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

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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

- 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
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

10 fast track, breakthrough, priority or accelerated approval

- 12 in oncology
- 3 in pulmonary
- 2 in anti-viral
- 4 in orphan
- 1 in gastro
- 1 in CNS

Almost 100 label claims informed by PBPK, including DDI, absorption, ethnic bridging, formulation
Regulatory agencies have issued draft guidance on PBPK modelling and reporting

• Draft guidance issued July 2016; Public meeting in November 2016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• FDA draft guidance issued December 2016

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**

**Body Surface Area**

**Genetics**

- CYP3A5
- NAT-2

**Haematocrit**

- Nwoye model

**Albumin**

- NAT
- SLOW
- INTERMEDIATE
- FAST

**Haematocrit (%)**

- Observed (rural)
- Observed (urban)
- Observed (tribal)

**HSA (g/L)**

- Observed (rural)
- Observed (urban)
- Observed (tribal)

**Observed (kg)**

- Male

**PM**

- EM

**Interpretation:**

- Genetic polymorphisms in CYP3A5 and NAT-2 are important factors in drug metabolism in South African populations.

- Age-distribution shows a peak in the 20-30 age group, with a gradual decrease after 70.

- Age-height and height-weight scatter plots indicate a correlation between age and body size.

- Body surface area is consistent with the Nwoye model, showing a slight variation between rural and urban populations.

- Haematocrit values vary significantly, with rural populations having lower values compared to urban and tribal populations.
Physiology changes in TB

- **Weight**
  - Body weight (Kg)
  - Healthy vs. TB

- **BMI**
  - BMI (Kg/m²)
  - Healthy vs. TB

- **AAG**
  - AAG (g/L)
  - Healthy vs. TB

- **Lung pH**
  - EBC pH
  - Control vs. Active TB

- **Albumin**
  - Serum Albumin (g/L)
  - Healthy vs. TB

- **Haematocrit**
  - Haematocrit (%)
  - Healthy vs. TB-infected
  - Male vs. Subject number

[Graphs and data showing comparisons between healthy and TB-infected individuals for various physiological metrics.]
Simulation of PK for anti-TB drugs

Isoniazid, Peloquin et al., 1999b
Pyrazinamide, Agrawal et al., 2002
Ethambutol, Peloquin et al., 1999a
Rifampicin, Goutelle et al., 2009

**NAT-2**
- SLOW
- INTERMEDIATE
- FAST

**Systemic Concentration (mg/L)**

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<tr>
<th>CL (ml/hr/kg)</th>
<th>Frequency (%)</th>
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<td>&gt;1000</td>
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**Observed**
**Simulated (EM/IM/PM)**
High-level PBPK representation of a human
PBPK description of the lungs

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

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<th>Clinical</th>
<th>Simulations</th>
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<tr>
<td>- P-gp</td>
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<td>+ P-gp (x2)</td>
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**Graph**

- Y-axis: ELF:PLASMA RATIO
- X-axis: Various conditions

Legend:
- Blue diamonds: - P-gp
- Green circles: + P-gp
- Orange triangles: + P-gp (x2)
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

- Predicted
- Observed

Isoniazid

- Simulated
- Observed (SD)
- Observed (MD)
- Min reported value
- Maximum reported value

Pyrazinamide

- Simulated
- Min reported value
- Maximum reported value
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