



Critical Path to TB Drug Regimens Role in Facilitating TB Drug Development

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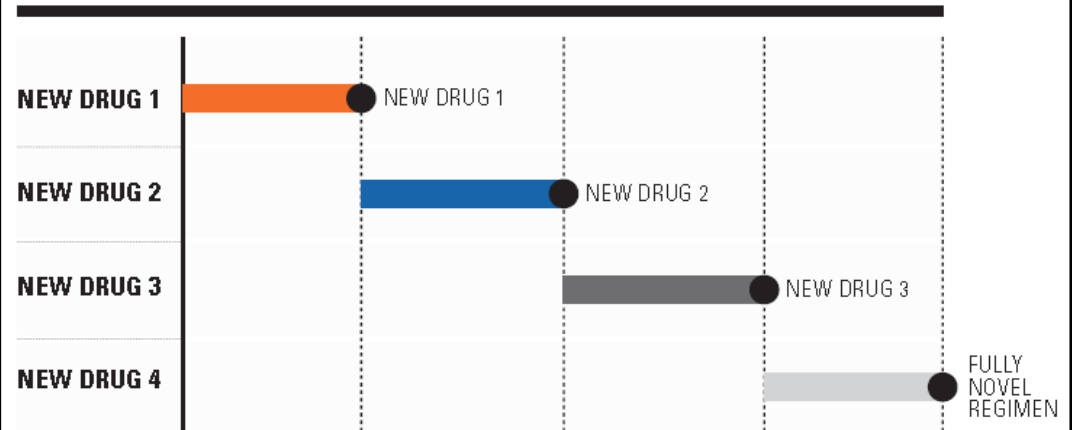
Novel regimen development requires emphasis on combination study approaches

Define, based on evidence, best drug development tools to de-risk compounds and improve understanding of efficacy

Define, based on evidence, novel biomarkers to inform improved trial design and adaptivity

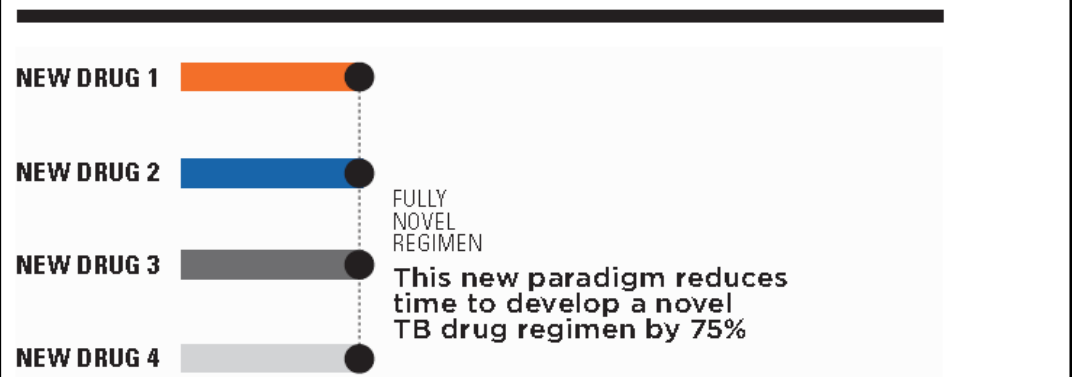
CURRENT REGIMEN DEVELOPMENT PARADIGM:

Existing regimen consists of four drugs



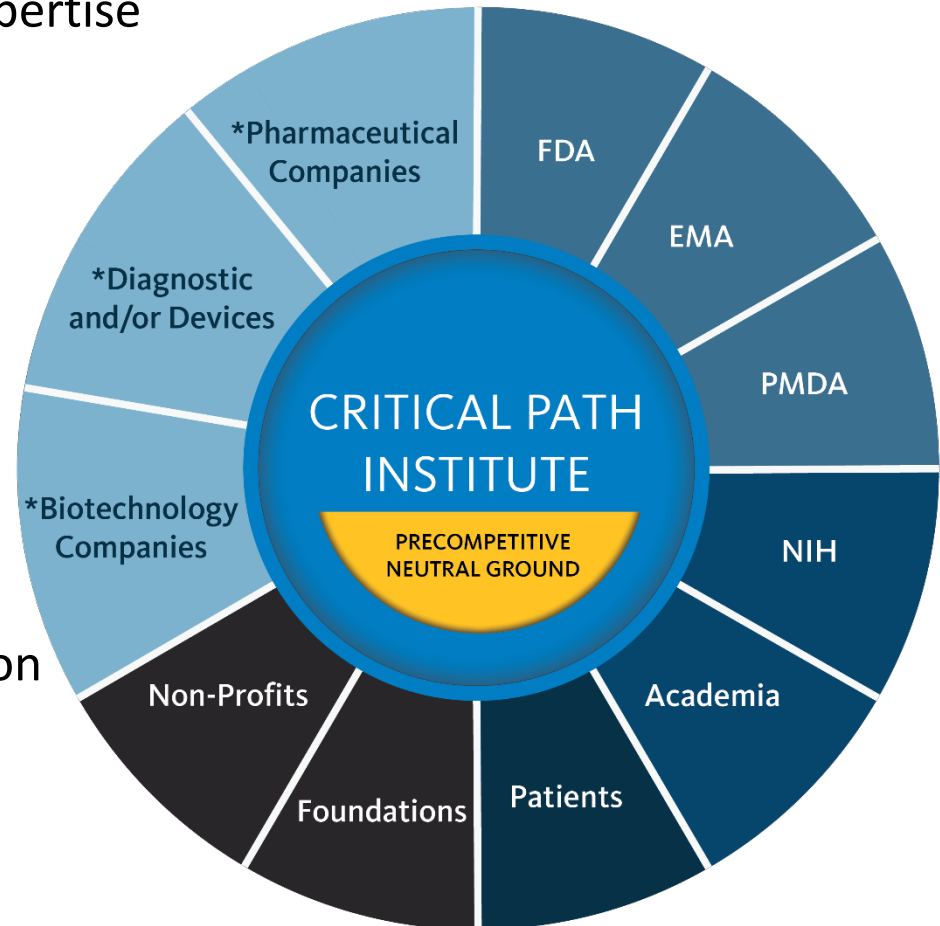
NOVEL COMBINATION TESTING PARADIGM:

Novel regimen development can reduce the time to develop a new TB drug regimen by 75%:



- **Mission:** The Critical Path to TB Drug Regimens (CPTR) is a cross-sector initiative that aims to speed the development of safer and shorter duration anti-tuberculosis (TB) drugs. Focus on:
 - drug development tools and methodologies to support go/no-go decisions during each stage of research and development
 - curation of supportive data through establishment of collaboration network to support new methods and tool validation (and ensure public access wherever possible)
 - developing pathways for new TB treatment regimens that include drugs that are not yet individually approved
 - providing regulatory excellence in the development, validation, and advancement of these drug development tools and methodologies
- **CPTR Partners and Members:** Consortium of 8 pharma / 18 diagnostic companies, 26 academic institutions, 20 NGOs, and 5 governmental bodies.

- Act as a trusted, neutral third party
- Convene scientific consortia of industry, academia, and government for pre-competitive sharing of data/expertise
 - ✓ The best science
 - ✓ The broadest experience
 - ✓ Active consensus building
 - ✓ Shared risk and costs
- Enable iterative EMA/FDA/PMDA participation in developing new methods to assess the safety and efficacy of medical products
- Pursue official regulatory recognition through “qualification” of Novel Methodologies and Drug Development Tools

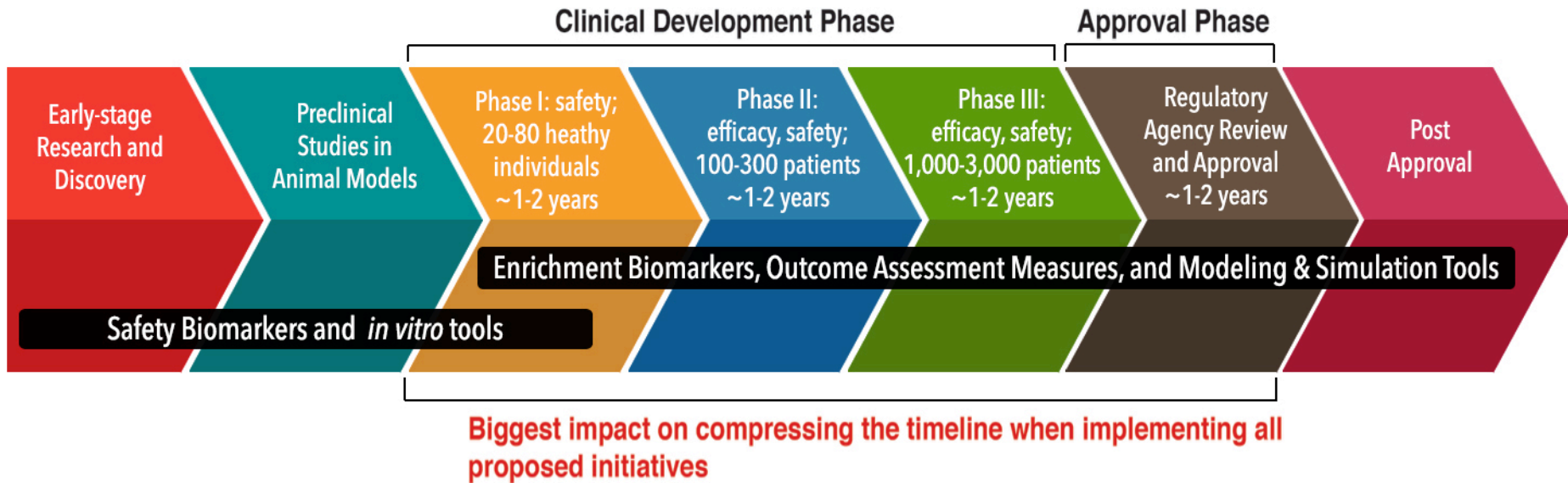


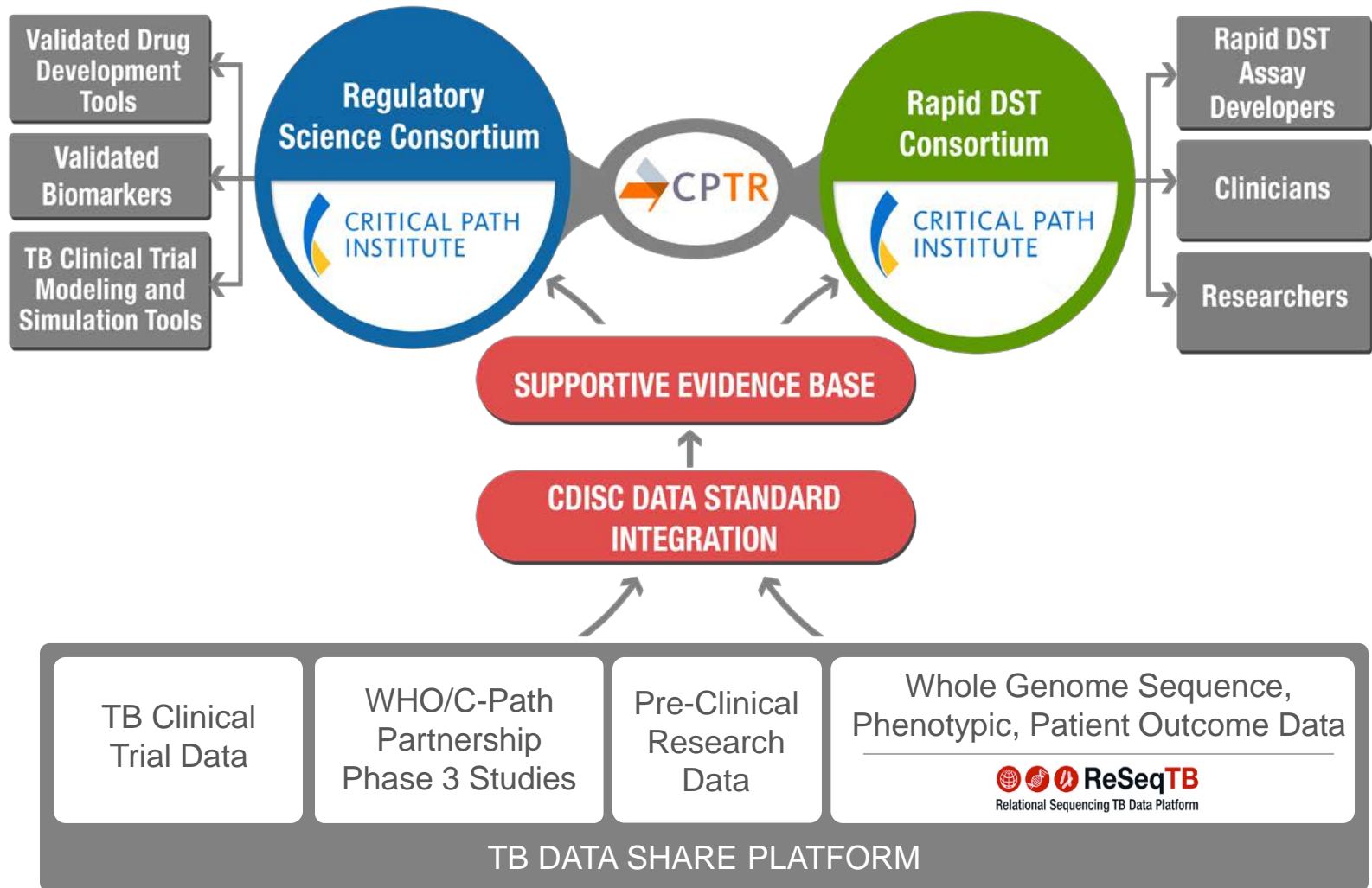
*Multiple companies within each sector



Start at the end approach: Up-front conversations around the context of use (COU) since the COU drives the level of evidence needed

- ✓ Data Standardization and Sharing
- ✓ Biomarker Development and Qualification
- ✓ Clinical Outcome Assessment Measures
- ✓ Modeling and Simulation Tools





GAPS IN THE TB DRUG DEVELOPMENT PROCESS



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

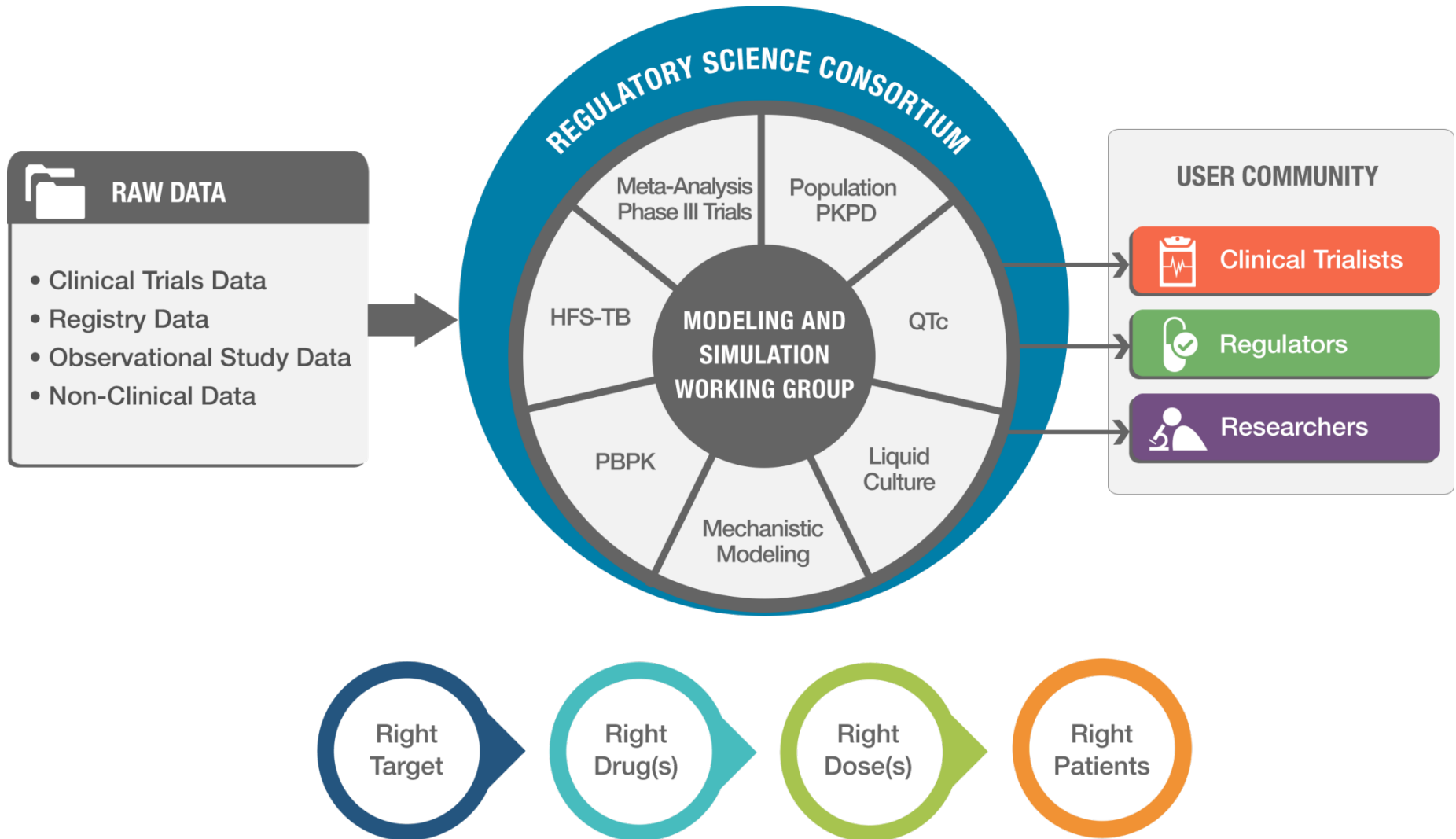
PENULTIMATE TB CLINICAL TRIAL SIMULATION TOOL

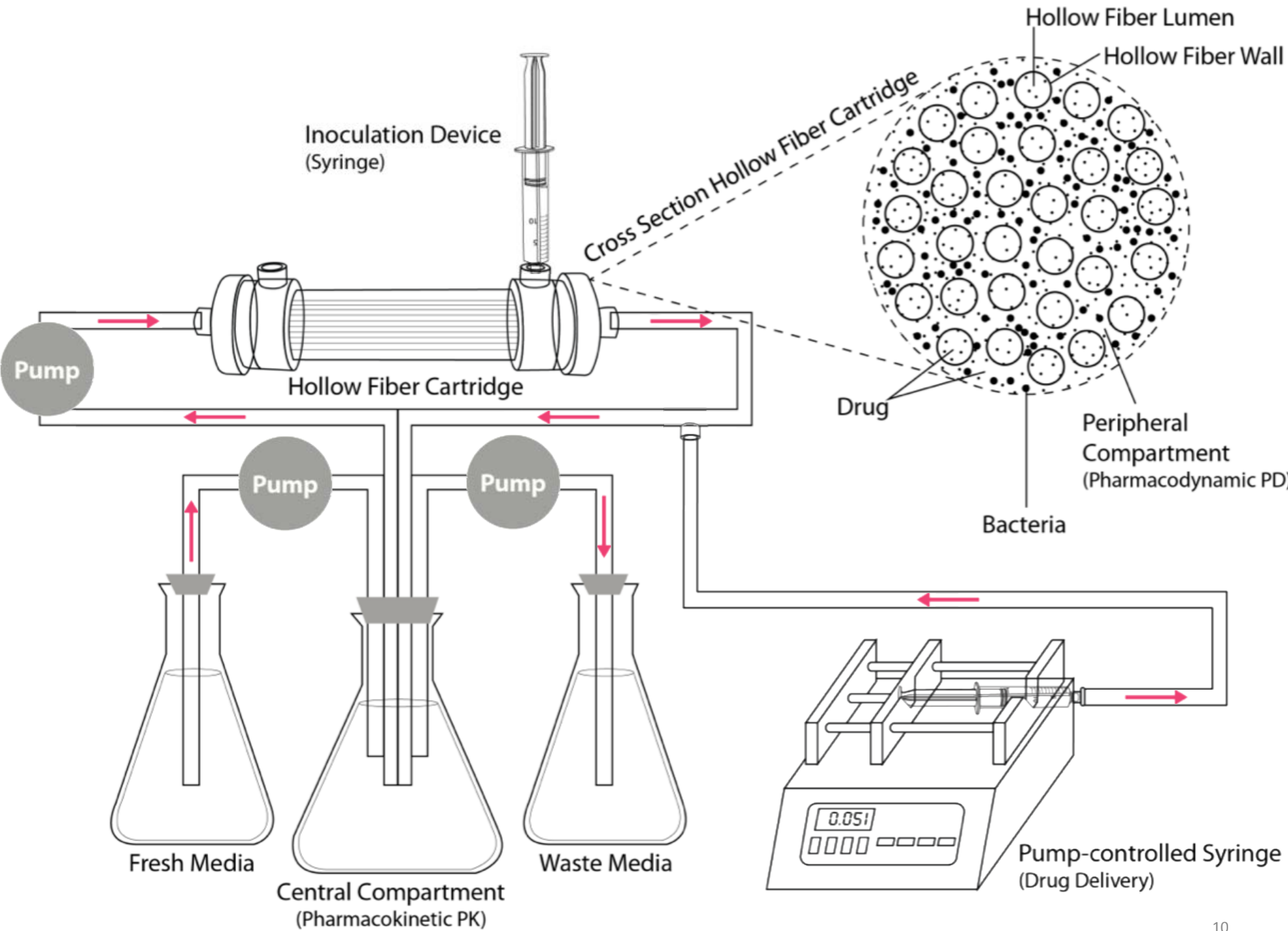
Accurate
PKPD
Translation

Early Indication of
Efficacy of Individual
Drugs and Data on
Combinations

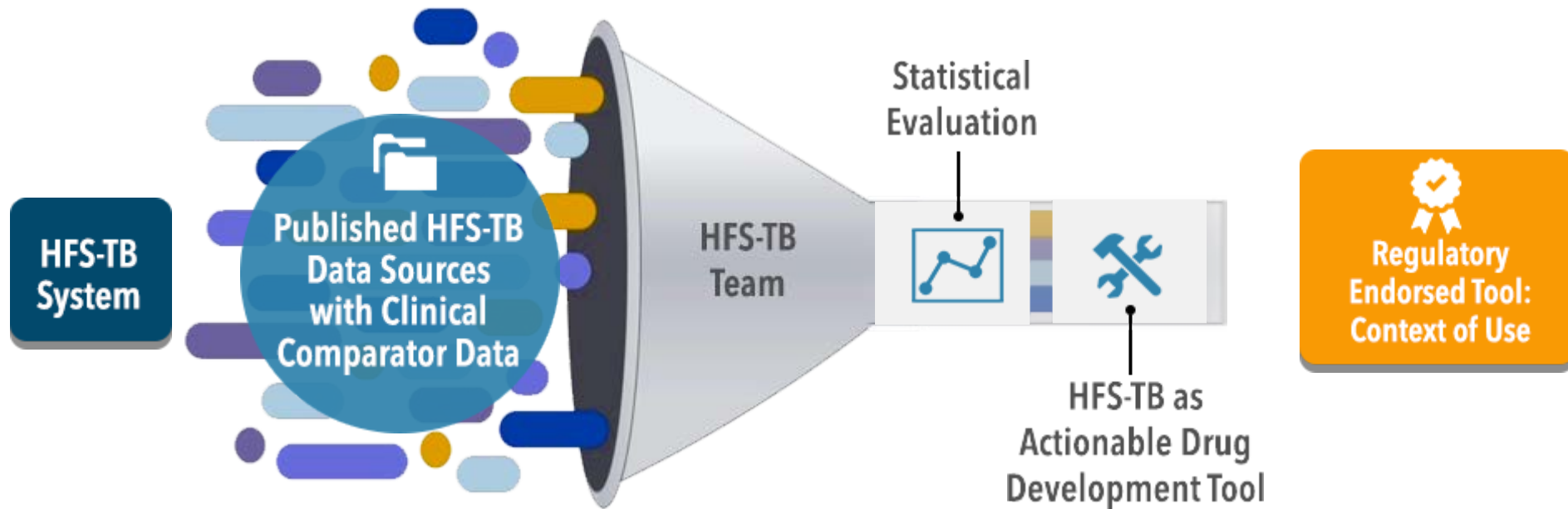
Dose Selection /
Regimen Evaluation

Increase Reliability of
Predictions for Dose
Selection and
Efficacy Outcomes





EVIDENCE BASED EVALUATION OF HOLLOW FIBER SYSTEM MODEL FOR TB

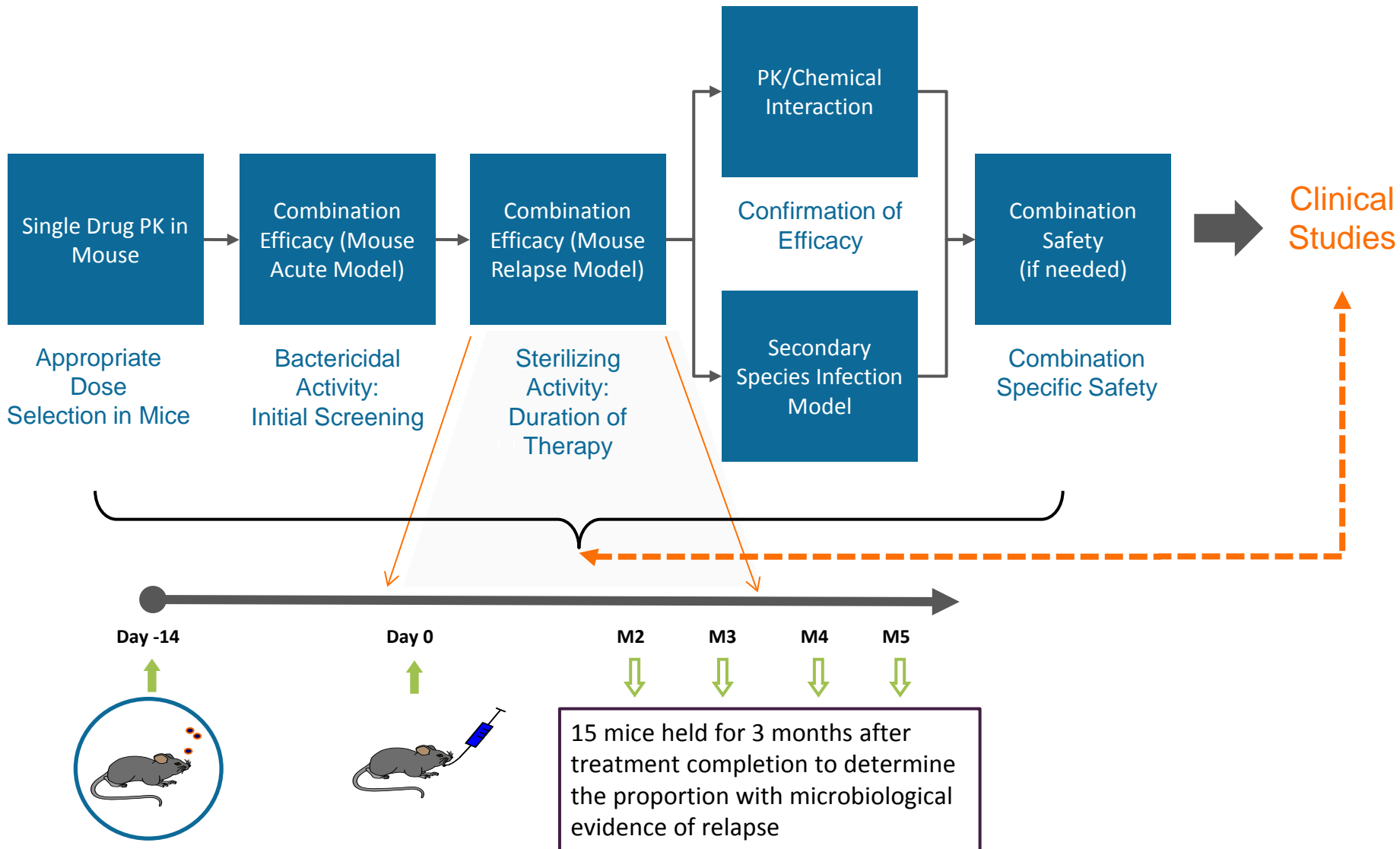


REGULATORY INTERACTIONS ON HFS-TB QUALIFICATION



- 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 TB
 - ✓ 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

MOUSE MODEL OF STERILIZING ACTIVITY



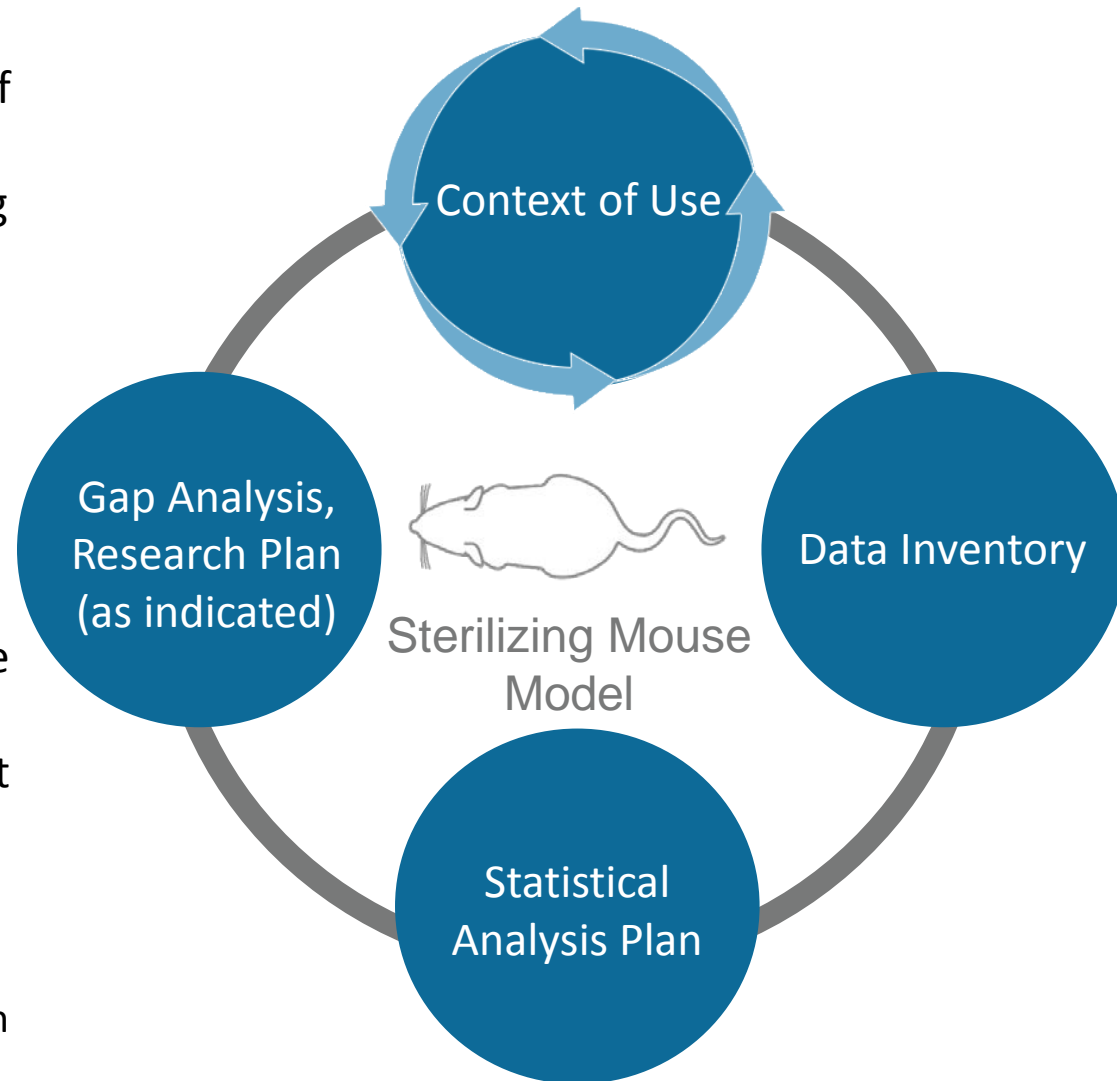
General Aim:

Quantify the predictive accuracy of mouse TB efficacy models to estimate the treatment-shortening potential of a test regimen, by evaluating differences in the treatment duration necessary to prevent relapse compared to control (standard TB regimen).

Intended Application:

The data from experiments in mice infected with *M. tuberculosis*, using relapse as the main endpoint will be used to:

- Calculate treatment effect sizes, to then rank-order regimens
- Estimate clinical treatment duration



High unmet need for real-time assessment of efficacy in TB drug development trials

- Field requires a tool that:
 - Assesses Early Bactericidal Activity (EBA) and Sputum Culture Conversion (SCC), endpoints recommended by FDA and EMA, in real-time, allowing for quick decision making
 - Reduces cost associated with delayed results in development of drugs for TB, a therapeutic area with limited treatment options and few commercial incentives
 - Can be easily utilized in any laboratories that are suitable for clinical trials
 - Is not affected by contamination or drug carry-over effect
- EBA and SCC are useful but challenging to conduct
 - Time delays and labor intensive
 - Issues with contamination and drug carry over effects

- LAM: Lipoarabinomannan; a major cell wall component
- A new immunoassay was developed (LAM-ELISA) that measures sputum LAM
 - Specific for LAM from MTB and a few slow growing mycobacterium strains
 - No cross-reactivity with oral bacteria
 - Strong correlation between sputum LAM and cfu counts/TTD
- Not affected by contamination or drug carry-over
- LAM-ELISA: 20 min LAM extraction; 5 hours ELISA
- Quicker tests being developed (results in <1 hour)

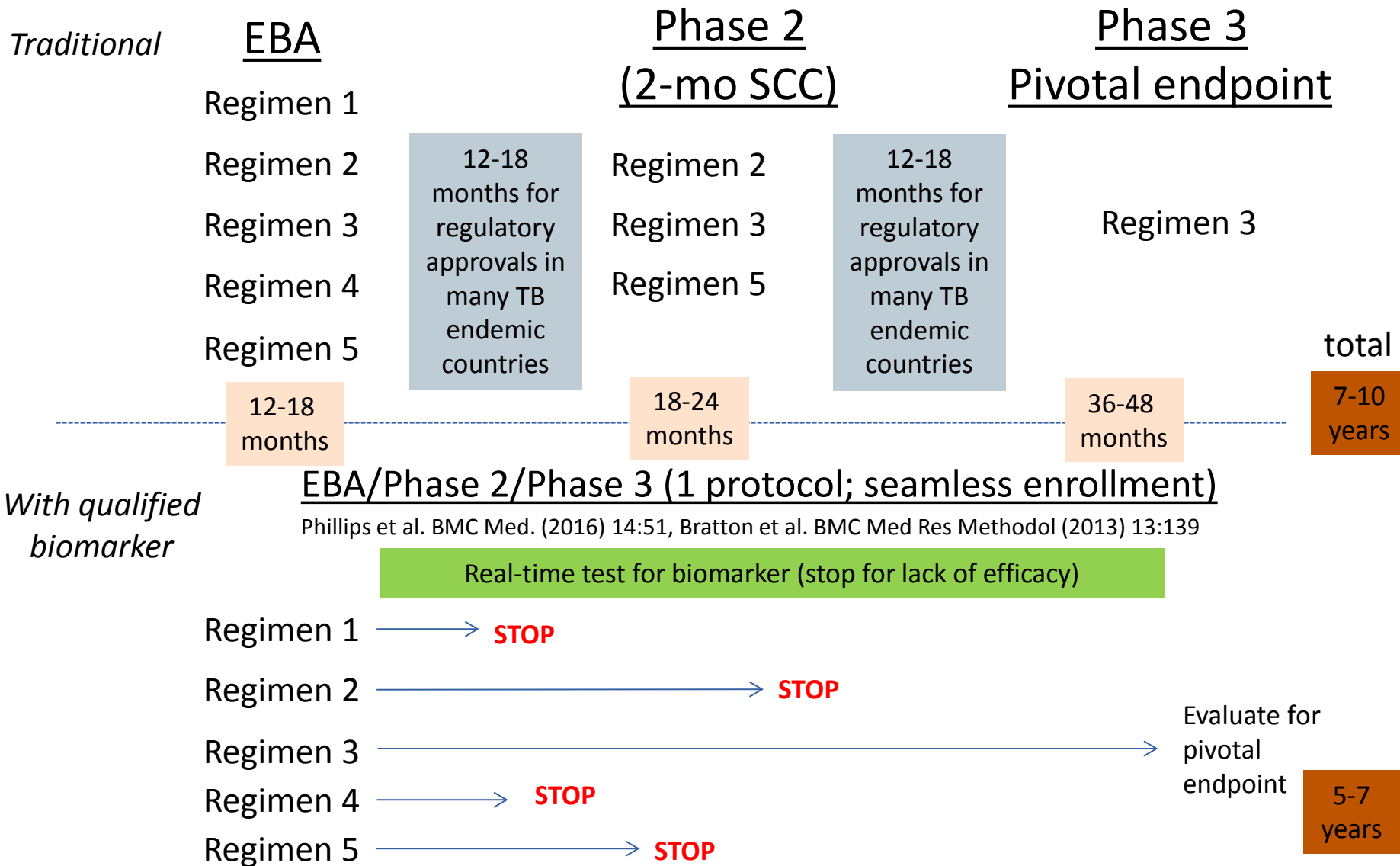
- An expert team convened to assess lipoarabinomannan (LAM) as a pharmacodynamic biomarker for quantitative measurement of bacterial load in sputum.
- This is one of the first pharmacodynamic biomarkers C-Path has advanced to a proposed Context of Use discussion with FDA.
- A Letter of Intent was submitted to FDA on June 9, 2017 to pursue regulatory qualification.



Use Statement

- LAM is a pharmacodynamic biomarker for quantitative measurement of bacterial load in sputum. A decrease of LAM in sputum likely reflects the reduction of bacterial load in the lung.
- This pharmacodynamic biomarker should be considered with other microbiological measurements, such as culture, as a real-time evaluation of treatment response in clinical trials of patients with pulmonary tuberculosis and positive smears and cultures, such as:
 - 14-day early bactericidal activity (EBA) trials,
 - Clinical trials of pulmonary tuberculosis up to 56 days, or
 - Clinical trials to provide evidence for early decision making in adaptive trial designs.

THE ENVISIONED IMPACT: POTENTIALLY SHORTENS DEVELOPMENT TIME BY 2-3 YEARS



CPTR INITIATIVE MEMBERS AND PARTNERS

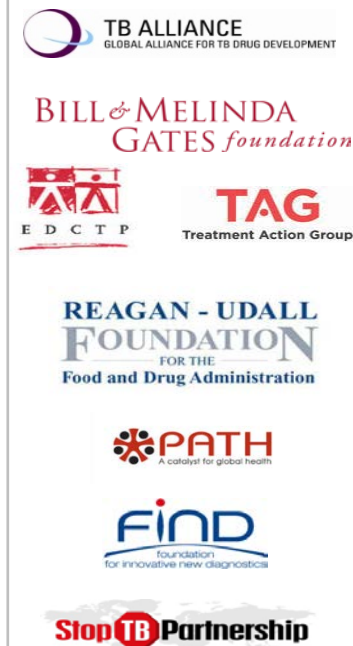
Government/Regulatory participants



Industry members



Nonprofit research members



Academic Partners

Baylor Institute for Immunology Research	O'Neill Institute at Georgetown Law Center	University College of London
Case Western Reserve University TB Research Unit	Radboud University	University of Arkansas for Medical Sciences
Colorado State University	RESIST-TB [Boston University]	University of Cape Town
Duke University	Rutgers [University Of Medicine & Dentistry]	University of Liverpool
Forschungszentrum Borstel	St. George's, University of London	University of St. Andrews
Harvard University	Stanford University	University of Virginia
Johns Hopkins University	Stellenbosch University	University of Texas Health Science Center at San Antonio
London School of Hygiene and Tropical Medicine	University of Florida	University of Toronto
Munich University	University of California, San Diego	Uppsala University, Dept. of Pharmaceutical Biosciences
NYU		Vanderbilt University School of Medicine

Thank you