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

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Critical Path to TB Drug Regimens

CRITICAL PATH INSTITUTE

TB DRUG REGIMEN DEVELOPMENT NEEDS

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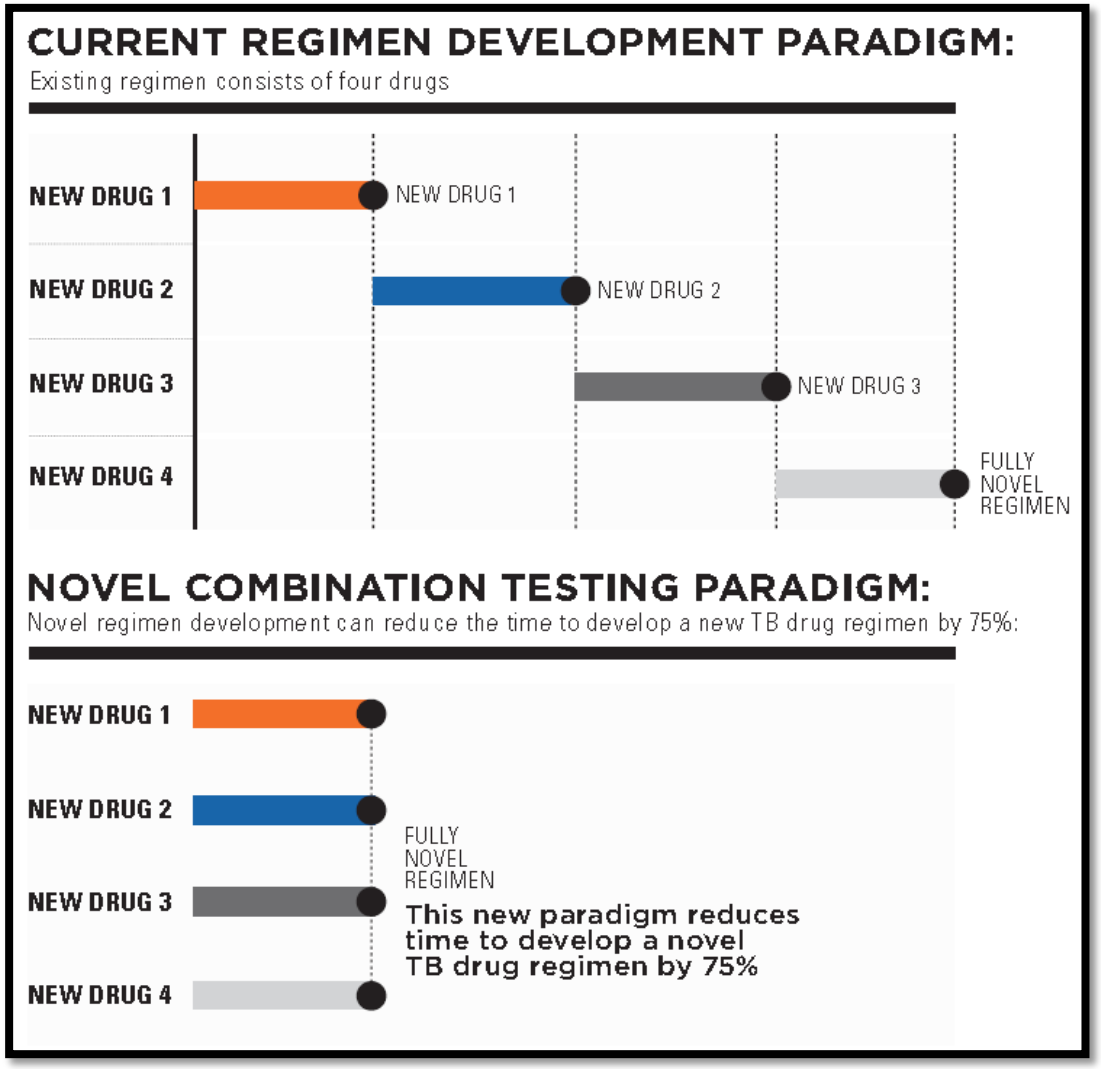
Novel regimen development requires emphasis on combination study approaches

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



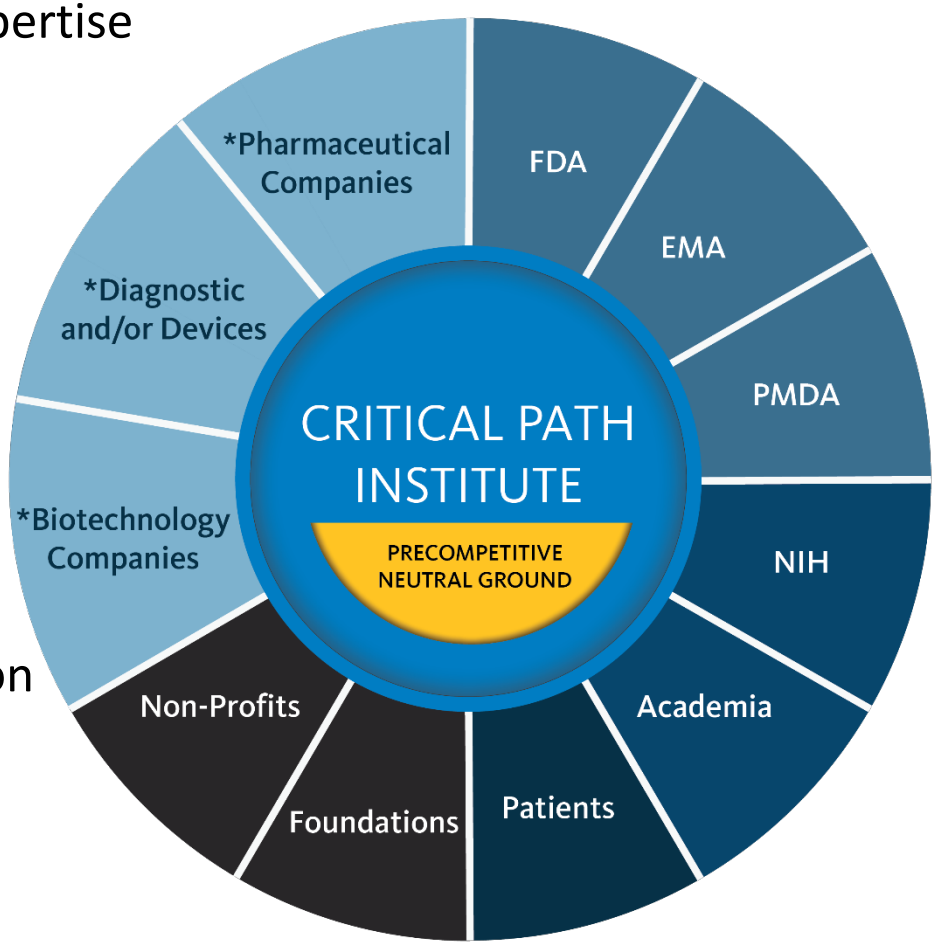
CPTR'S MISSION AND FOCUS

Critical Path to TB Drug Regimens

- 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.

PUBLIC PRIVATE PARTNERSHIP MODEL

- 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

CPTR LEVERAGES REGULATORY QUALIFICATION STRATEGY

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

SHARED LEARNING CAN SHORTEN THE TIMELINE

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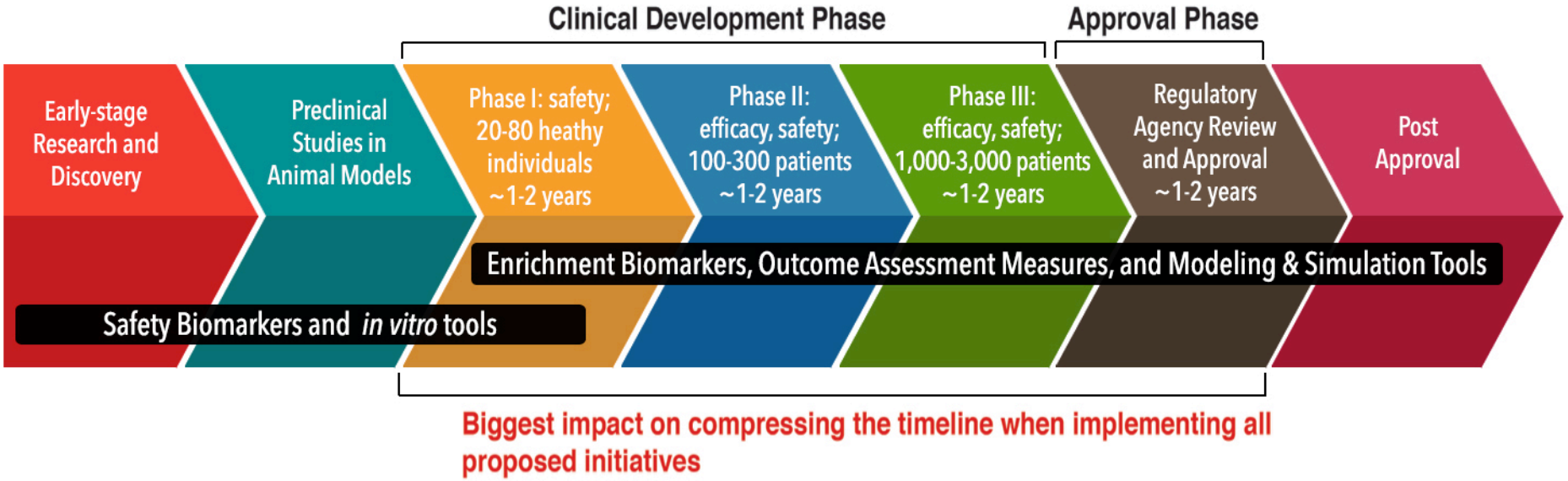
- ✓ Data Standardization and Sharing
- ✓ Biomarker Development and Qualification
- ✓ Clinical Outcome Assessment Measures
- ✓ Modeling and Simulation Tools



Adapted from *"A virtual space odyssey"*, Cath O'Driscoll (2004)
http://www.nature.com/horizon/chemicalspace/background/odyssey.html

DATA COLLABORATION IS CRITICAL

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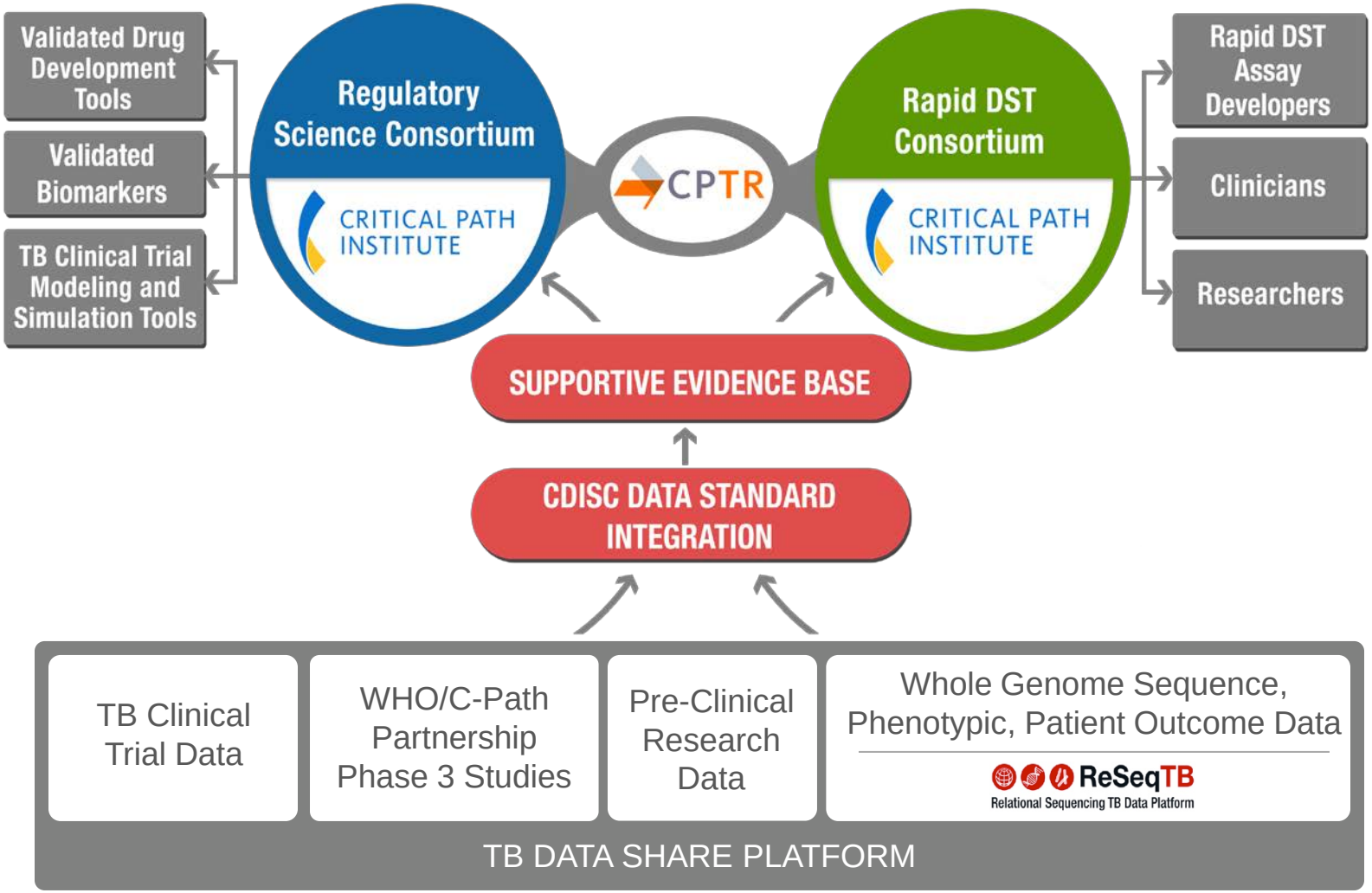

GAPS IN THE TB DRUG DEVELOPMENT PROCESS

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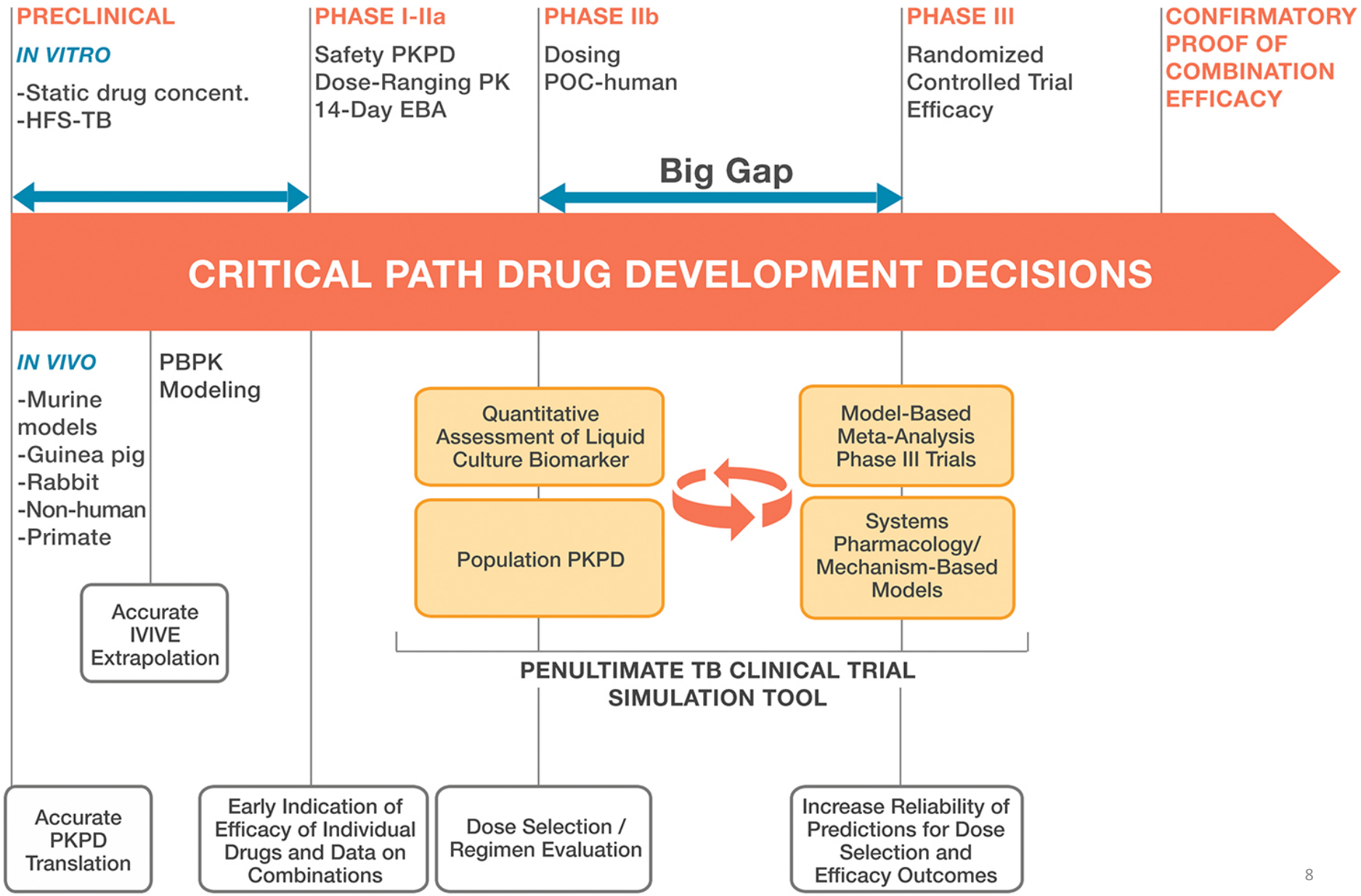

CPTR MODELING AND SIMULATION PROGRAMS

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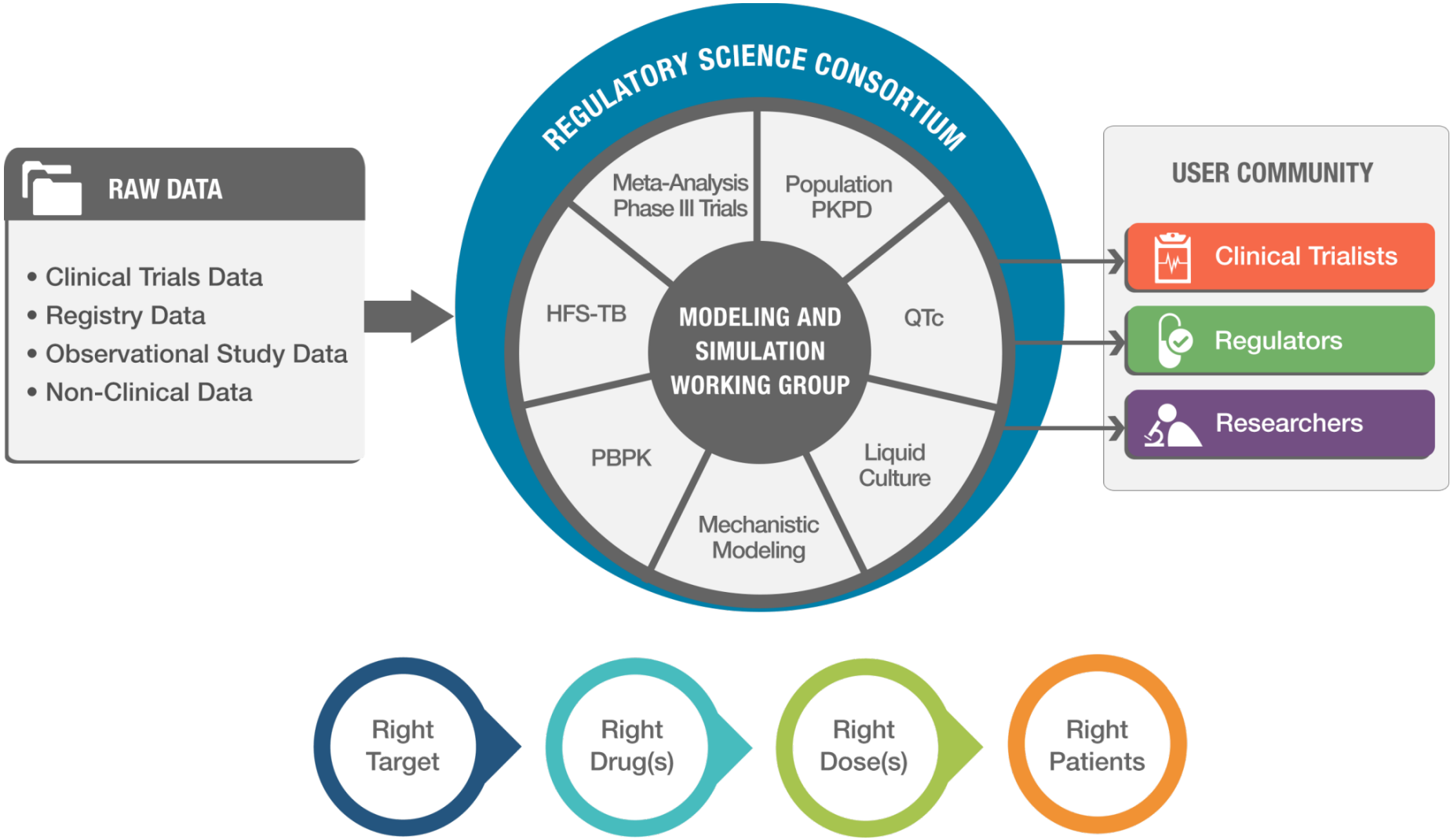

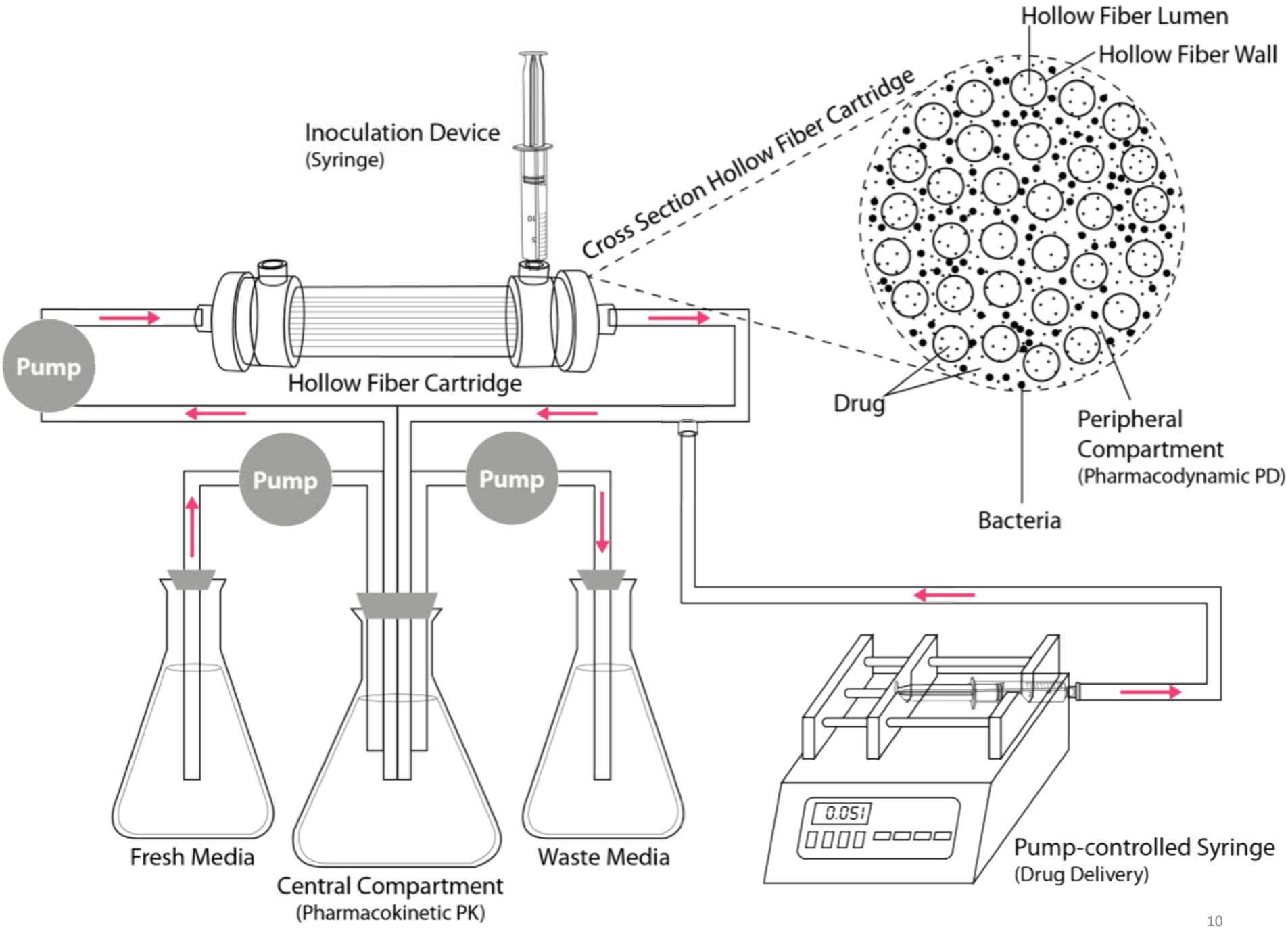
Hollow Fiber Lumen
Hollow Fiber Wall
Cross Section Hollow Fiber Cartridge
Inoculation Device
(Syringe)
Pump
Hollow Fiber Cartridge
Drug
Peripheral
Compartment
(Pharmacodynamic PD)
Bacteria
Pump
Pump
Fresh Media
Central Compartment
(Pharmacokinetic PK)
Waste Media
0.051
Pump-controlled Syringe
(Drug Delivery)

EVIDENCE BASED EVALUATION OF HOLLOW FIBER SYSTEM MODEL FOR TB

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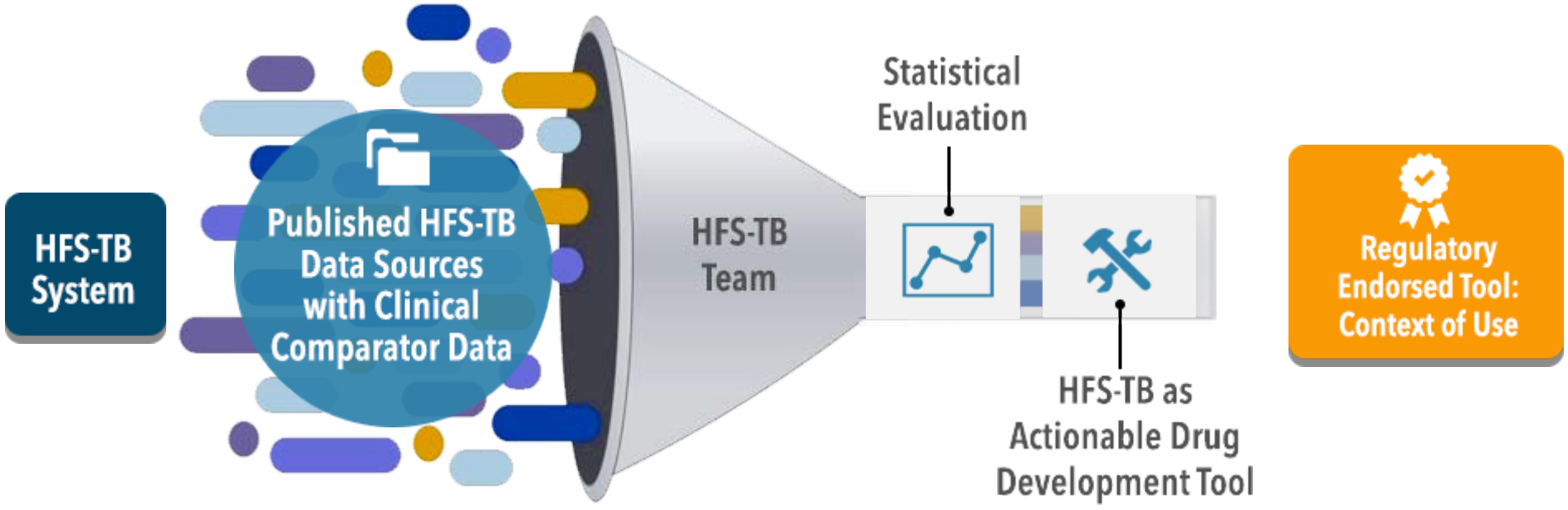

REGULATORY INTERACTIONS ON HFS-TB QUALIFICATION

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- 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

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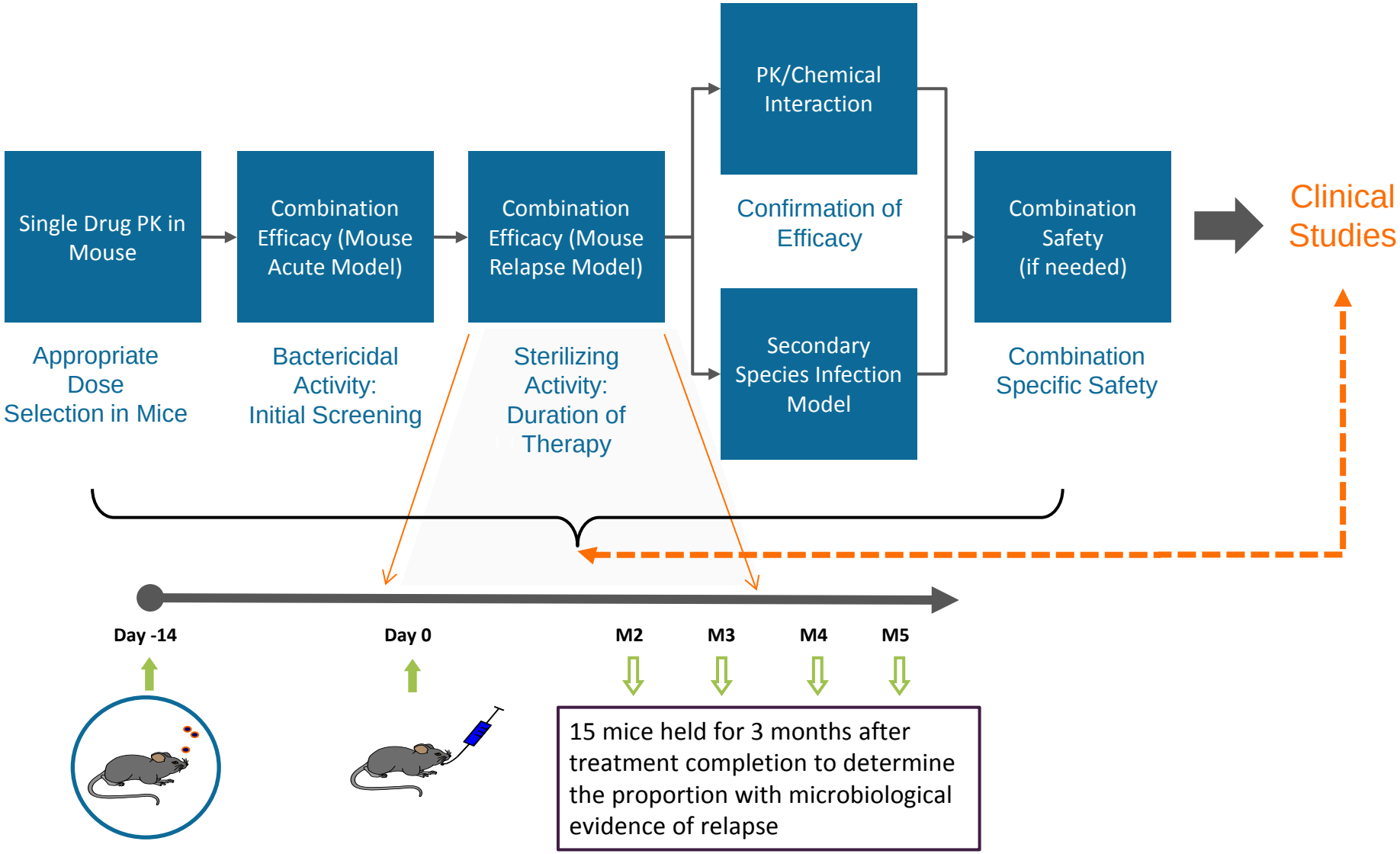

EVIDENCE-BASED EVALUATION OF STERILIZING MOUSE MODEL

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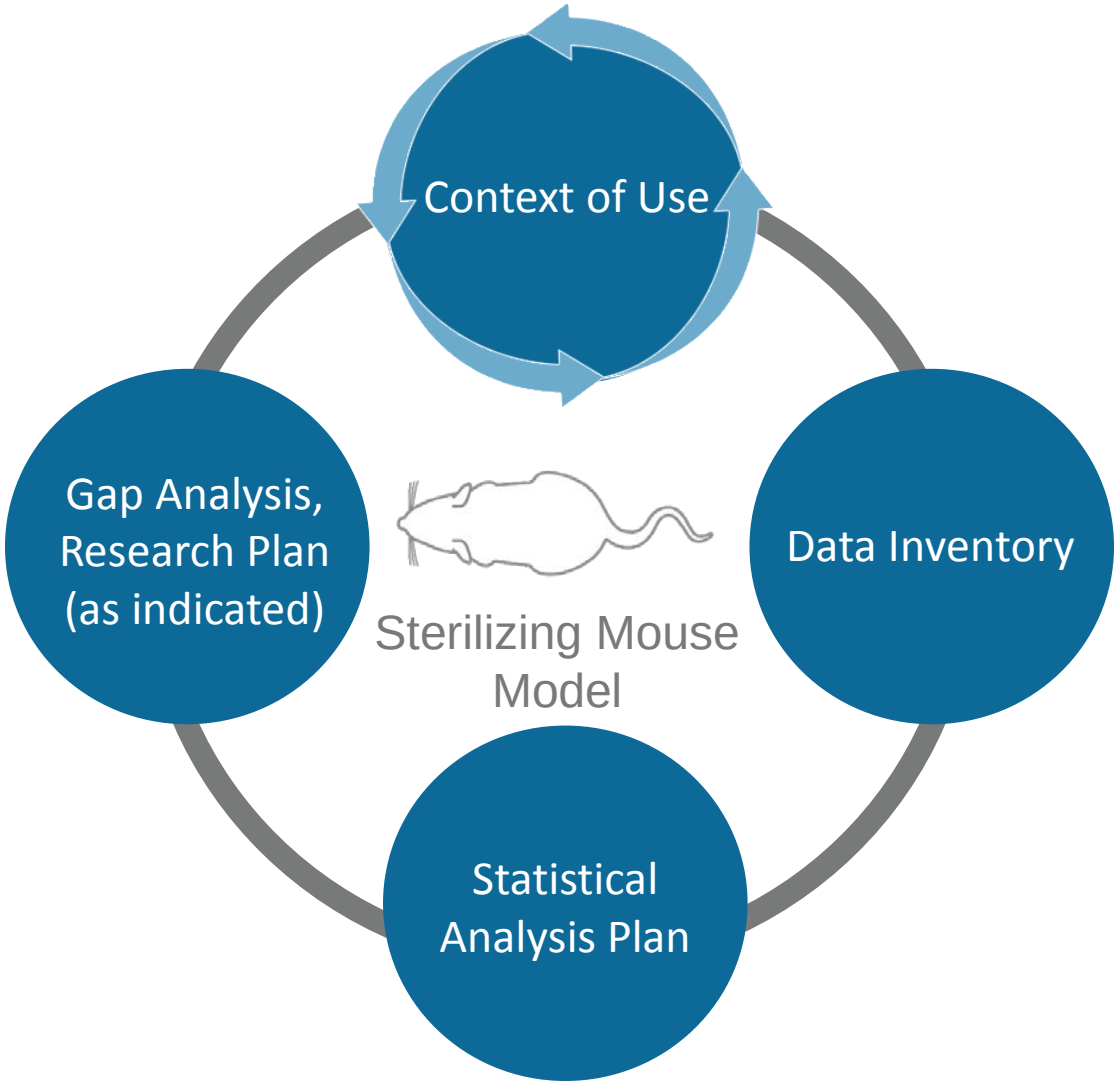
General Aim:

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

THE OPPORTUNITY: LAM AS A REAL-TIME EVALUATION OF TREATMENT RESPONSE

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- 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)

LAM BIOMARKER EFFORT

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- 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

Critical Path to TB Drug Regimens

Traditional

EBA

Regimen 1
Regimen 2
Regimen 3
Regimen 4
Regimen 5

12-18 months

12-18 months for regulatory approvals in many TB endemic countries

Phase 2 (2-mo SCC)

Regimen 2
Regimen 3
Regimen 5

18-24 months

12-18 months for regulatory approvals in many TB endemic countries

Phase 3 Pivotal endpoint

Regimen 3

36-48 months

total 7-10 years

With qualified biomarker

EBA/Phase 2/Phase 3 (1 protocol; seamless enrollment)

Phillips et al. BMC Med. (2016) 14:51, Bratton et al. BMC Med Res Methodol (2013) 13:139

Real-time test for biomarker (stop for lack of efficacy)

Regimen 1 → **STOP**

Regimen 2 → **STOP**

Regimen 3 → Evaluate for pivotal endpoint

Regimen 4 → **STOP**

Regimen 5 → **STOP**

5-7 years

CPTR INITIATIVE MEMBERS AND PARTNERS

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Government/Regulatory participants

CDC
FDA
European Medicines Agency
World Health Organization
imi Innovative Medicines Initiative
National Institutes of Health
National Institute of Allergy and Infectious Diseases
DAIDS RSC Regulatory Support Center

Industry members

AstraZeneca
Pfizer
SANOFI
Celgene Global Health
Cepheid A better way.
VERTEX The Science of Possibility
epistem
gsk GlaxoSmithKline
BIOMÉRIEUX
Alere
Otsuka
QIAGEN
janssen Pharmaceutical Companies of Johnson & Johnson
tibotec
Abbott Molecular
SEQUELLA Incorporated
ThermoFisher Scientific
BD

Nonprofit research members

TB ALLIANCE Global Alliance for TB Drug Development
Bill & Melinda Gates foundation
EDCTP
TAG Treatment Action Group
Reagan - Udall Foundation for the Food and Drug Administration
PATH A catalyst for global health
FIND foundation for innovative new diagnostics
Stop TB Partnership

Academic Partners

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

Thank you