CPTR Scientific Advice Meeting with EMA: Hollow Fiber System for TB (HFS-TB)

May 6, 2014
| 10 mins. | 1. **Introduction and Overview of CPTR Mission**  
| | • Welcome: Review Goals for the Meeting and Agenda  
| | • Participant Introductions  
| | • Rationale for PCS-WG and HFS-TB Objective  |
| 15 mins. | 2. **Current Landscape of Pre-clinical Tools Utilized in Drug Development**  
| | • Advantages, limitations, and impact on drug development  
| | • Advantages of HFS-TB as an additional DDT and proposed use in drug development  |
| 20 mins. | 3. **The HFS-TB Model**  
| | • Overview and description of the model  
| | • Example of key compound in progression  |
| 20 mins. | 4. **Overview of Methods and Project Literature Search Survey and Analysis**  
| | • Methods  
| | • Literature search and analysis  
| | • Detailed overview and description of analysis 2c  |
| 5 mins. | 5. **Proposed Planned Studies**  |
| 5 mins. | 6. **Follow Up Actions**  |
Meeting Objectives

• Introduction to CPTR mission and initiative

• Review the technical schema of the HFS tool and its proposed placement in the TB drug development process

• Review scientific rationale for the program

• Review the supporting data/evidence, analysis strategy, and output from the HFS-TB project

• Address issues raised by EMA (in an order that fits the flow of the information being presented)

• Brief review of future project work

• Scientific feedback and discussion
The Challenge

Need emphasis on combination study approaches—rather than development of single agents

Increasingly “fragile” TB drug development pipeline with the continued divestment of companies in the anti-infective space

Focus on best tools to de-risk compounds and improve understanding of efficacy and PKPD relationships
Accelerate the development of new, safe, and highly effective regimens for TB by enabling early testing of drug combinations
Mission

Develop and validate tools and innovative approaches to address pre-clinical issues including \textit{in vitro} and \textit{in vivo} efficacy, PKPD analyses using appropriate biomarkers, drug safety toxicology, metabolism, DDI, etc. These tools may be submitted to regulatory authorities for regulatory review and/or qualification as appropriate.

\textbf{Early goal related to pre-clinical \textit{in vitro} and \textit{in vivo} models}

Evaluate the evidence base and develop criteria for the utility of various pre-clinical models to inform and test new drug candidates and regimens.

\textbf{Early Evidence}

White Paper Identified HFS-TB as having appropriate data inventory to assess predictive accuracy of a pre-clinical model for clinical outcomes.
Current State
TB Regimen Development

PRECLINICAL
Static drug concent.
Rodent
Guinea pig
Rabbit
Primate
PBPK Modeling

PHASE I-IIa
Safety PKPD
Dose-Ranging
PK 14-Day EBA
(Whole Blood Assay?)

PHASE IIb
Dosing
POC-human

PHASE III
Randomized Controlled
Trial Efficacy

CONFIRMATORY PROOF OF COMBINATION EFFICACY

BIG GAP

Critical Path Drug Development Decisions

Accurate PKPD Translation
Accurate IVIVE Extrapolation
Early Indication of Efficacy of Individual Drugs and Data on Combinations
Dose Selection / Regimen Evaluation
Increase Reliability of Predictions for Dose Selection and Efficacy Outcomes
Future State
TB Regimen Development

Critical Path Drug Development Decisions
Pre-Clinical TB Models

**PRE-CLINICAL**

Static drug concentrations (extracellular, intracellular)
HFS (extracellular, intracellular)

Rodent (mouse, rat)
Guinea pig
Rabbit
Non-human primate (marmoset, macaque)
Zebrafish
Mini-pig

PBPK Modeling

**PHASE I-IIa**

Safety PKPD Dose-Ranging PK 14-Day EBA (*Whole Blood Assay?*)
An unbiased, empirical approach:

- **Single Drug PK in Mouse**
- **Combination Efficacy (Mouse Acute Model)**
- **Combination Efficacy (Mouse Relapse Model)**
- **PK/Chemical Interaction**
- **Confirmation of Efficacy**
- **Secondary Species Infection Model**
- **Combination Safety (if needed)**

**Process for Regimen Discovery**

- **Day -14**: Bactericidal Activity: Initial Screening
- **Day 0**: Sterilizing Activity: Duration of Therapy
- **M2**, **M3**, **M4**, **M5**: 15 mice held for 3 months after treatment completion to determine the proportion with microbiological evidence of relapse

**Clinical Studies**
The Applicant should discuss to what extent they perceive that the HFS-TB could i.) **minimise** the need for **non-clinical** efficacy data, ii.) **reduce** the need for **clinical dose-finding** studies, and iii.) **shorten** the duration of the **drug development programme**.

**Response:**

Pyrazinamide (PZA) example *(following five slides)*
HFS-TB Model

Integrated HFS-TB Model Components

- Inoculation Device (Syringe)
- Hollow Fiber Cartridge
- Cross Section Hollow Fiber Cartridge
- Hollow Fiber Lumen
- Hollow Fiber Wall
- Peripheral Compartment (Pharmacodynamic PD)
- Drug
- Bacteria
- Pump-controlled Syringe (Drug Delivery)

Fresh Media
Central Compartment (Pharmacokinetic PK)
Waste Media
## Quantitative Outputs of HFS-TB

### Outputs from HFS-TB experiments
- Drug-resistant Mtb CFU count
- Drug concentration
- Macrophage count and no. bacteria/macrophage
- RNA expression
- Whole genome sequencing of sampled material

### Monte Carlo simulations of combinations yield
- Quantitative understanding of PK/PD relationship
- Dose-response curves expected in patients and choice of optimal doses
- Expected rates of, and time to, resistance emergence for concentration related resistance
HFS and PZA dose-finding

- Experiments performed at pH 5.8, with semi-dormant bacteria that grow at very slow rates
- Dose effect studies to examine doses of 0-120 mg/kg (standard dose: 15-30 mg/kg)
- Study over 28 days with 9 sampling times
- Took into account drug penetration indices into lung and macrophages
- Followed by dose scheduling study over 28 days
- Then Monte Carlo simulations to identify clinical doses based on output
HFS-TB Forecasting PZA

- HFS-TB PK/PD: Optimal effect AUC/MIC=209 (11.7)
- Monte Carlo Simulation of HFS-TB findings for dose finding prediction

Result: higher doses of up to 4 grams needed in the clinic, as predicted by HFS-TB and MCS

Two clinical studies that examined effect of PZA exposure in combination on microbial effect

**Study 1**
- 142 patients in Western Cape of South Africa
- Prospective cohort with measurement of drug concentrations
- Quality of study score = 2
- Published 2013

**Study 2**
- 58 patients in Western Cape of South Africa
- Part of a randomized controlled trial
- Drug concentrations and MICs measured
- Quality of study score = 1
- Oral Presentation at TB pharmacology meeting 2013
### PZA Clinical Findings (Analysis 2C)

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<thead>
<tr>
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<tbody>
<tr>
<td>PK/PD driver selected</td>
<td>AUC/MIC</td>
<td>AUC/MIC</td>
<td>AUC/MIC</td>
</tr>
<tr>
<td>Optimal AUC$_{0-24}$/MIC</td>
<td>Lung: 209</td>
<td>-</td>
<td>Serum: 11.3</td>
</tr>
<tr>
<td></td>
<td>Serum: 11.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with optimal exposure at 2g</td>
<td>58%</td>
<td>-</td>
<td>57%</td>
</tr>
<tr>
<td>Optimal dose (g)</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Breakpoint MIC (mg/L)</td>
<td>50</td>
<td>-</td>
<td>50</td>
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</table>

FE = (T-P)*100/T

FE = (|11.3-11.7|)*100/11.3

FE = 3.54%

Accuracy = 100-FE = 96.46% for optimal AUC/MIC
Optimize doses of drugs in regimens to obviate the need for dose response clinical study

➤ Use Best Dose First Time

Optimize selection of drugs for regimen design by evaluating synergy and antagonism

➤ Which drugs should each new drug be combined with?

Rank regimens by speed of sterilizing effect
Discussion – EMA Issue 4
The Applicant is requested to summarise the minimum amount of *in-vitro* and human PK data (healthy subjects and/or infected patients) that is necessary before commencing use of the HFS-TB to identify i.) **PK/PD relationships**, and ii.) **initial doses and regimens**. The Applicant should explain how additional data that emerge during the development programme can be factored in to refine or expand the use of the model. Provision of a diagrammatic algorithm as part of the response would be helpful.

**Response:**

**Non-Clinical**
- Estimate from animal models based on allometric scaling

**Clinical *(if available)***
- PK data from clinical trials
- TB strains of interest
Based on the **retrospective** searches conducted the Applicant proposes that HFS-TB has a high predictive accuracy for clinical trial outcomes. The Applicant should summarise instances in which the **predictions** arising from use of the HFS-TB did not correlate well with clinical findings and discuss the possible reasons. In particular, to identify and discuss any instances in which the HFS-TB has **underestimated or overestimated** the mycobacterial responses in patients.

**Response:**
- Predictive accuracy analysis (following seven slides)
Literature Search Objectives

• **Literature Search A** conducted to identify relevant HFS-TB published studies

• **Literature Search B** conducted to identify TB clinical studies published prior to corresponding HFS-TB studies and used to examine descriptive correlations (*Analysis 1*)

• **Literature Search C** conducted to identify TB clinical studies published at least six months after publication of HFS-TB studies and used to examine predictive accuracy (*Analysis 2a, 2b, and 2c*)
HFS-TB Objective and Strategy

• **Analysis Objective** to determine predictive accuracy of HFS-TB outputs and clinical trial results

• **Literature Review** of relevant data from published literature (January 1, 1943 – December 31, 2012)

• **PZA** as comprehensive example
## Quality of Evidence Score

<table>
<thead>
<tr>
<th>Quality Of Evidence Score</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>1</td>
<td>Evidence from $\geq 1$ properly randomized, controlled trial; meta-analysis of randomized, controlled trials that followed PRISMA recommendations</td>
</tr>
<tr>
<td>2</td>
<td>Evidence from $\geq 1$ well-designed <em>prospective</em> clinical trial, without randomization; from prospective cohort or case-controlled analytic studies; dramatic experimental study results of uncontrolled clinical studies</td>
</tr>
<tr>
<td>3</td>
<td>Evidence from multiple time-series; evidence from dramatic epidemiological data</td>
</tr>
<tr>
<td>4</td>
<td>Evidence from a large retrospective case series in single center; examination of clinical isolates from case series</td>
</tr>
</tbody>
</table>

Estimates from key opinion leaders based on clinical experience, or reports of expert committees, or historical precedence, considered NOT to be evidence, rather opinion.
Studies Identified by Searches

**Literature Search A:** 26 HFS-TB studies (12 combination studies, 10 monotherapy, 4 Monte Carlo simulations)

**Literature Search B:** 17 TB clinical studies, published prior to HFS-TB studies; quality of evidence score of 1 in 15/17

**Literature Search C:** 20 TB clinical studies, published at least six months after HFS-TB studies; quality of evidence of 1 or 2 in 11/20

➢ *Weighting reflected clinical study quality score*
Data Analysis Methods

Analysis 1: Descriptive Correlations (not today’s focus)

Analysis 2: Predictive Accuracy or Forecasting

• 2a: Correct ranking of PK/PD indices relevant to dose scheduling

• 2b: Accuracy in generating or refuting hypotheses with relevance to therapeutic strategies

• 2c: Quantitative accuracy in forecasting PK/PD indices relevant to dose scheduling, dose selection, and breakpoints

➤ Weighted by clinical study quality score and number of patients in study
Predictive Accuracy Approach

• Error (E) was defined as the observed results in a clinical study at time T, minus the predicted value P:

   \[ E = T - P \]

• For a number of trials or experiments \( i \) of up to \( n \), this takes the form of the mean absolute percentage error (MAPE), which is given by:

   \[ \text{MAPE} = \frac{1}{n} \left[ \sum_{i=1}^{n} \left| \frac{T_i - P_i}{T_i} \right| \right] \times 100 \]

• Accuracy (A) was defined as:

   \[ A = 100\% - \text{MAPE} \]

• Bias (B) was defined as:

   \[ B = \sum_{i=1}^{n} (T_i - P_i) / n \]
Summary of Analyses

14 HFS-TB quantitative predictions

8 clinical studies:  14 quantitative outcomes

Overall predictive accuracy of HFS-TB:

94.4% (CI=84.3-99.9%)

Overall bias of HFS-TB predictions:

1.8% (CI=-13.7-6.2%)
Summary of Analyses

HFS-TB Predicted vs. Clinic Observed

$r^2 = 0.986$
Discussion – EMA Issue 5
The Applicant should present any available data that could further support the claim that the HFS-TB model can select dose regimens and drug combinations that are least likely to select for drug resistant strains. The answer should include a discussion of dose selection if the HFS predicts that much higher doses are needed to suppress the selection for resistant organisms vs. those needed for adequate efficacy.

Response:

Kill rates and time-to-resistance emergence (next slide)
# PZA Standard Doses

## HFS-TB vs. Patients

<table>
<thead>
<tr>
<th>HFS-TB</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Kill Rates ($\log_{10}$ CFU/mL/day):</strong></td>
<td></td>
</tr>
<tr>
<td>Day 0-4: 0.10±0.00</td>
<td>-0.10</td>
</tr>
<tr>
<td>Day 4-14: 0.12±0.05</td>
<td>0.09-0.10</td>
</tr>
<tr>
<td><strong>Time to resistance emergence (weeks):</strong></td>
<td></td>
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<tr>
<td>2-3</td>
<td>2-3</td>
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</tbody>
</table>

Moxifloxacin

Relationship between Bactericidal Activity and Resistance Emergence

AUC/MIC = 0

AUC/MIC = 24

AUC/MIC = 40

AUC/MIC = 102
Ciprofloxacin

Hollow Fiber (1 year prior to first reports of XDR-TB)

- CIPRO had a substantial microbial kill over the first 3 days of therapy, optimal bactericidal effect at this dose
- However, by day 7 the total population replaced by resistant population
- Predicted the emergence of quinolone and other second-line therapy if CIPRO and ofloxacin were used at standard doses in developing countries

Discussion – EMA Issue 6
EMA Issues 2 & 3

**Issue 2:** The Applicant should discuss **whether and how** the HFS-TB could take into account **drug concentrations** that may occur at the **site(s) of infection** and other factors that could affect **drug activity** and/or organism **susceptibility** (e.g. physiological conditions).

**Issue 3:** The Applicant should further justify the **ability** of the HFS-TB to evaluate **antibacterial activity** against **non-log phase** organisms.

**Response (below and following two slides):**

The HFS-TB takes drug penetration, and concentration-time profiles at site of infection (if known)

The HFS-TB is a collection of several systems that consider: (a) in log-phase growth under ambient air, (b) semi-dormant under acidic conditions, (c) non-replicating persisters, or (d) in macrophages
HFS-TB studies

*Mtb* physiological conditions & host pharmacokinetics

Total of 26 studies; 22 wet lab HFS-TB studies

- 12 log-phase growth
- 5 non-replicating
- 5 semi-dormant
- Additional non-log phase growth experiments, but reported in aggregate in fewer papers

**Pharmacokinetics**

- Concentrations at site of effect when available
- Drug penetration and protein binding taken into account in ALL Monte Carlo Simulations
### Excerpt from Literature Search

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Year</th>
<th>Drug</th>
<th>Findings/Conclusions</th>
</tr>
</thead>
</table>
| Gumbo et al.10  | 2004 | Moxifloxacin | ● Biphasic kill  
● Acquired drug resistance (ADR)  
● Identification of optimal moxifloxacin dose |
| Gumbo et al.41  | 2007 | Isoniazid  | ● Slow/rapid isoniazid pharmacokinetics mimicked  
● PK/PD indices identified; described by series of “U” shaped curves  
● 300mg/day inadequate for optimal kill in some ethnic populations |
| Gumbo et al.39  | 2007 | Rifampin | ● Rifamycin half-life has little relevance to efficacy  
● Rifampin efficacy measures driven by peak/MIC  
● Microbial kill linked to AUC/MIC  
● Standard doses are inadequate for ADR suppression and optimal microbial kill  
● Derivation of quadratic function describing concentration vs. ADR |
| Gumbo et al.23  | 2009 | Pyrazinamide  | ● For optimal kill, doses >60mg/kg (not 15-30mg/kg) identified |

- This excerpt for monotherapy shows how the HFS-TB predictions correctly rank relevant PK/PD indices.
- The CPTR team plans to assess these against those published for *in vivo* models used for drug development and for PK/PD where *Mtb* metabolic states were also validated using similar methods to calibrate the collective understanding across the pre-clinical space.
• HFS-TB study that examined dose-effect and dose-scheduling

• Semi-dormant bacilli at pH 5.8 (grow 10-20 fold slower than log-phase)

• Considered concentrations and penetration into alveolar macrophages, as well as epithelial lining fluid
Discussion – EMA Issues 2 & 3
EMA Issue 7a

Provide any accessible **additional data** that concern the recent use of the HFS-TB to **select dose** regimens for **clinical studies**.

**Response:**

**Additional HFS-TB Data**

- The team is aware of unpublished work with Sequella’s (formerly Pfizer’s) Oxazolidinone
- The team continues to pursue these data under our CPTR secure data use agreement
- TB related studies not typically performed in-house due to BSL-3 requirements

**Non-TB HFS Data**

- Several companies have established HFS laboratories
- Varied application: Efficacy driver confirmation vs. time course studies
  - Validation work critical
The applicant is requested to discuss how the **various uses** of the HFS-TB could be **further evaluated prospectively**.

**Response:**

<table>
<thead>
<tr>
<th>REMOX: Moxifloxacin/rifampin/pyrazinamide ± either isoniazid or ethambutol (Each experiment repeated 3 times)</th>
<th>PA824: Dose-effect for microbial kill &amp; resistance suppression; dose-scheduling (Each experiment repeated 3 times)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log phase growth</td>
<td>Log phase growth</td>
</tr>
<tr>
<td>Intracellular</td>
<td>Intracellular</td>
</tr>
<tr>
<td>Semi-dormant/β-slope</td>
<td>Semi-dormant/β-slope</td>
</tr>
</tbody>
</table>
Future CPTR HFS-TB Work

Second, expanded literature review and analyses funded to include all new references and studies conducted after December 2012 to current date.

HFS-TB studies funded by Bill & Melinda Gates Foundation via CPTR to:

• Develop Standard Operating Procedures/Lab Manual that will standardize the tool for industry and inform:
• Studies to evaluate intra and inter lab variability to deeper extent
• Generate HFS-TB data on new TB Drugs and emerging regimens in multiple growth states and conditions
Discussion – EMA Issue 7 a & b
Acknowledgements

CPTR PCS-WG & Hollow Fiber System Sub-team:

Dr. Tawanda Gumbo (University of Texas Southwestern Medical Center)
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Dr. Tian Yang (Global Alliance for TB Drug Development)
Dr. Omar Vandal (Bill & Melinda Gates Foundation)
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