Reproducibility and Industrialization of the *in vitro* Hollow-Fiber System (HFS-TB)

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Critical Path to TB Drug Regimens

CRITICAL PATH INSTITUTE

Outline

Critical Path to TB Drug Regimens

Critical Path to TB Drug Regimens Methodologies Landscape

- Methods landscape
- Academic approach to method development ***versus***
- Methodologies designed as drug development tools

In vitro HFS-TB Model

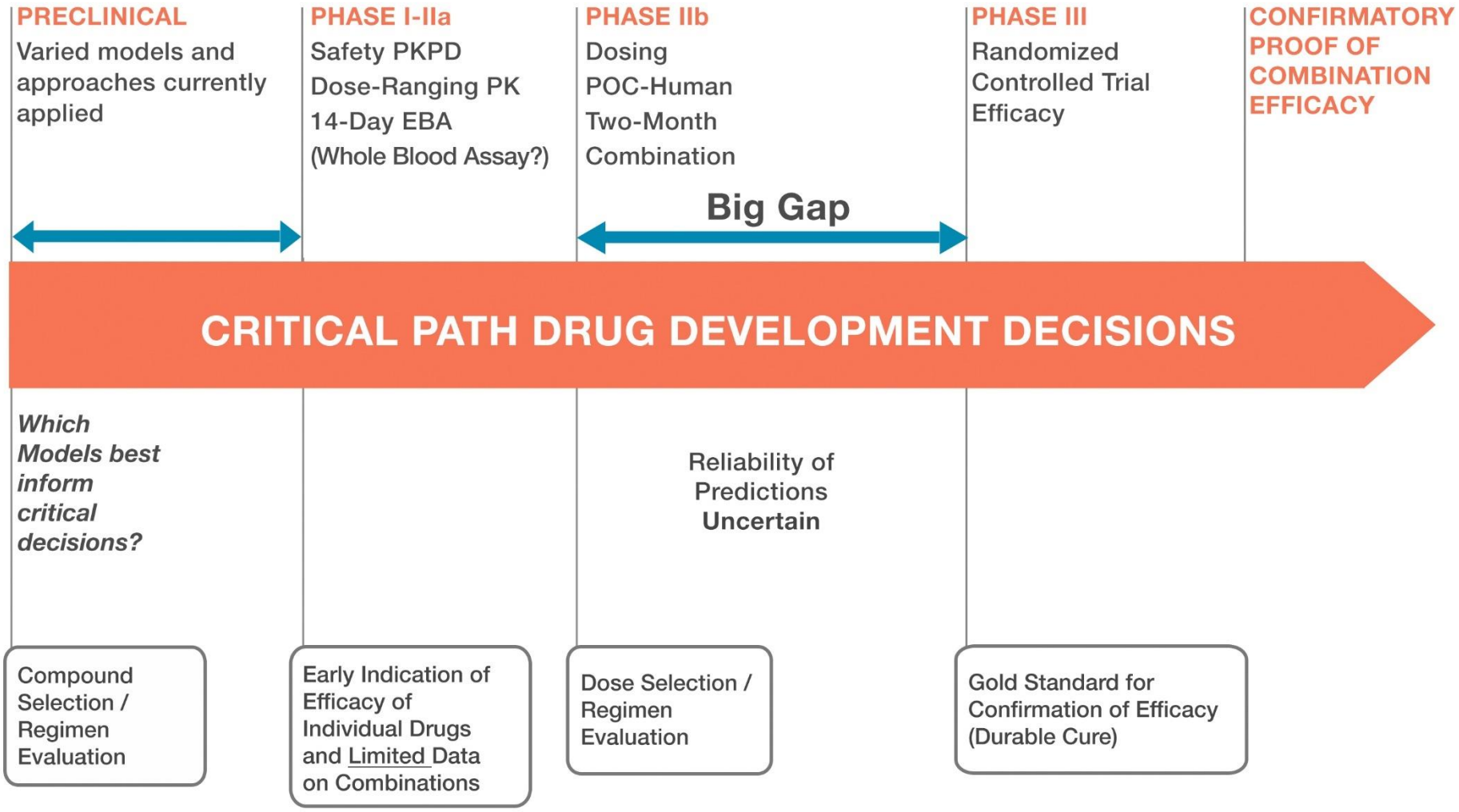
- HFS-TB model system
- CPTR multi-stage assessment evidence-based approach
- Predictive accuracy assessment leading to EMA qualification for use

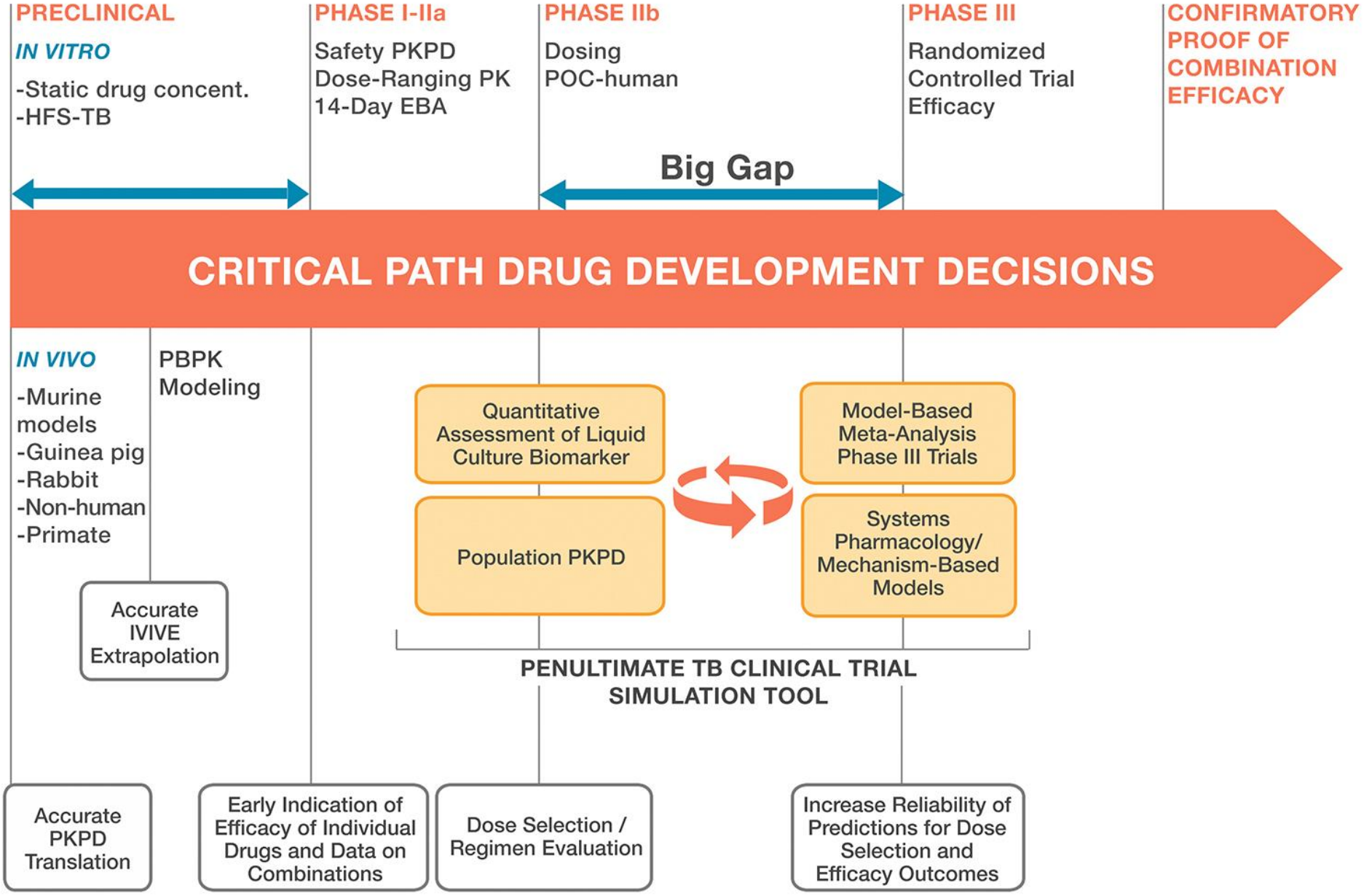
Reproducibility Assessment, Industrialization, Implementation

- Design and approach
- Summary results of experiments
- New work

Current TB Regimen Development
Risk of Late-Stage Attrition

Critical Path to TB Drug Regimens




PRECLINICAL
IN VITRO
-Static drug concent.
-HFS-TB
PHASE I-IIa
Safety PKPD
Dose-Ranging PK
14-Day EBA
PHASE IIb
Dosing
POC-human
PHASE III
Randomized
Controlled Trial
Efficacy
CONFIRMATORY PROOF OF COMBINATION EFFICACY
Big Gap
CRITICAL PATH DRUG DEVELOPMENT DECISIONS
IN VIVO
-Murine models
-Guinea pig
-Rabbit
-Non-human
-Primate
PBPK Modeling
Accurate IVIVE Extrapolation
Quantitative Assessment of Liquid Culture Biomarker
Population PKPD
Model-Based Meta-Analysis Phase III Trials
Systems Pharmacology/ Mechanism-Based Models
PENULTIMATE TB CLINICAL TRIAL SIMULATION TOOL
Accurate PKPD Translation
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

Mission

- Evidence-based evaluation of innovative drug development tools to address preclinical to clinical translation
- Focus on *in vitro* methodologies supporting efficacy and safety toxicology assessment
- Submission for regulatory endorsement

Goal

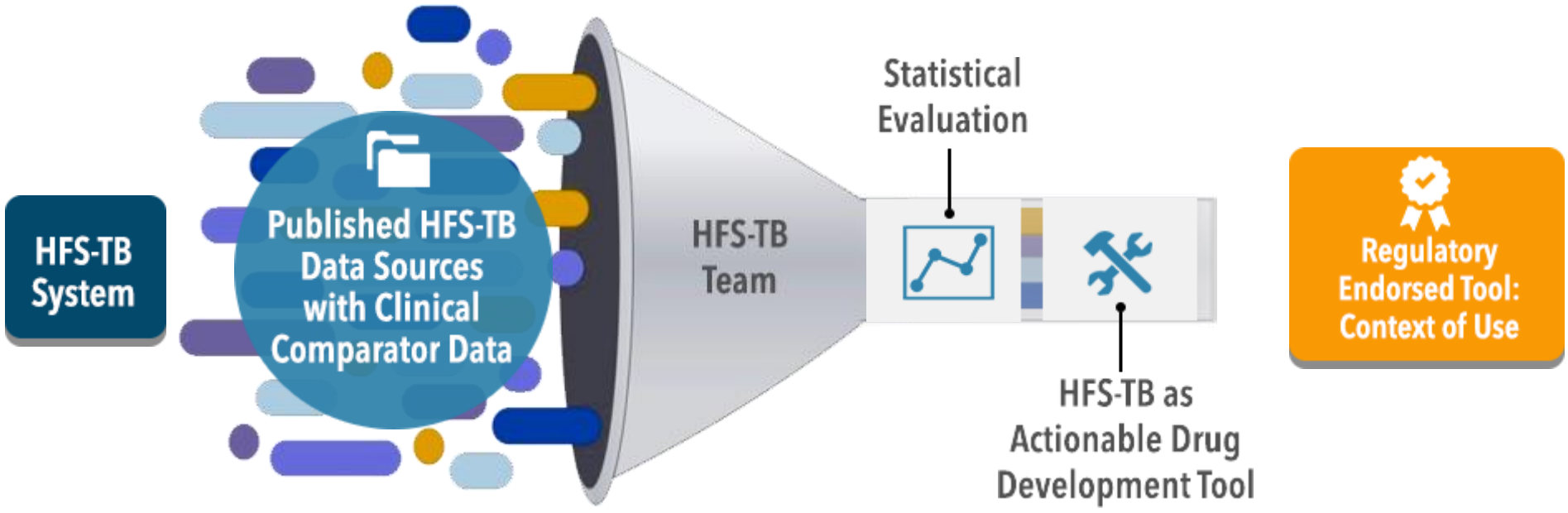
- Follow EMA and FDA Guidance on novel methodology and DDT qualification
- Gather all relevant published and unpublished data sources or aggregation
- Assess clinical translation of innovative preclinical novel methodologies/DDTs to test new TB drug candidates and regimens

HFS-TB Evidence

- Significantly more quantitative HFS-TB PKPD data available than for any *in vivo* methodology for TB
- Supported thorough assessment of predictive accuracy for clinical outcomes

Supportive Data Aggregation

Critical Path to TB Drug Regimens

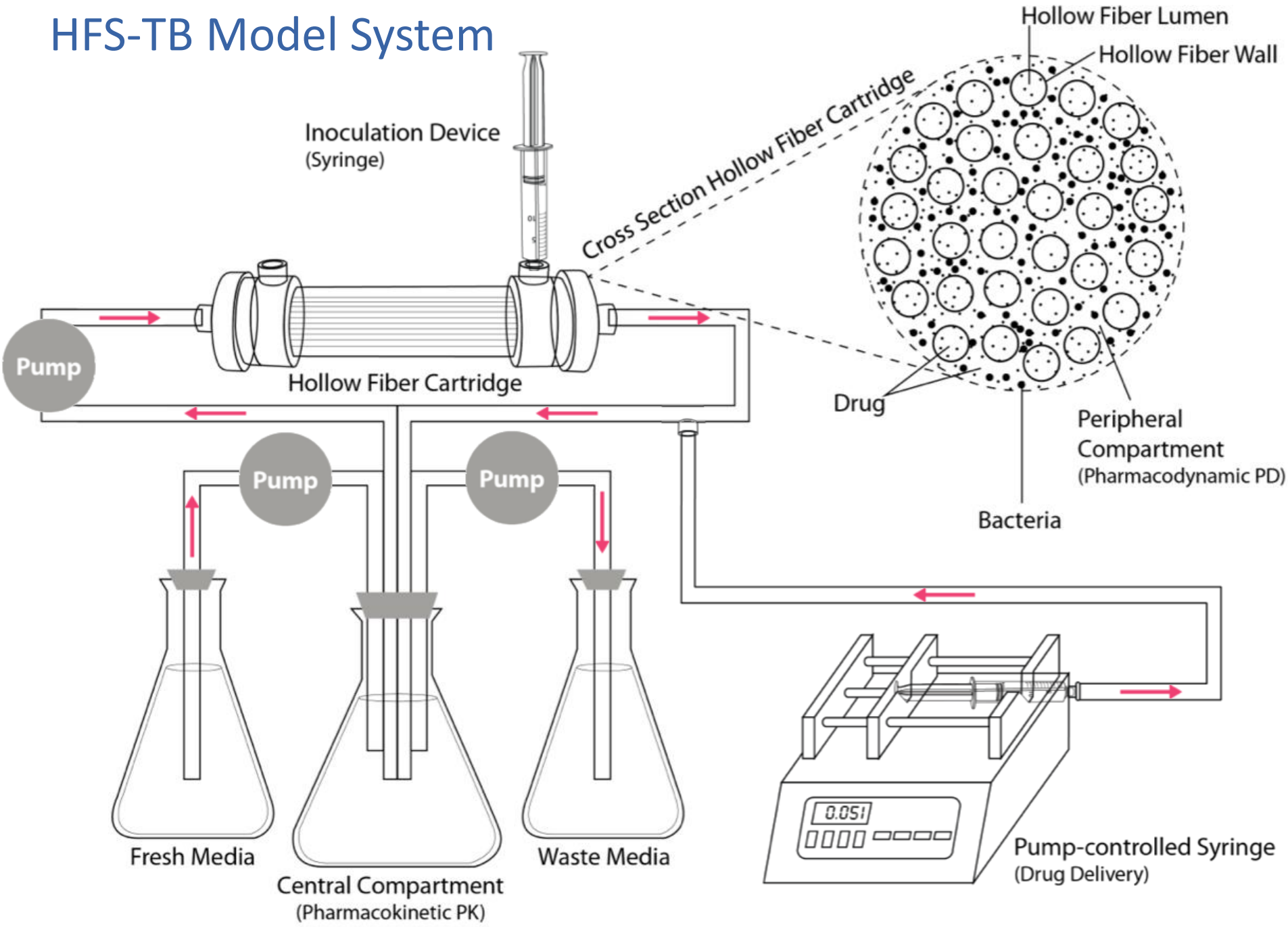


Regulatory Interactions for HFS-TB

Critical Path to TB Drug Regimens

- *HFS-TB qualified for use in drug development programs as additional and complementary tool*
- *HFS-TB can be used in regulatory submissions, esp. for informed design and interpretation of clinical studies*
- *HFS-TB is recommended to be useful as follows:*
  - ✓ To provide preliminary proof of concept for developing a specific drug or combination to treat tuberculosis
  - ✓ To select the pharmacodynamic target (e.g. $T_{>MIC}$, AUC/MIC)
  - ✓ To provide data to support PK/PD analyses leading to initial dose selection for non-clinical and clinical studies
  - ✓ To assist in confirming dose regimens for later clinical trials taking into account human PK data and exposure-response relationships

HFS-TB Model System



HFS-TB Inputs and Outputs

Critical Path to TB Drug Regimens

INPUTs

- Human PK Parameters
- Static, in vitro MICs or in vivo preclinical PK/PD

Experimental Conditions

- Monotherapy, Combinations, Staged
- Log-Growth
- Semi-Dormant
- Intracellular
- Future: Mimic granuloma or lung tissue PK and growth condition
- Dynamic, longitudinal

OUTPUTs

- PDI, Dose Fractionation
- Target Clinical Dose
- Additive/Synergistic/ Sub-additive
- Rate of killing
- Rate of resistance emergence
- Rank regimens
- EBA slope prediction
- SSCC prediction
- ADR prediction

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Reproducibility Assessment, Industrialization, Implementation

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- Summary results of experiments
- New work

Objectives

- Characterize signal-to-noise in HFS-TB system under all growth conditions
- Jan 2014-Feb2016

Design
162 Experiments

- 6 Treatment arms
  - Positive control = HRZE
  - REMox1 = MRZE
  - REMox2= HRZM
  - High Dose MRZ
  - H 3 days = MRZ
  - Untreated Control
- 3 Growth Conditions
  - Log
  - Semi-dormant
  - Intracellular
- 3 Teams
  - Leader + 4 laboratorians
- All Expts in Triplicate

Experimental Questions

- Variability in PK measurement
  - Intra and inter experiment
  - Ability to achieve targeted AUC and Cmax
- Variability in kill rates
  - Across growth phases

Results: HFS-TB REMox Reproducibility

Critical Path to TB Drug Regimens

System Reliably Achieves Targets for Cmax and AUC

Drug	PK parameter	Target	Observed Mean ±SD	%CV	MAPE (%)	% Accuracy (95% CI)	% Bias (95% CI)
INH	Peak (mcg/mL)	6.80	6.65±0.29	4.03	3.87	96.10 (95.40-96.90)	2.19 (1.32 to 3.06)
INH	AUC_{0-24} (mcg*hr/mL)	24	25.80±1.30	5.05	8.07	91.90 (90.90-93.00)	-7.58 (-8.75 to -6.38)
RIF	Peak (mcg/mL)	6.0	6.1±0.11	1.75	1.50	98.00 (98.00-99.00)	-1.17 (-1.58 to -0.80)
RIF	AUC_{0-24} (mcg*hr/mL)	22	25.00±1.30	5.45	12.00	88.00 (87.00-89.00)	-11.81 (-13.19 to -10.45)
Hi RIF	Peak (mcg/mL)	18.0	18.00±0.30	1.65	1.8	98.0 (98.00-99.00)	1.67 (-2.17 to -1.22)
Hi RIF	AUC_{0-24} (mcg*hr/mL)	66.0	70.00±2.90	4.11	6.50	93.00 (92.00-95.00)	-6.36 (-7.27 to -5.00)
PZA	Peak (mcg/mL)	54	50.0±0.11	3.48	7.35	92.60 (91.90-93.40)	7.94 (7.18 to 8.72)
PZA	AUC_{0-24} (mcg*hr/mL)	390	430±29.5	6.85	10.80	89.20 (87.70-90.70)	-9.53 (-11.95 to -8.62)
Hi PZA	Peak (mcg/mL)	108	99.50±2.88	2.89	7.85	92.10 (91.40-92.90)	7.85 (7.13 to 8.58)
Hi PZA	AUC_{0-24} (mcg*hr/mL)	780	815.0±56.90	6.98	6.08	93.90 (92.30-95.50)	-4.43 (-6.42 to -2.44)

Results: HFS-TB REMox Reproducibility

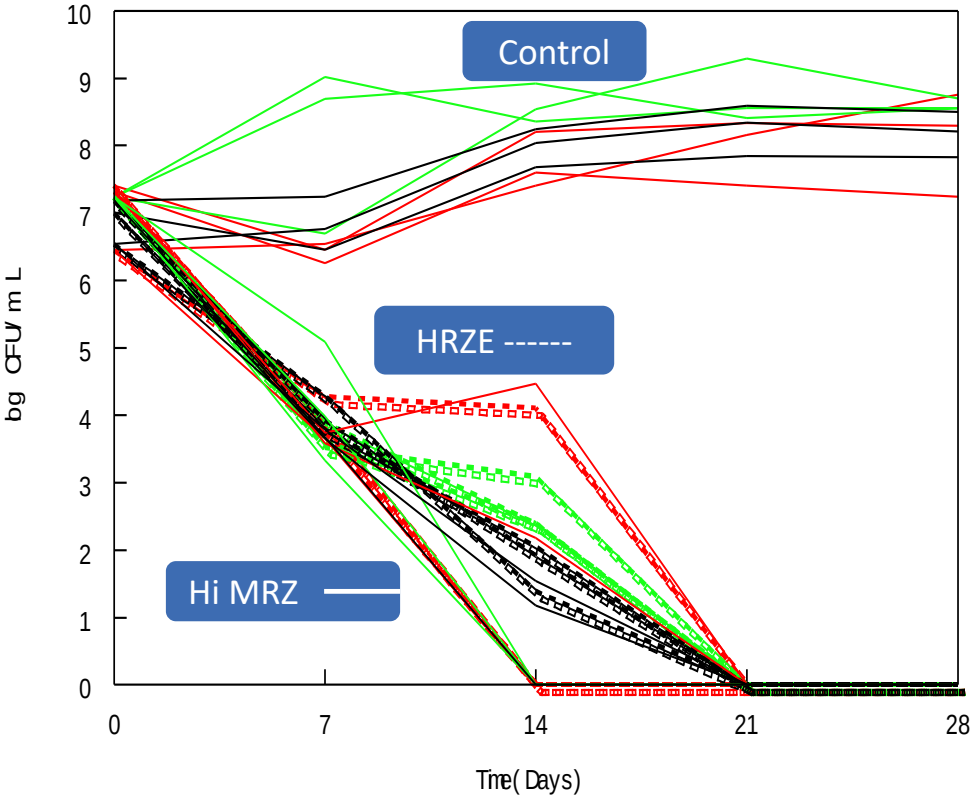
Critical Path to TB Drug Regimens

System Reliably Achieves Targets for Cmax and AUC

Drug	PK parameter	Target	Observed Mean ±SD	%CV	MAPE (%)	% Accuracy (95% CI)	% Bias (95% CI)
E	Peak (mcg/mL)	6.30	6.29±0.07	1.18	0.88	99.10 (98.90-99.30)	0.11 (-0.22 to 0.43)
E	AUC_{0-24} (mcg*hr/mL)	23	22.50±0.55	2.44	2.72	97.30 (96.80-97.80)	2.34 (1.68 to 2.99)
M	Peak (mcg/mL)	4.2	4.10±0.09	2.16	2.66	97.30 (96.90-97.80)	2.30 (1.73 to 2.88)
M	AUC_{0-24} (mcg*hr/mL)	45	42.30±2.80	6.60	7.50	92.50 (91.40-93.60)	5.93 (4.24 to 7.62)
Hi M	Peak (mcg/mL)	8.4	8.13±0.20	2.50	3.39	96.60 (96.0-97.20)	3.20 (2.54 to 3.86)
Hi M	AUC_{0-24} (mcg*hr/mL)	90	84.50.±4.88	5.70	6.45	93.50 (92.20-94.90)	6.14 (4.67 to 7.62)

Log Phase Time Course

(Control, HRZE, High Dose MRZ)

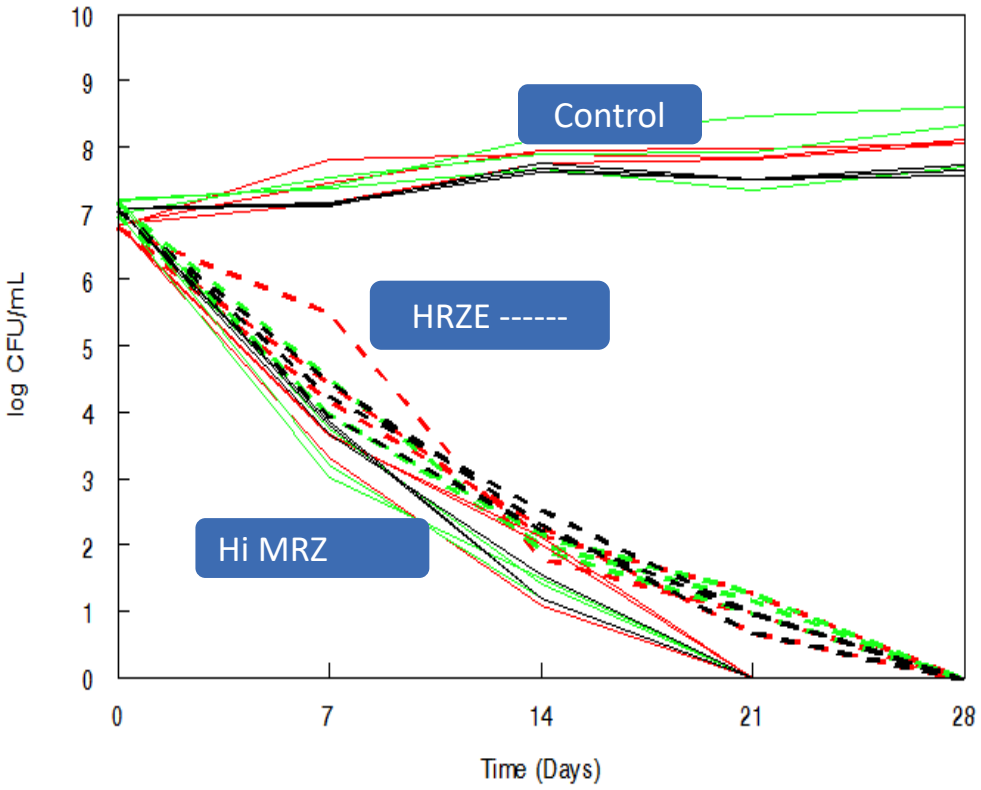


- All teams found equivalent results for the different groups
- The HRZE and High MRZ groups showed a marked difference against the untreated control
- However, the HRZE and High MRZ groups achieved similar treatment effects

*Updated 20JAN2017

Semi-Dormant Time Course

(Control, HRZE, High Dose MRZ)

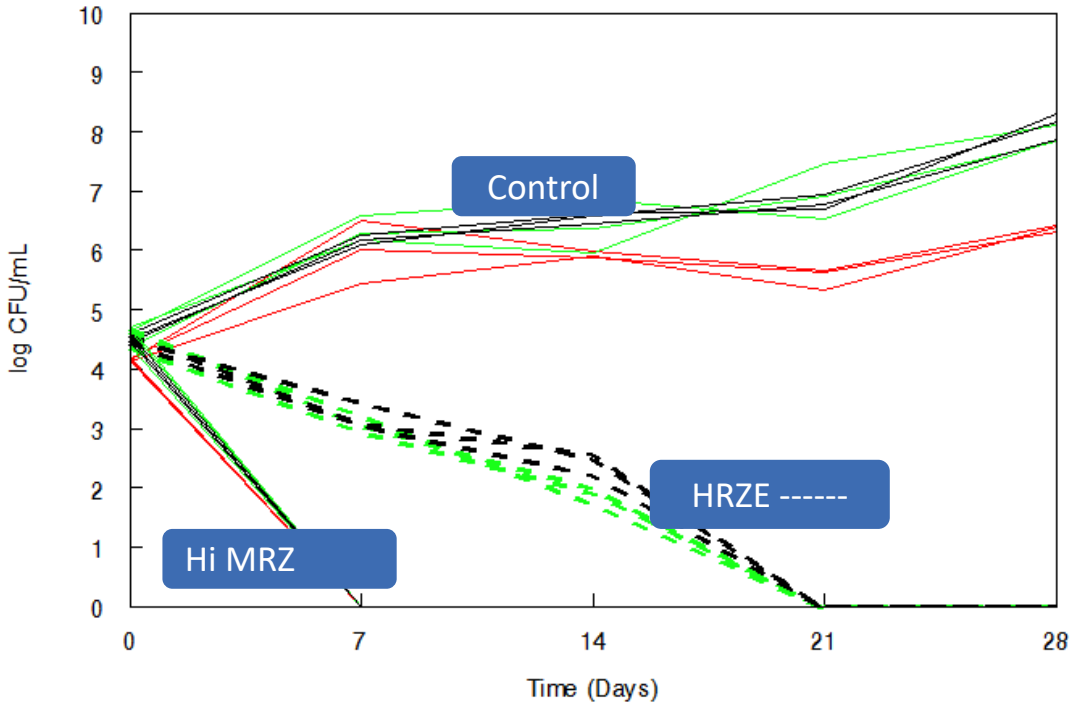


- As in the Log-Phase condition, the experimental teams found equivalent results for the different groups
- The HRZE and High MRZ groups showed a marked difference against the untreated control
- However, the HRZE and High MRZ groups achieved similar treatment effects
- Given the reduced bacterial activity in semi-dormant condition, the overall variability in results was reduced across groups

*Updated 20JAN2017

Intracellular Time Course

(Control, HRZE, High Dose MRZ)



- The results were consistent across teams
- The HRZE and High MRZ groups showed a marked difference against the untreated control
- However, unlike in the other two metabolic conditions, the intracellular experiments showed a marked difference between all three groups, favoring the High MRZ regimen

*Updated 20JAN2017
Data Issue: HRZE

When to Apply HFS-TB

Critical Path to TB Drug Regimens

- ✓To provide preliminary proof of concept for developing a specific drug or combination to treat tuberculosis
- ✓To select the pharmacodynamic target (e.g. T/MIC, AUC/MIC)
- ✓To provide data to support PK/PD analyses leading to initial dose selection for non-clinical and clinical studies, with the aim of limiting the number of regimens that are to be tested in vivo
- ✓To assist in confirming dose regimens for clinical trials taking into account the accumulated human PK data in healthy volunteers, patients 7 available information on exposure-response relationships

New HFS-TB Work

Critical Path to TB Drug Regimens

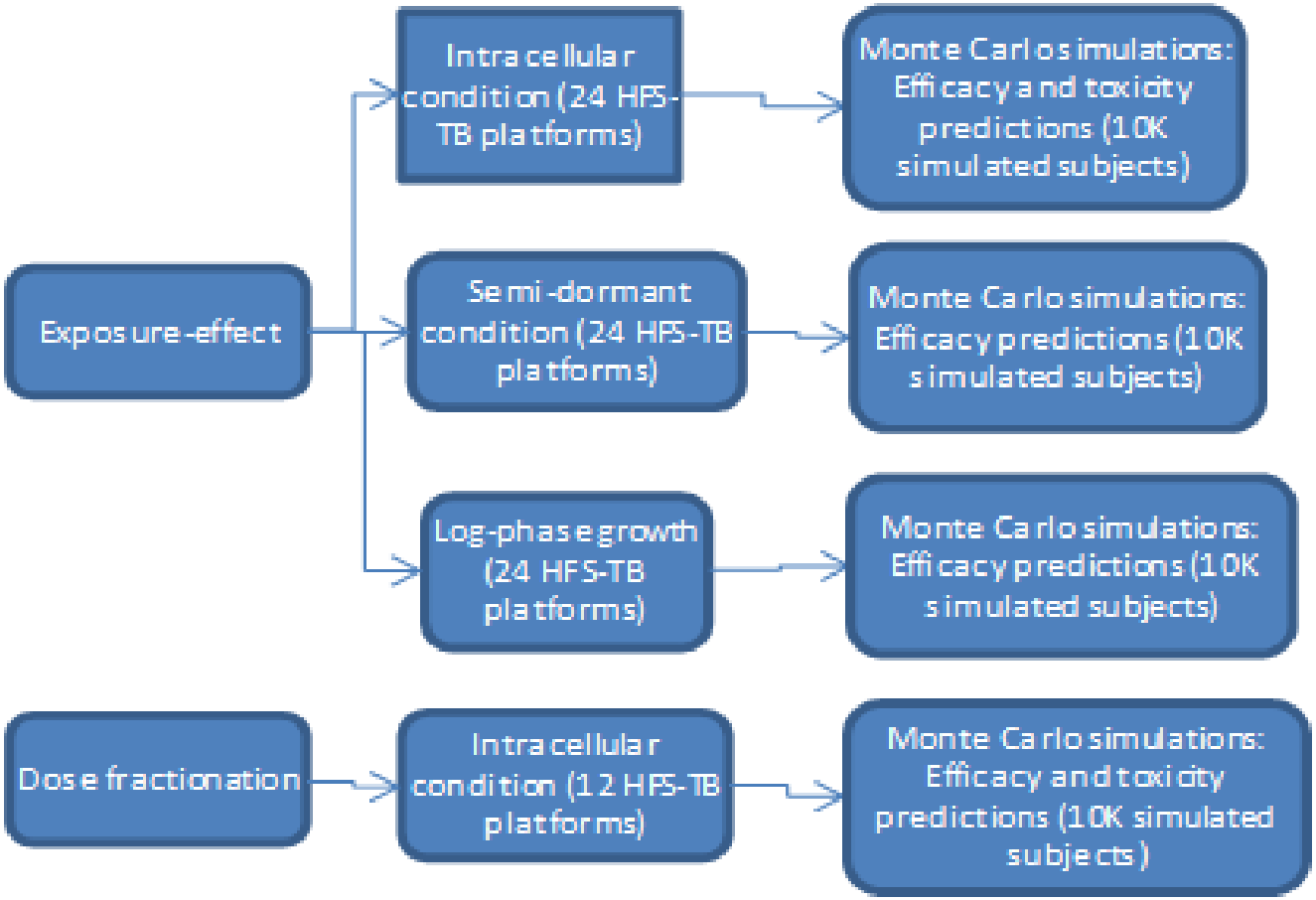
- Prospective combination studies (1000 + HFS TB Units)
  - Ex: PaMZ
- New, emerging drugs of interest aligning with Pharma and TB Accelerator partners
- Expand capacity with partner lab

Thank you

A special thank you to the Baylor laboratory team and the CPTR Pre-Clinical and Clinical Sciences Workgroup

HFS-TB New Work Experimental Schema

Critical Path to TB Drug Regimens



HFS-TB Stage New Work Experimental Schema (continued)

Summary Points

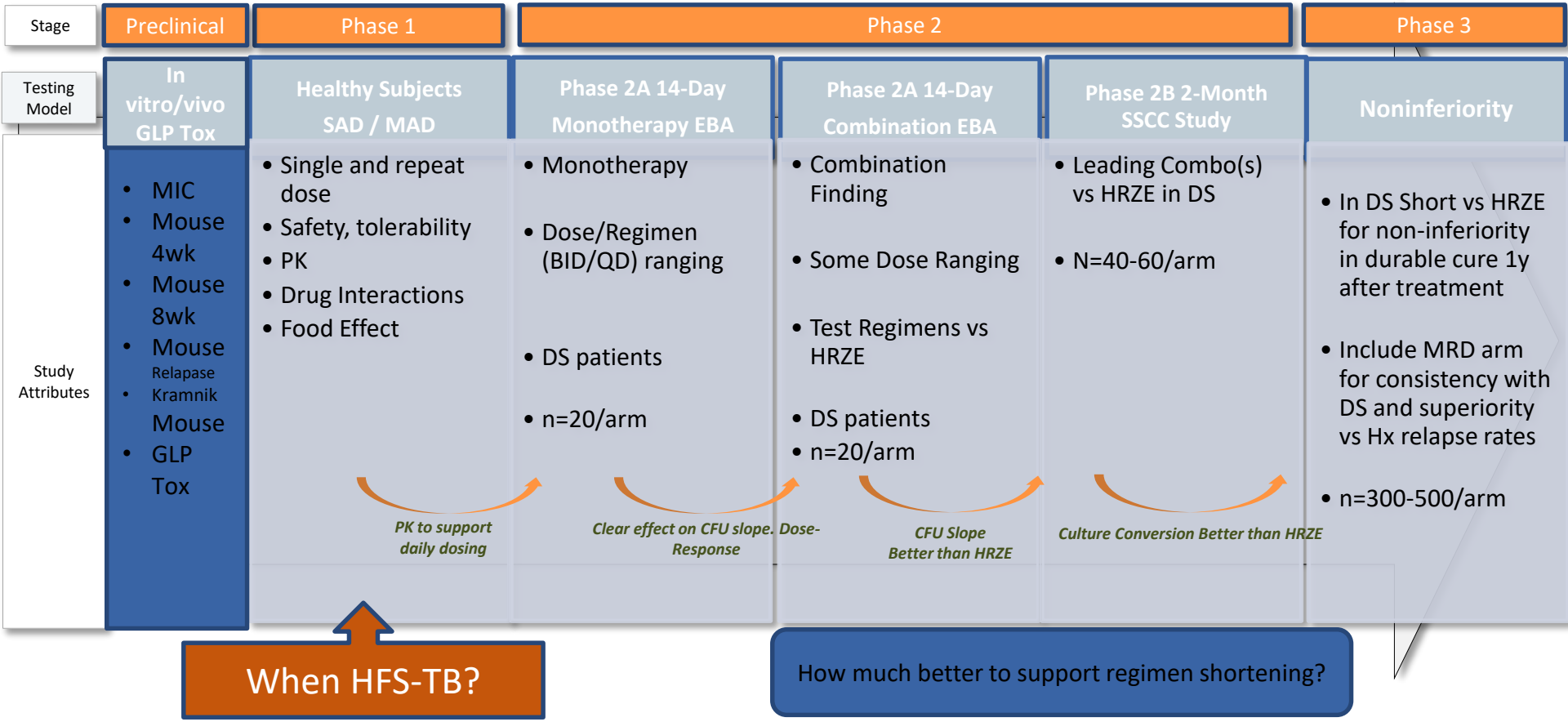
Critical Path to TB Drug Regimens

- Initial step to address the “translational gap” is to learn what data from what models analyzed in what way informs key trial design decisions
- Evidence-based validation of preclinical models is important:
  - To confidently place preclinical models on the critical development path
  - To increase the efficiency of regulatory interactions
  - To set a precedent for objective, data-driven process to apply to other models and tools (e.g., C3HeB/FeJ mouse, marmoset)
  - To identify/clarify knowledge and tool gaps to drive future research
- The successful HFS-TB qualification process has accomplished each of these goals
- Evaluation of sterilizing mouse model is the appropriate next step, with other models to follow

- **Analysis Objective** to determine predictive accuracy of HFS-TB outputs for clinical trial results
- **Literature Search** to identify relevant HFS-TB and clinical data from published literature
- **Systematic Review** to summarize HFS-TB-generated hypotheses and outcomes of clinical trials
- **Quality of Evidence Scoring** to provide basis for weighting in the predictive accuracy analysis
- **Statistical Analysis** comparing HFS-TB predictions with clinical findings to examine:
  - descriptive correlations where HFS-TB studies post-dated clinical studies
  - predictive accuracy where HFS-TB studies pre-dated clinical studies

Unified Development Pathway

Critical Path to TB Drug Regimens



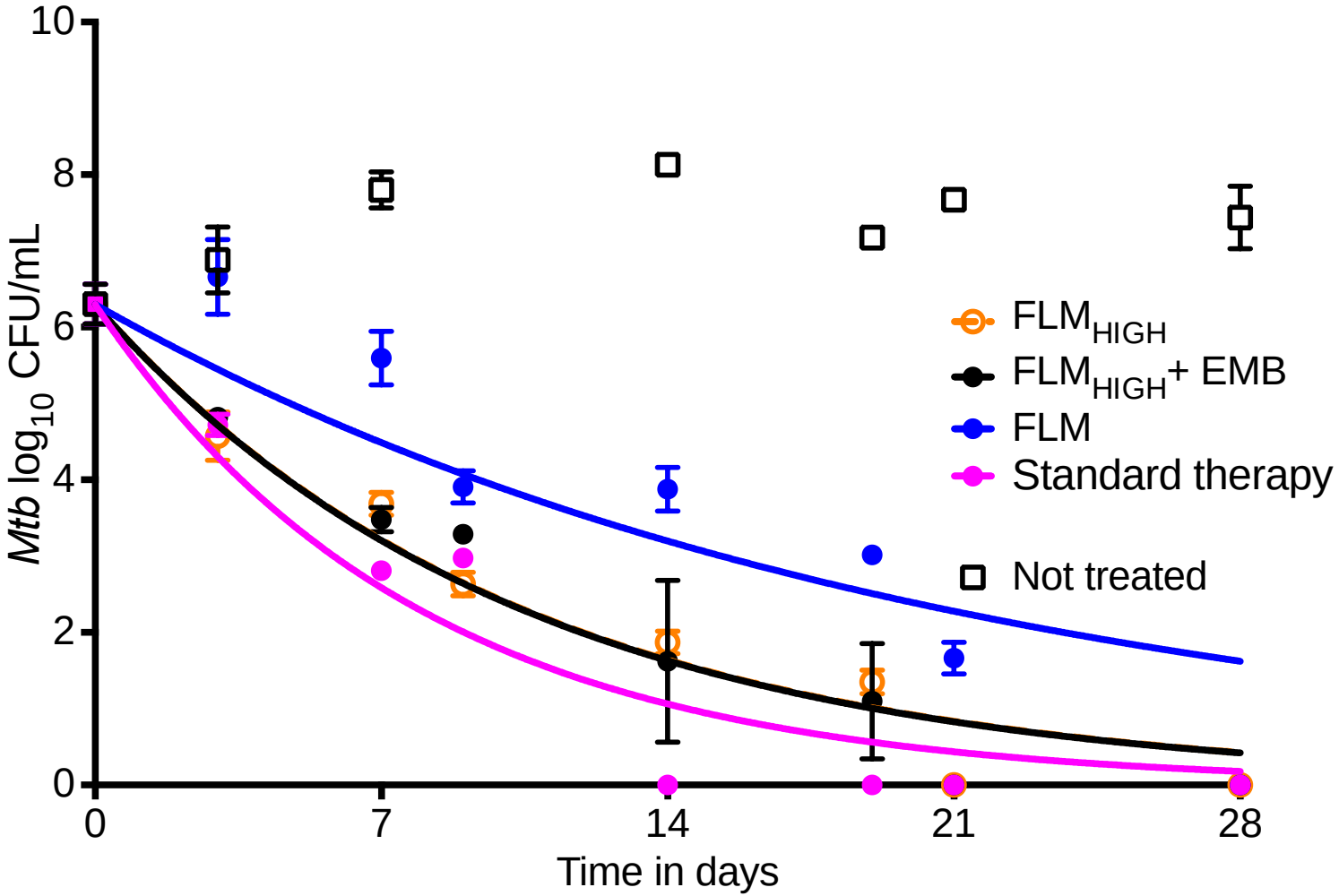
HFS-TB Stage II – Project Plan

Critical Path to TB Drug Regimens

	Intracellular	SDB	Log-phase	# of experiments	# HFS	Time in weeks	Start Date	End Date
PaMZ	9	9	15	3	33	8	1/2/2017	2/24/2017
Del PK	8	5	5	3	18	1	2/27/2017	3/6/2017
Del	36	24	24	3	84	8	2/27/2017	4/21/2017
OPC-167832	36	24	24	3	84	8	4/24/2017	6/16/2017
Break						2	6/19/2017	6/30/2017
OPC-167832 + Del	36	24	24	3	84	8	7/3/2017	8/25/2017
OPC-167832 + Del + Oxa	36	24	24	3	84	8	8/28/2017	10/20/2017
Del & Ba	36	24	24	3	84	8	10/23/2017	12/8/2017
OPC-167832 + Del + Ba	36	24	24	3	84	8	12/11/2017	2/2/2018
Break						2	2/5/2018	2/16/2018
Sutezolid	36*	24	24	3	84	8	2/19/2018	4/13/2018
BaPZ	9	9	15	3	33	8	4/16/2018	6/8/2018
Oxa + Far + Del	18	18	30	3	66	8	6/11/2018	8/3/2018
Break						2	8/6/2018	8/17/2018
Oxa + Pa + Ba	18	18	30	3	66	8	8/20/2018	10/12/2018
AZD5847	36	24	24	3	84	8	10/15/2018	12/7/2018
Oxa + Far + Pa	18	18	30	3	66	8	12/10/2018	2/1/2019
Break						2	2/4/2019	2/15/2019
Oxa + Pa + Ba + Far	15	15	20	3	50	8	2/18/2019	4/12/2019
Oxa +M + Far + Z	15	15	20	3	50	8	4/15/2019	6/7/2019
Final Report Preparation						8	6/10/2019	8/1/2019
TOTAL	362	299	357	48	1054	137		

New Regimen Design: "FLAME"

Critical Path to TB Drug Regimens



Deshpande et al. A faropenem, linezolid, and moxifloxacin regimen for both drug susceptible and multidrug-resistant tuberculosis in children. Clin Infect Dis. 2016;63:S95

HFS-TB REMox Reproducibility Assessment

Critical Path to TB Drug Regimens

- Objectives: Characterize reproducibility and signal to noise in HFS-TB system under different growth conditions (Jan 2014-Feb 2016)
- Design:
  - 6 treatment arms
    - Positive Control – HRZE
    - REMox 1 – MRZE
    - REMox 2 – HRZM
    - Hi Dose MRZ
    - H 3 Days+Hi Dose MRZ
    - Control
  - Three conditions: Log-Phase, Semi-dormant, Intracellular
  - Three separate teams (Each team included a Team Leader and 4 supporting lab techs)
  - Each team runs each experiment in triplicate
  - Total of 162 HFS-TB experiments (6 regimens x 3 conditions x 3 teams x 3 replicates)

Results: HFS-TB REMox Reproducibility

Critical Path to TB Drug Regimens

- Typical inter-day assay variability (CV%) is 5-10% for a PK assays
- In HFS experiments CV%s in drug concentration across time were typically ≤ **(Passed Go / No Go)**
- At end of dosing intervals for INH and RIF CV%s up to 25% were observed, however SDs remained consistent with other time points (e.g., this is a function of low mean conc where CV% is SD/mean)
- Variability in PK concentrations attributed to TEAM was very low across drugs (<0.1% of total variance).
- Low variability expected due to administration via programmed syringe pump