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

CRITICAL PATH INSTITUTE

Critical Path to TB Drug Regimens

Agenda

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

CURRENT REGIMEN DEVELOPMENT PARADIGM:
Existing regimen consists of four drugs

NEW DRUG 1 — NEW DRUG 1
NEW DRUG 2 — NEW DRUG 2
NEW DRUG 3 — NEW DRUG 3
NEW DRUG 4 — FULLY NOVEL REGIMEN
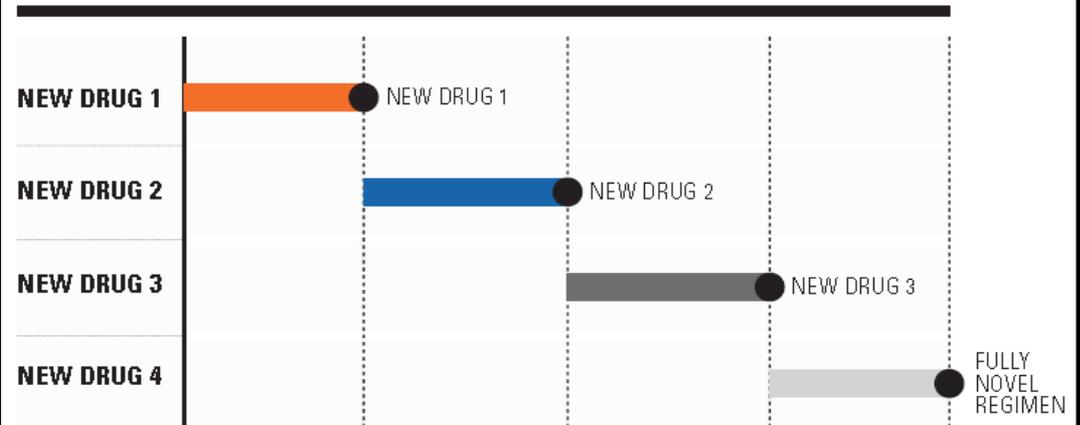
NOVEL COMBINATION TESTING PARADIGM:
Novel regimen development can reduce the time to develop a new TB drug regimen by 75%:

NEW DRUG 1
NEW DRUG 2
NEW DRUG 3
NEW DRUG 4

FULLY NOVEL REGIMEN

This new paradigm reduces time to develop a novel TB drug regimen by 75%

CPTR Mission & Purpose
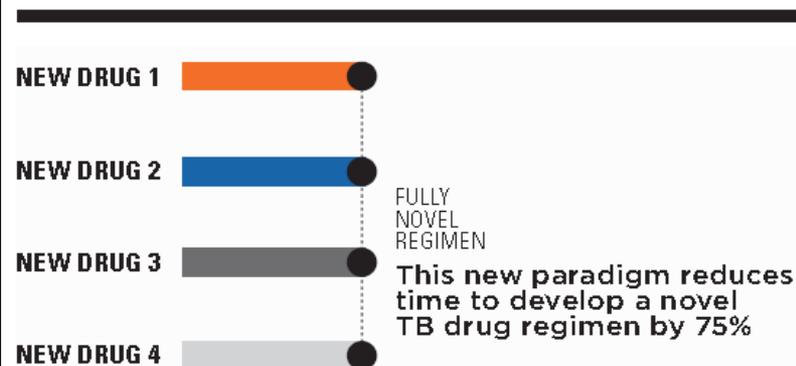
Accelerate the development of new, safe, and highly effective regimens for TB by enabling early testing of drug combinations

PCS-WG Mission & Goals

Mission

Develop and validate tools and innovative approaches to address pre-clinical issues including *in vitro* and *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.

Early goal related to pre-clinical *in vitro* and *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.

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

CRITICAL PATH INSTITUTE **CPTR**

PRECLINICAL	**PHASE I-IIa**	**PHASE IIb**	**PHASE III**	**CONFIRMATORY PROOF OF COMBINATION EFFICACY**
Static drug concent. Rodent Guinea pig Rabbit Primate	Safety PKPD Dose-Ranging PK 14-Day EBA *(Whole Blood Assay?)*	Dosing POC-human	Randomized Controlled Trial Efficacy	
PBPK Modeling				

BIG GAP

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

Critical Path Drug Development Decisions

Future State
TB Regimen Development

CRITICAL PATH INSTITUTE · CPTR

PRECLINICAL		PHASE I-IIa	PHASE IIb	PHASE III	CONFIRMATORY PROOF OF COMBINATION EFFICACY
Static drug concent. Rodent Guinea pig Rabbit Primate HFS	PBPK Modeling	Safety PKPD Dose-Ranging PK 14-Day EBA *(Whole Blood Assay?)*	Dosing POC-human	Randomized Controlled Trial Efficacy	

BIG GAP

Quantitative Assessment of Liquid Culture Biomarker

Drug Disease Model

PopPKPD Modeling
Population PKPD

Systems Pharmacology/ Mechanism Based Models

Penultimate Clinical Trial Simulation Tool

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

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*?)

Process for Regimen Discovery

CRITICAL PATH INSTITUTE   CPTR

An unbiased, empirical approach:

Single Drug PK in Mouse

Combination Efficacy (Mouse Acute Model)

Combination Efficacy (Mouse Relapse Model)

PK/Chemical Interaction

Secondary Species Infection Model

Combination Safety (if needed)

Confirmation of Efficacy

Combination Specific Safety

Clinical Studies

Appropriate Dose Selection in Mice

Bactericidal Activity: Initial Screening

Sterilizing Activity: Duration of Therapy

Day -14   Day 0   M2   M3   M4   M5

15 mice held for 3 months after treatment completion to determine the proportion with microbiological evidence of relapse

EMA Issue 4

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)

Cross Section Hollow Fiber Cartridge

Hollow Fiber Lumen

Hollow Fiber Wall

Pump

Hollow Fiber Cartridge

Drug

Peripheral
Compartment
(Pharmacodynamic PD)

Bacteria

Pump

Pump

Fresh Media

Waste Media

Central Compartment
(Pharmacokinetic PK)

0.051

Pump-controlled Syringe
(Drug Delivery)

Quantitative Outputs of HFS-TB
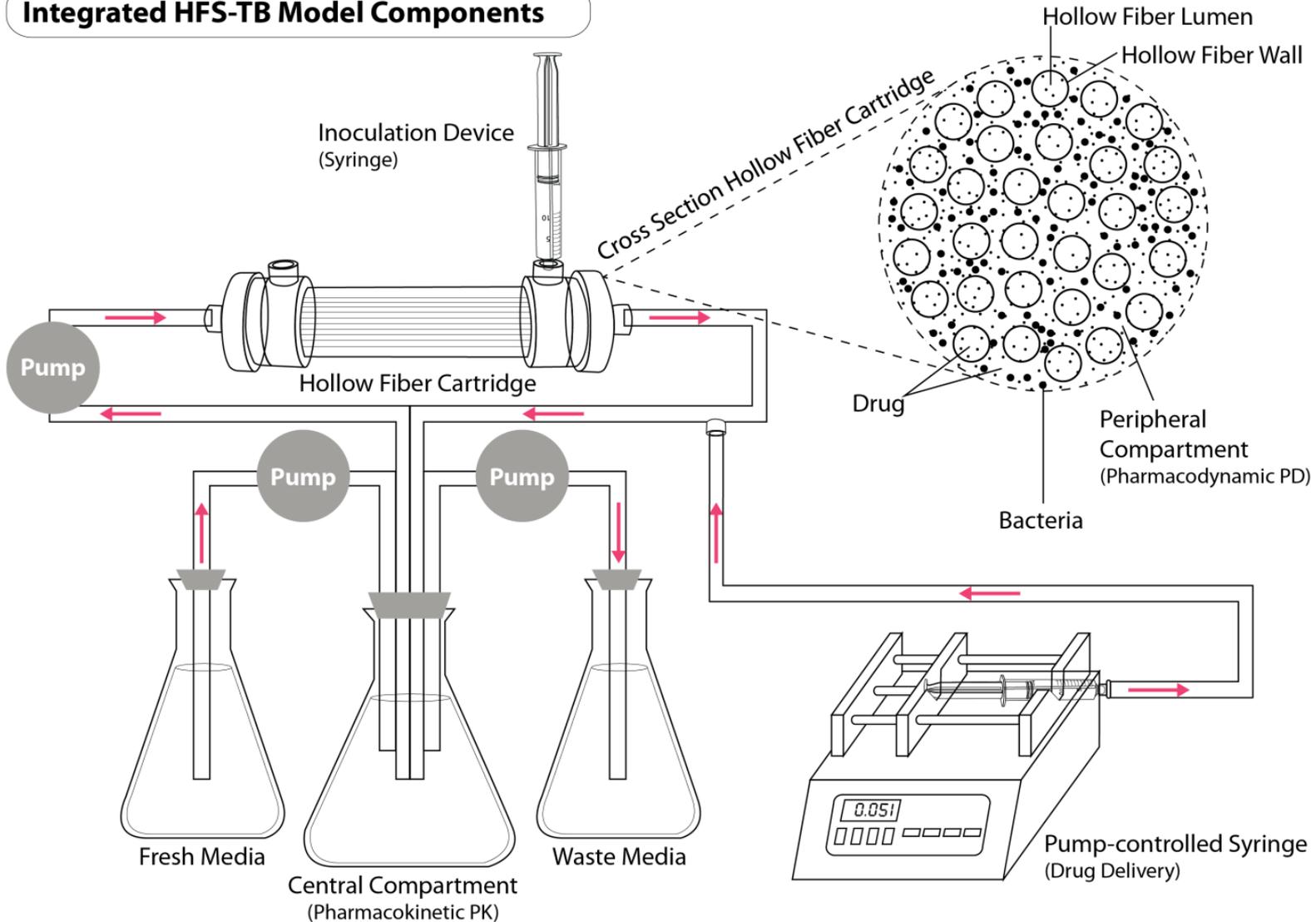
Outputs from HFS-TB experiments

- 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
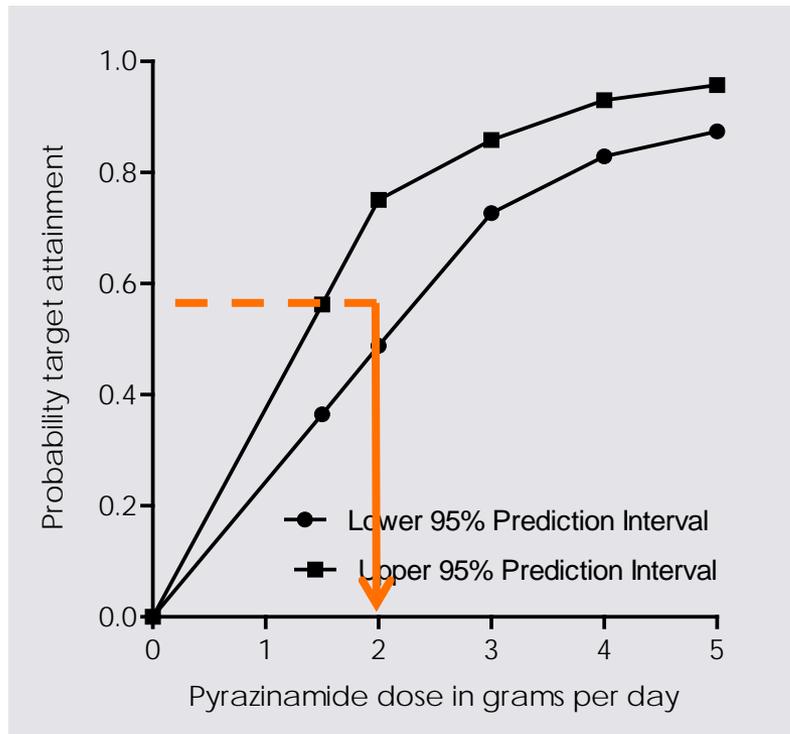
58% target attainment with 2g in 10,000 simulated subjects

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

Gumbo et al. Antimicrob. Agents Chemother. 2009:53;3197-3204.

PZA Example

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

Study 1	Study 2
142 patients in Western Cape of South Africa	58 patients in Western Cape of South Africa
Prospective cohort with measurement of drug concentrations	Part of a randomized controlled trial
	Drug concentrations and MICs measured
Quality of study score = 2	Quality of study score = 1
Published 2013	Oral Presentation at TB pharmacology meeting 2013

PZA Clinical Findings (Analysis 2C)

Study	HFS-TB Prediction (2009)	Guinea Pigs/Mice (2011)	Clinical Study #2 (2013)
PK/PD driver selected	AUC/MIC	AUC/MIC	AUC/MIC
Optimal AUC_{0-24} /MIC	Lung: 209 Serum: 11.7	-	Serum: 11.3
Patients with optimal exposure at 2g	58%	-	57%
Optimal dose (g)	4	4	
Breakpoint MIC (mg/L)	50	-	50

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

HFS-TB Proposed Use

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

EMA Issue 1

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

Quality Of Evidence Score	Criteria
1	Evidence from ≥1 properly randomized, controlled trial; meta-analysis of randomized, controlled trials that followed PRISMA recommendations
2	Evidence from ≥1 well-designed **prospective** clinical trial, without randomization; from prospective cohort or case-controlled analytic studies; dramatic experimental study results of uncontrolled clinical studies
3	Evidence from multiple time-series; evidence from dramatic epidemiological data
4	Evidence from a large retrospective case series in single center; examination of clinical isolates from case series

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 <u>observed</u> results in a clinical study at time T, minus the <u>predicted</u> 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:

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

- Accuracy (A) was defined as:

$$A=100\%-MAPE$$

- 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%)

HFS-TB Predicted vs. Clinic Observed
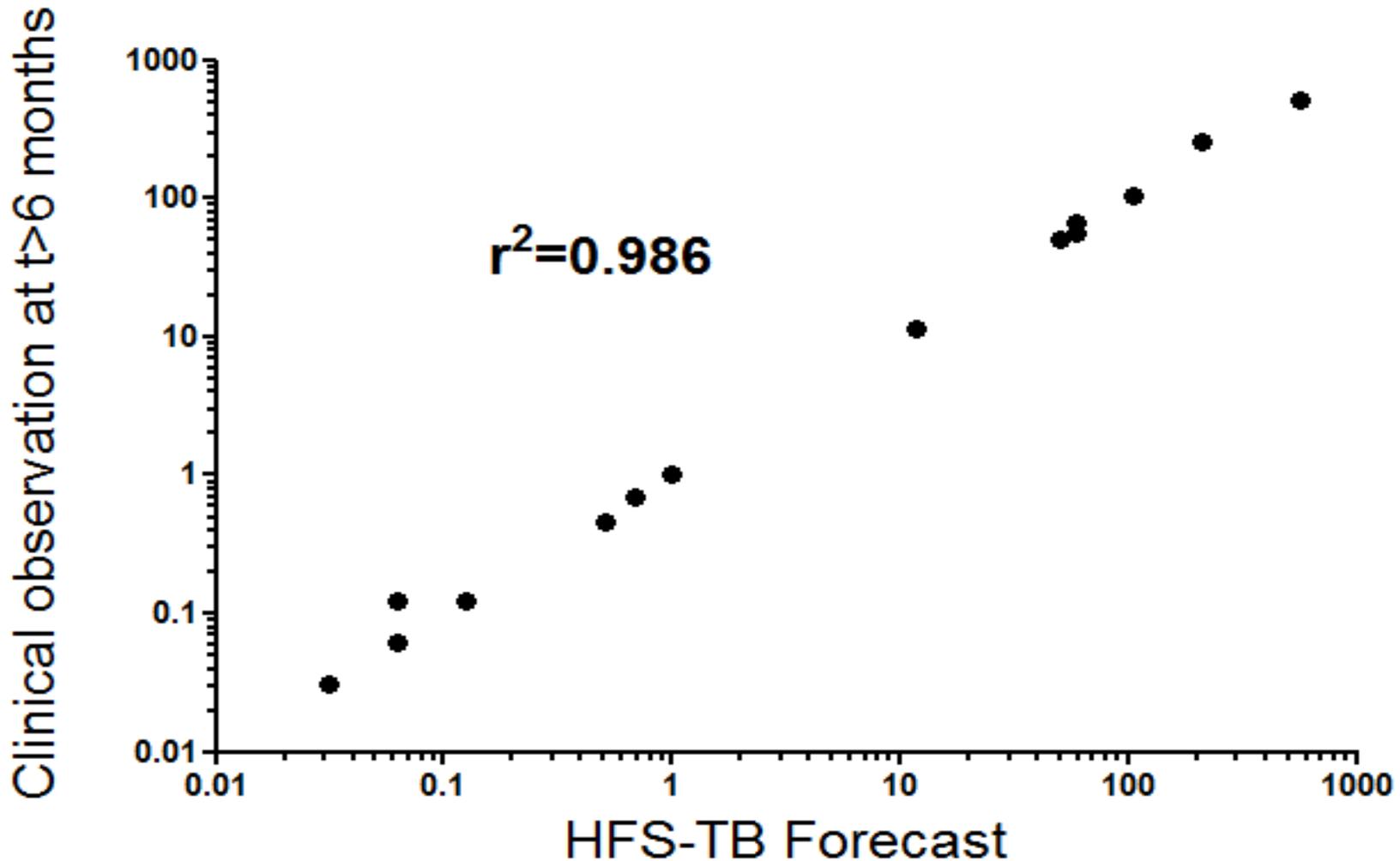
Discussion – EMA Issue 5

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

HFS-TB	Patients
Kill Rates (log$_{10}$ CFU/mL/day):	
Day 0-4: 0.10±0.00	-0.10
Day 4-14: 0.12±0.05	0.09-0.10
Time to resistance emergence (weeks):	
2-3	2-3

Patient data: Jindani et al. Am. Rev. Respir. Dis. 1980; 121: 939-49.

Yeager et al. Trans. Annu. Meet. Natl. Tuberc. Assoc. 1952; 48: 178-201.

Gumbo et al. Antimicrob. Agents Chemother. 2009: 53;3197-3204.

Moxifloxacin

Relationship between Bactericidal Activity and Resistance Emergence
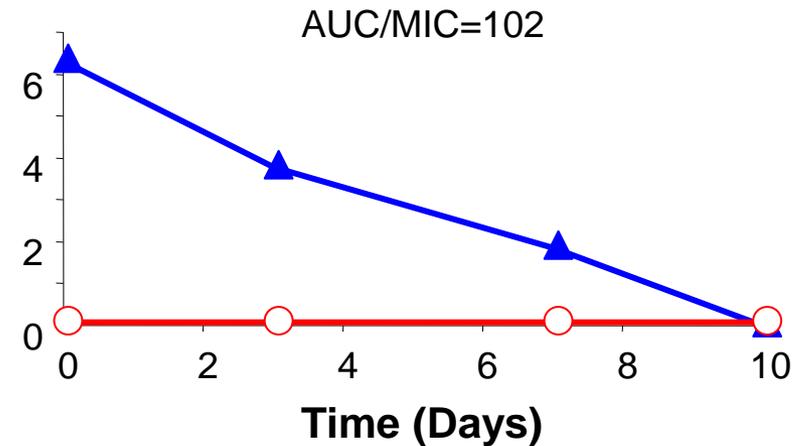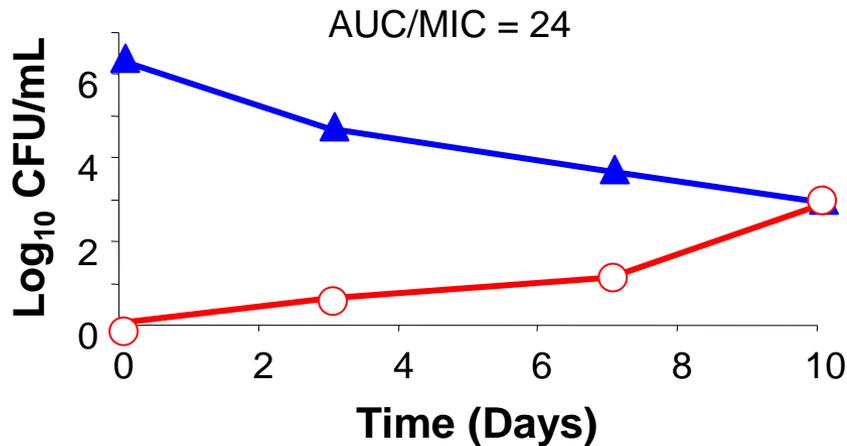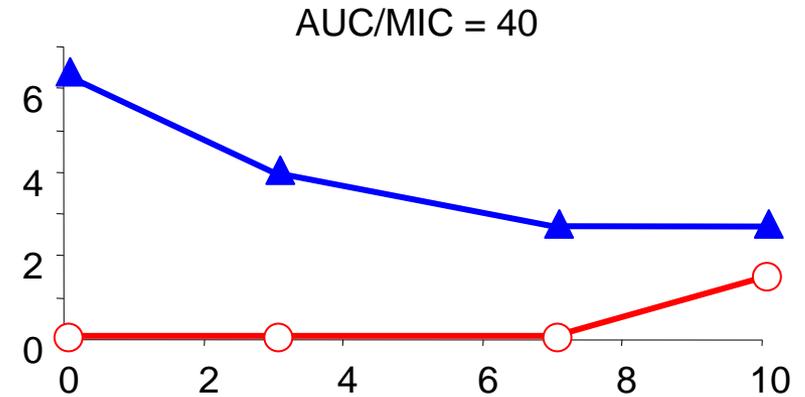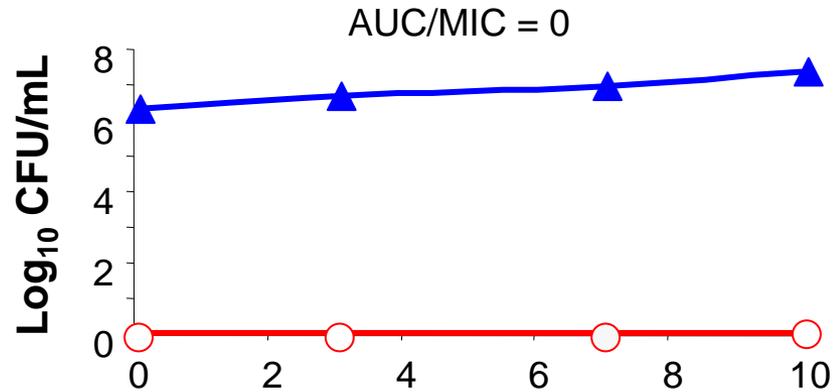
Ciprofloxacin

Hollow Fiber (1 year prior to first reports of XDR-TB)
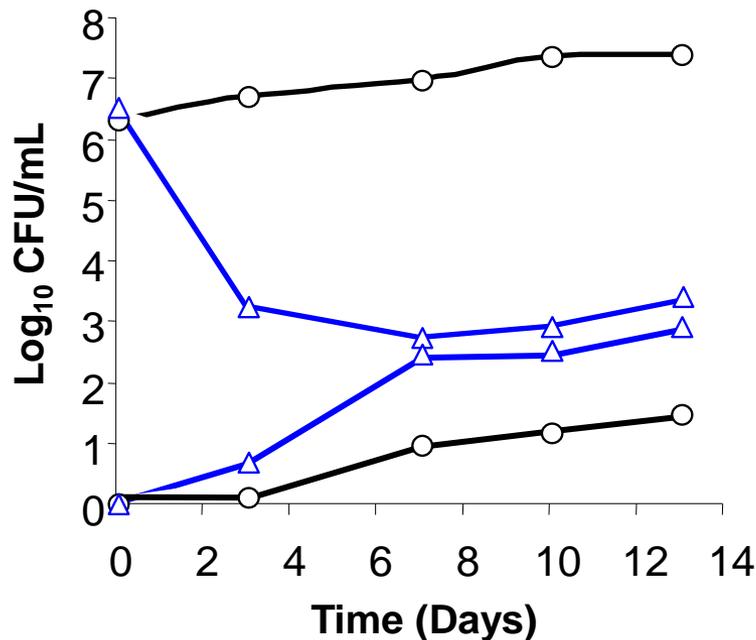
Control: Total population
Control: Resistant population
Ciprofloxacin treated: Total population
Ciprofloxacin treated: Resistant Population

- 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

Gumbo T, et al. Antimicrob. Agents Chemother. 2005 49: 3178-3181.

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

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

Study Reference	Year	Drug	Findings/Conclusions
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

PZA Forecast

- 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

EMA Issue 7b

The applicant is requested to discuss how the **various uses** of the HFS-TB could be **further evaluated prospectively**.

Response:

REMOX: Moxifloxacin/rifampin/pyrazinamide ± either isoniazid or ethambutol (Each experiment repeated 3 times)	PA824: Dose-effect for microbial kill & resistance suppression; dose-scheduling (Each experiment repeated 3 times)
Log phase growth	Log phase growth
Intracellular	Intracellular
Semi-dormant/β-slope	Semi-dormant/β-slope

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)

Dr. Debra Hanna (Critical Path Institute)

Dr. Klaus Romero (Critical Path Institute)

Dr. Eric Nuermberger (Johns Hopkins University)

Dr. Jotam Pasipanodya (University of Texas Southwestern Medical Center)

Dr. Christine Sizemore (National Institutes of Health)

Dr. Tian Yang (Global Alliance for TB Drug Development)

Dr. Omar Vandal (Bill & Melinda Gates Foundation)

Lindsay Lehmann (Critical Path Institute)

Dr. Nandini Konar (Critical Path Institute)

CPTR Health Authorities Submission Team:

Robin Keen (Janssen Pharmaceuticals)

Dr. Ann Kolokathis (C-Path)

Dr. Bob Clay (Consultant)