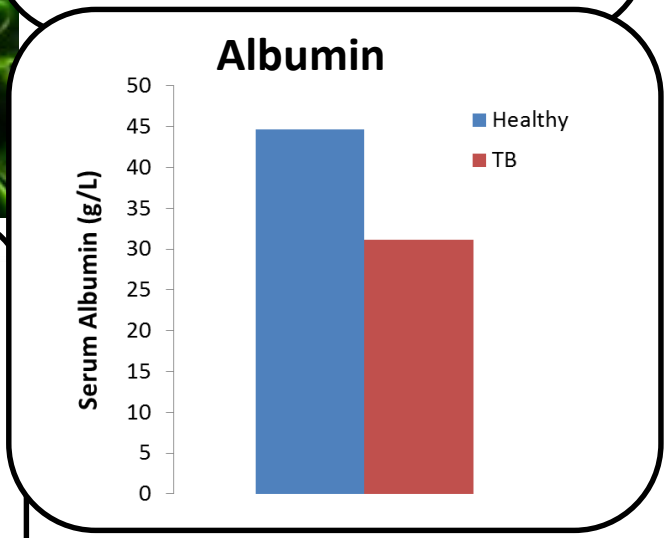




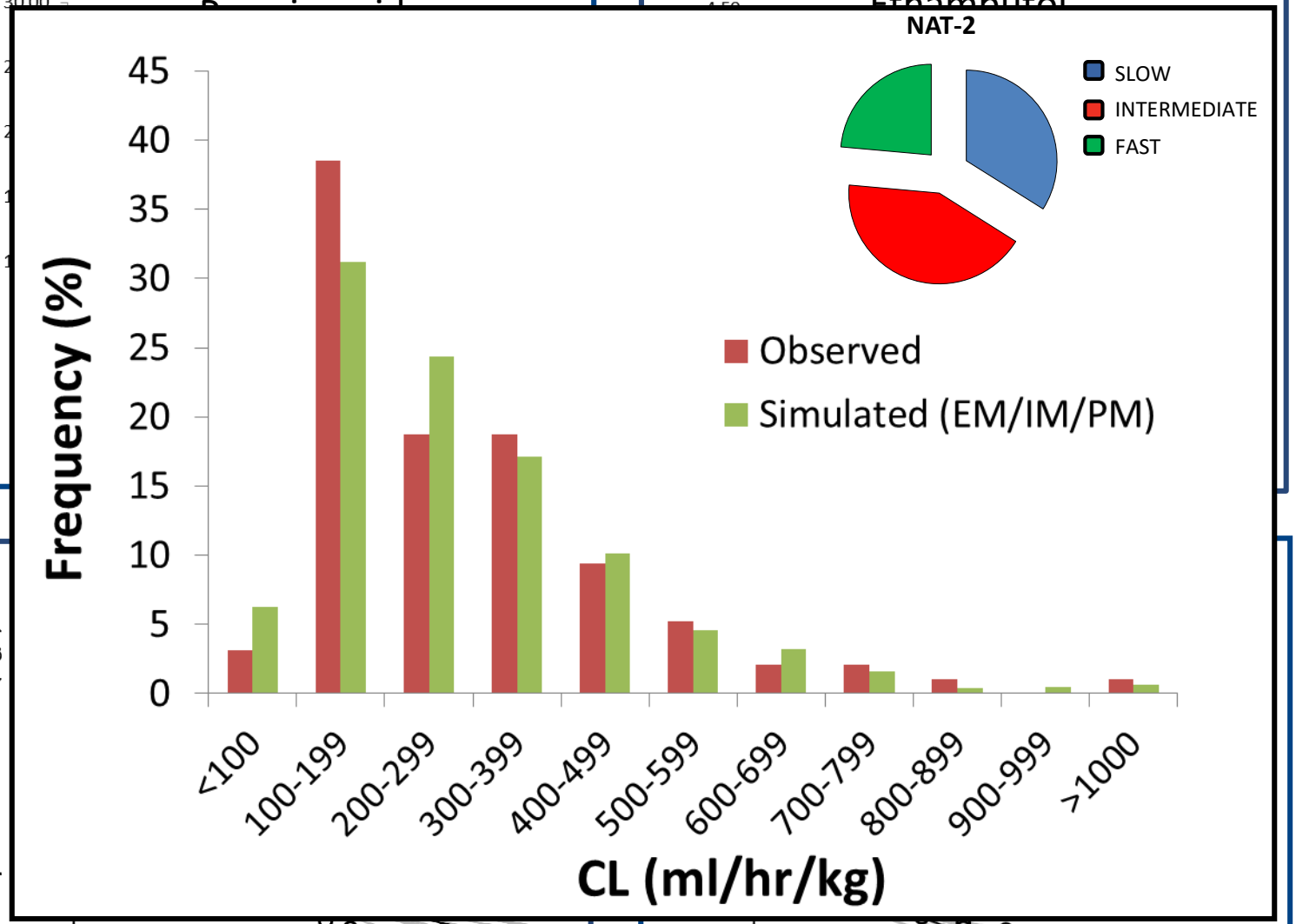




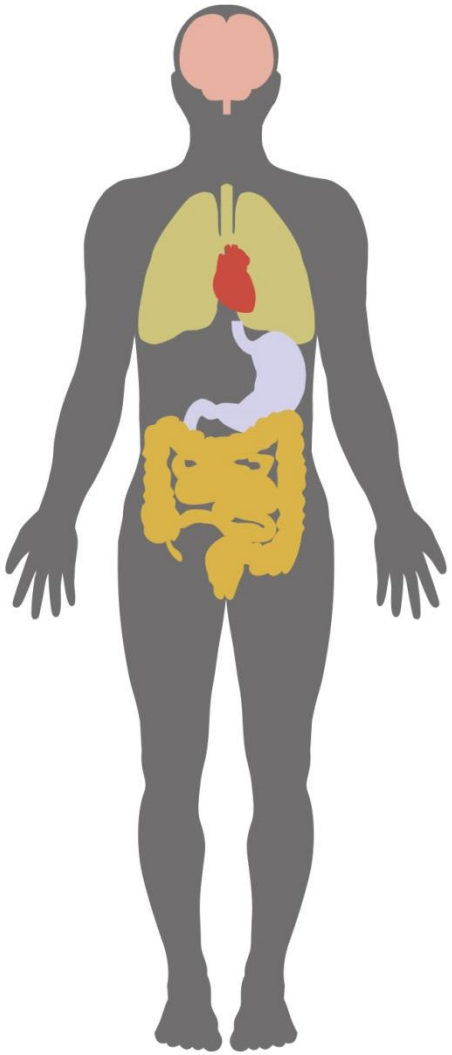


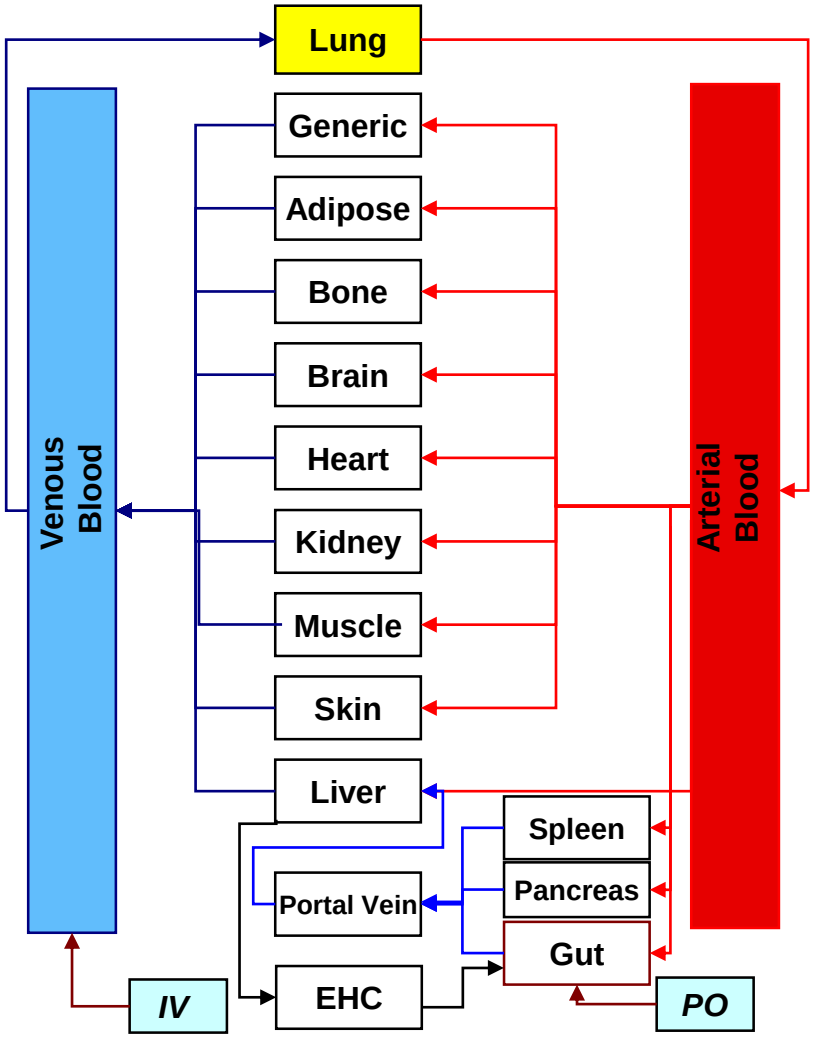


Simulation of PK for anti-TB drugs

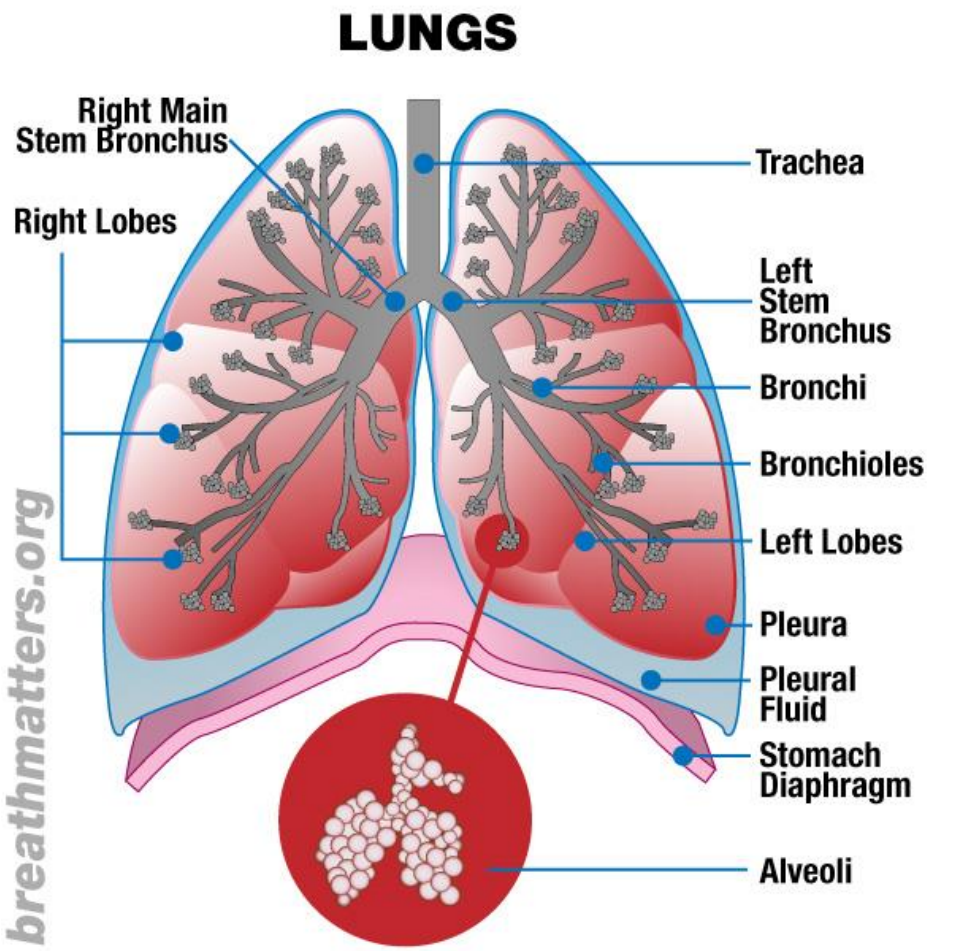


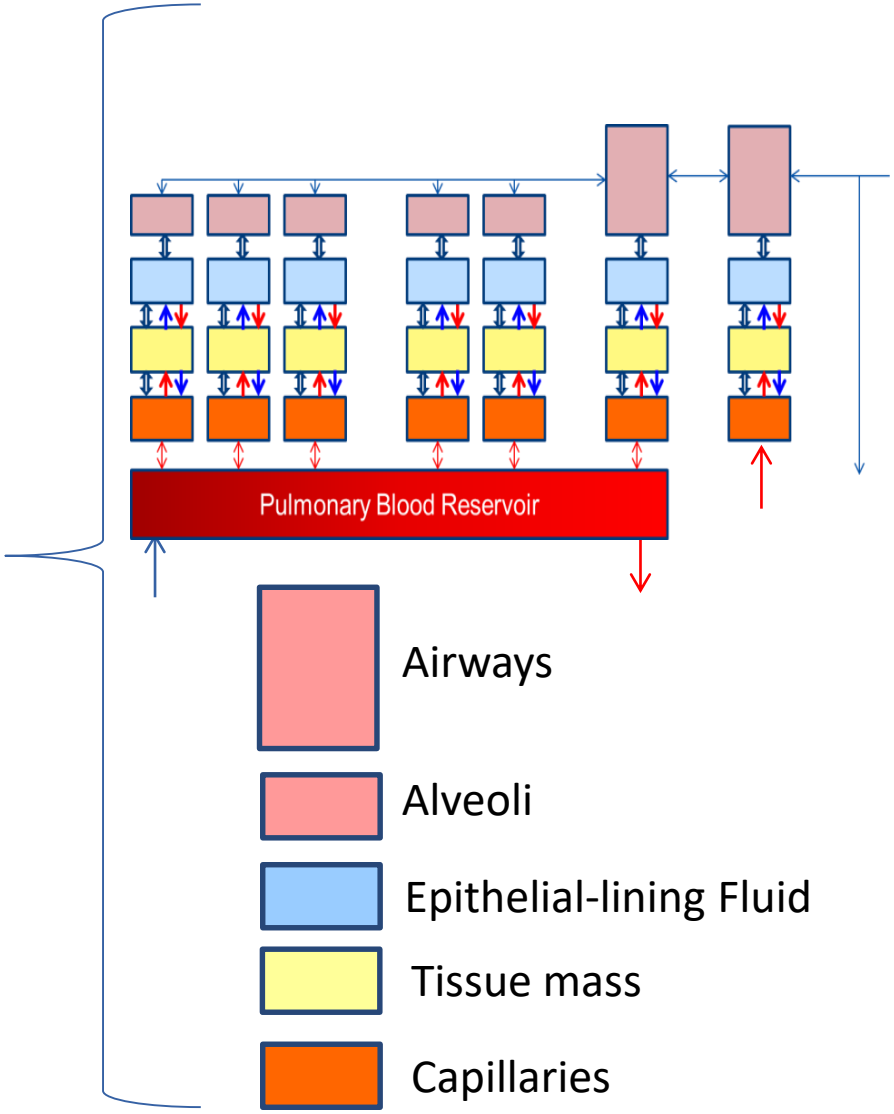
High-level PBPK representation of a human





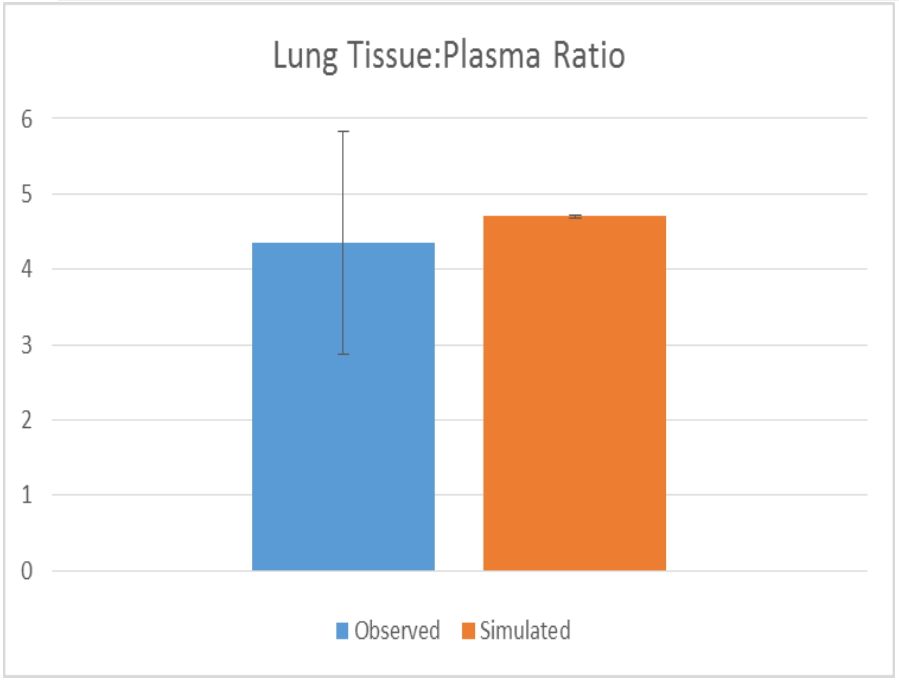
PBPK description of the lungs

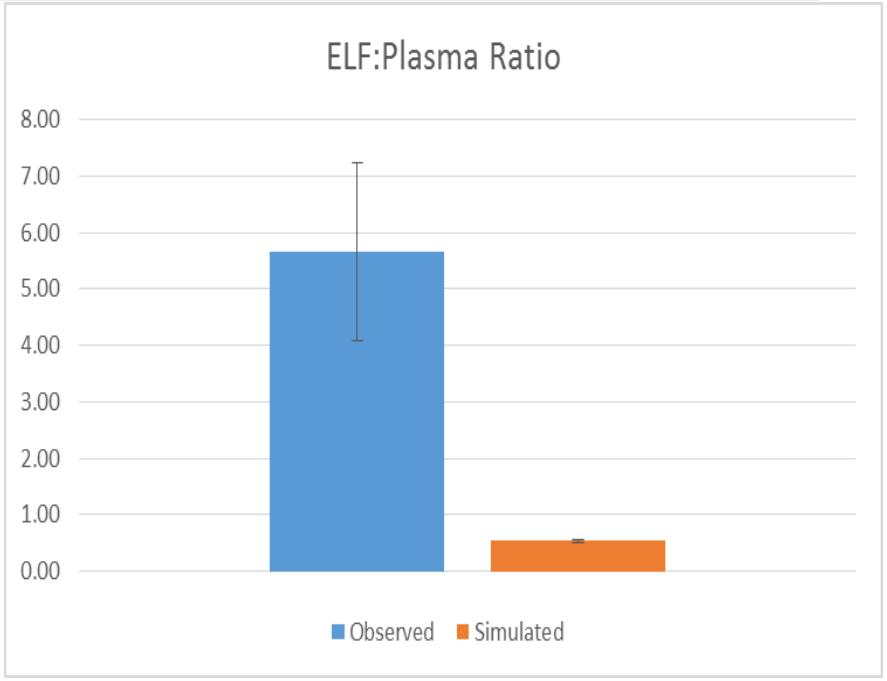




Gaohua L, Wedagedera J, Small BG, Almond L, Romero K, Hermann D, Hanna D, Jamei M, Gardner I. Development of a Multicompartment Permeability-Limited Lung PBPK Model and Its Application in Predicting Pulmonary Pharmacokinetics of Antituberculosis Drugs. CPT Pharmacometrics Syst Pharmacol. 2015;4(10):605-13.

Predicted and observed lung concentrations of moxifloxacin



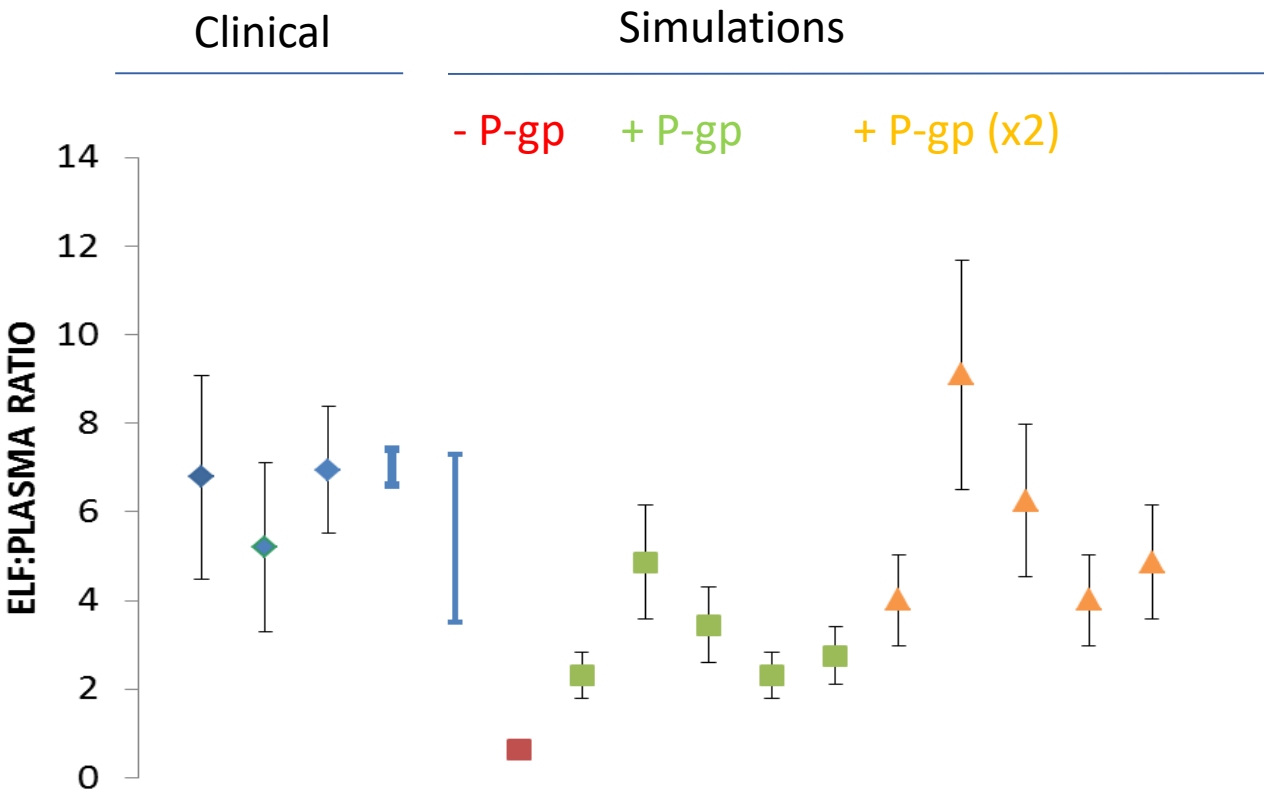


- Only accounting for passive movement of Moxifloxacin underpredicts ELF-concentration
- Moxifloxacin is a P-gp substrate (Brillault et al., 2009)
- P-gp is located on the apical side of the lung
  - Between mass and fluid/air

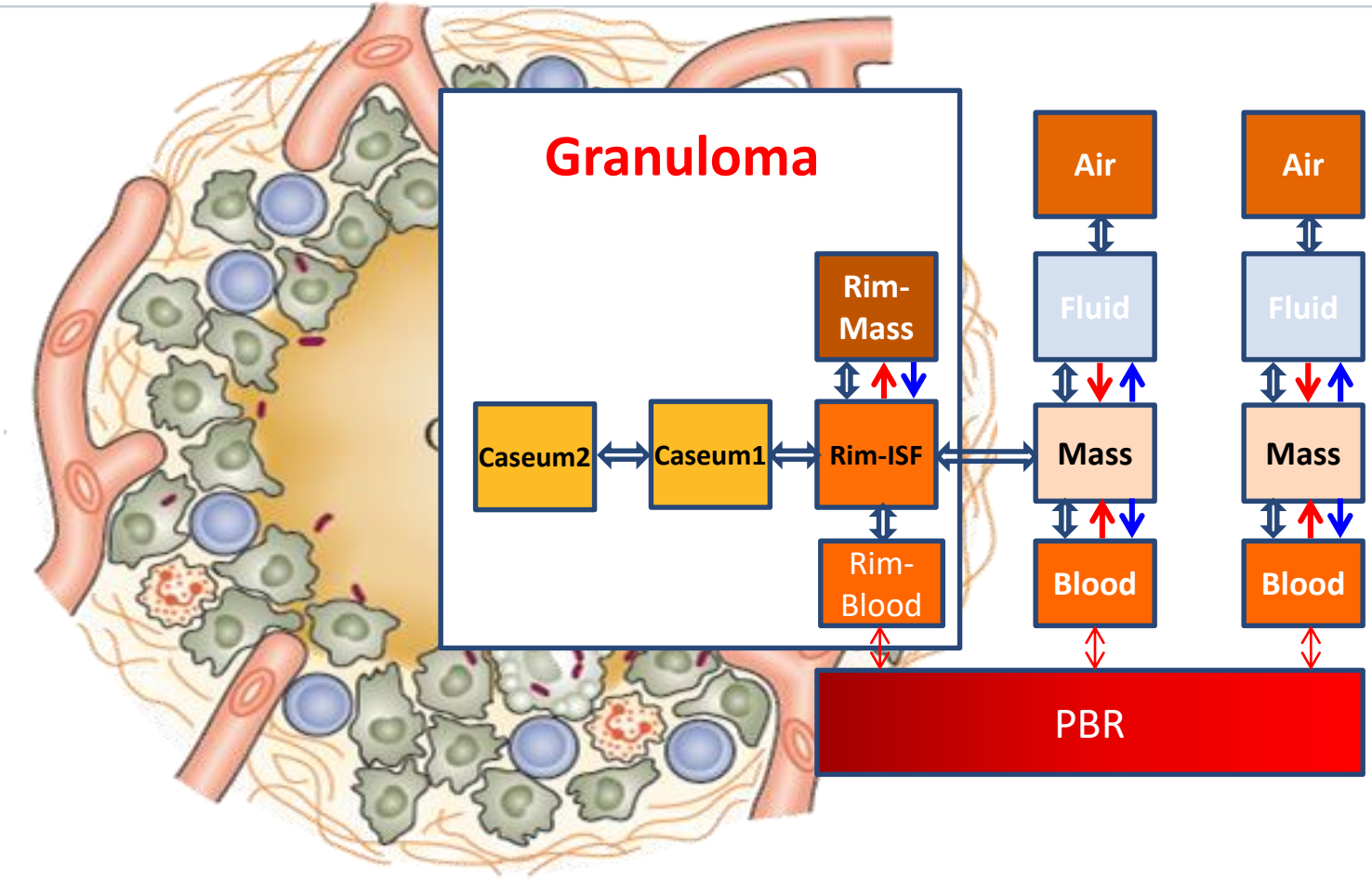
(Soman et al., 1999; Breilh et al., 2003; Capitano et al., 2004; Brillault et al., 2009)

Scaling P-gp effect for moxifloxacin

- *In vitro* permeability data was extracted and analysed to obtain transporter intrinsic clearance (36.1 µl/min)
- Scaled to the whole lung accounting for differences in surface area between *in vitro* and *in vivo* situation



Multi-layer granuloma model – concentration at the site of action

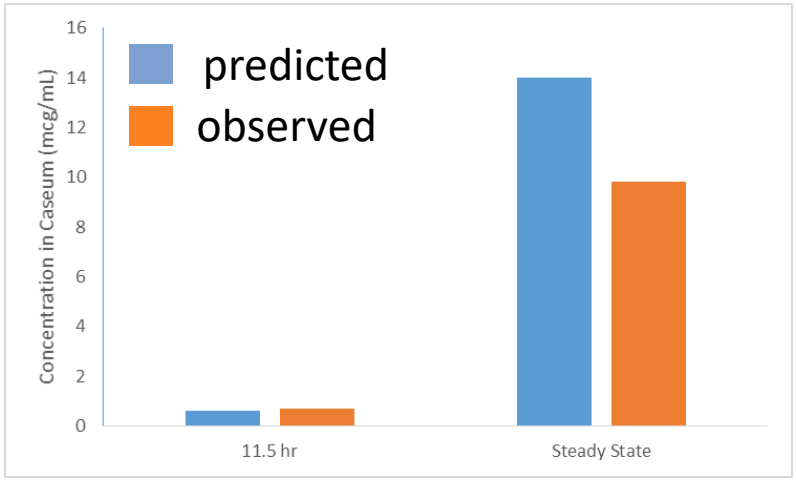


- **Drug concentrations modelled in macrophages, interstitial fluid, inner and outer parts of caseum**

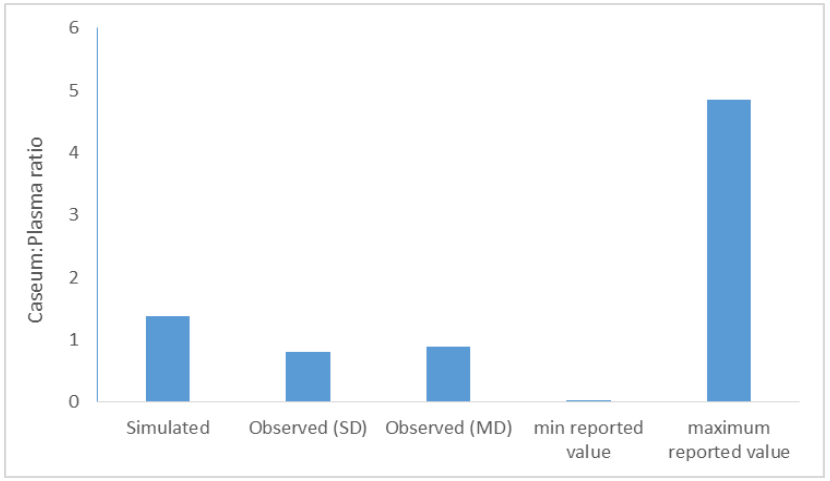
(Dartois, 2014)

Simulated and Observed concentrations in the caseum

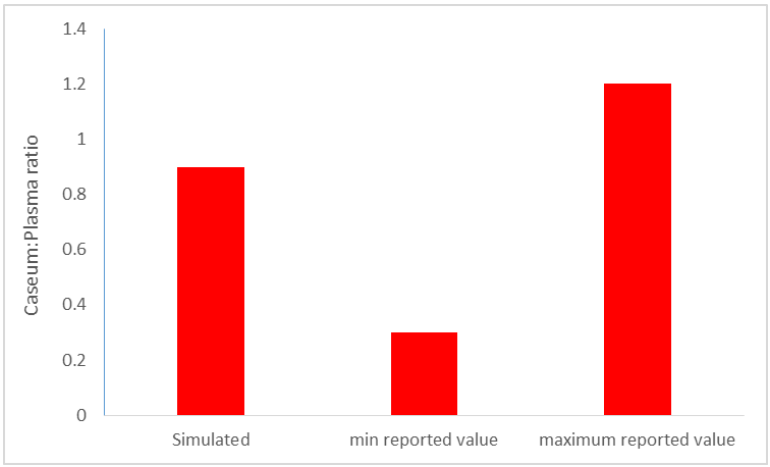
Rifampicin



Isoniazid



Pyrazinamide



Paths to qualification

- Initial TC discussions with EMA about PBPK model for TB
  - September 2016
- Face to Face meeting the day after the public workshop
  - November 2016
- Drafting proposed context of use

Proposed Context of Use

- **General Area:** Physiologically-Based Multi-Compartment Permeability-Limited Lung and Granuloma Model for Anti-TB drugs.
  - **COU Scenario 1** : Monotherapy prediction of plasma, lung and ELF concentrations in healthy volunteer subjects prior to First-in-Human (FIH) studies (Low/Medium Impact)
  - **COU Scenario 2**: Prediction of lung and ELF concentrations in Healthy volunteer/TB patients (Low/Medium impact)
    - a list of additional compounds with human *in vivo* data for use in verification exercise has been assembled
  - **COU Scenario 3**: Prediction of lung and ELF concentrations in Healthy volunteer/TB patients of compounds that are substrates for P-glycoprotein (Low/Medium impact)
  - A further 4 COU scenarios are possible but will be held back from initial discussions

Summary

- Use of PBPK models in different regulatory scenarios has increased dramatically over the past 5 years
- Draft guidelines on PBPK model qualification proposed by EMA
- Ongoing discussions with EMA and FDA about qualification of the PBPK model for TB drug development
  - Different context of use for the models have been discussed
  - Narrowed down to most feasible options for initial qualification
    - Can be expanded at a later date