Conflict of Interest

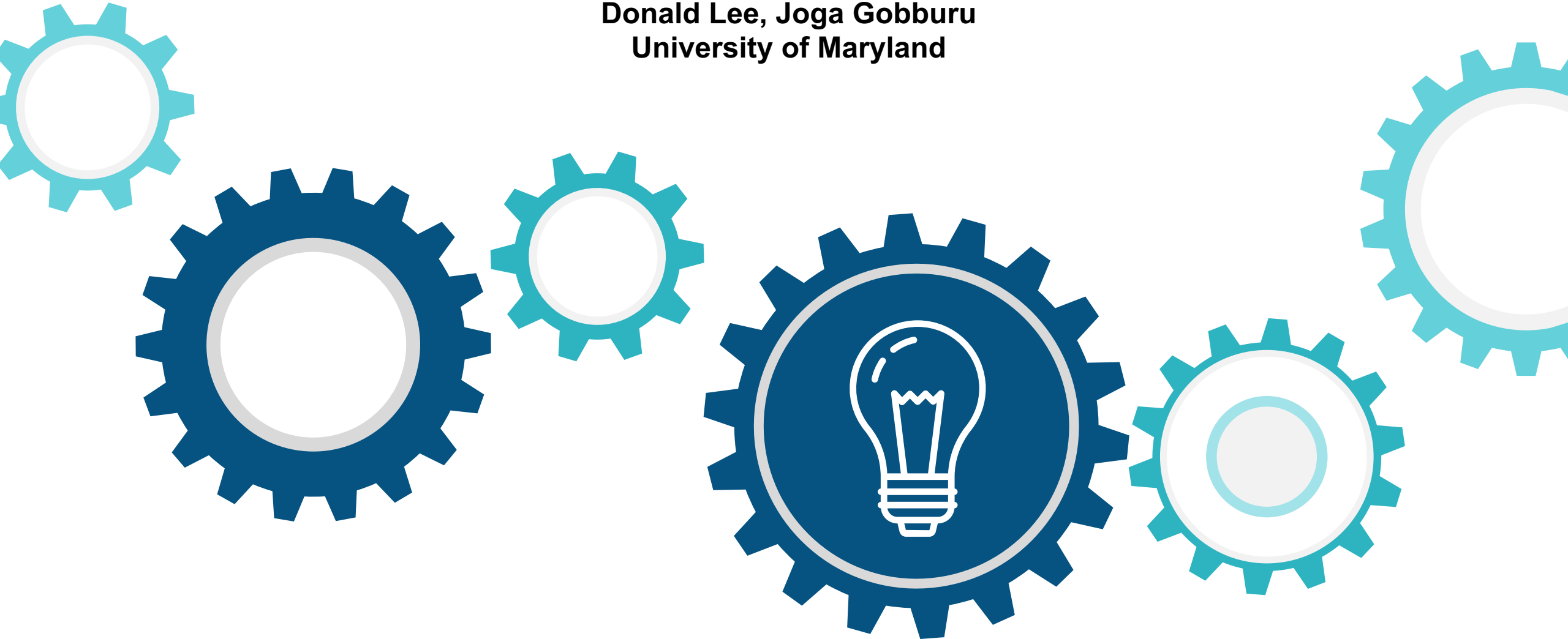
UNIVERSITY of MARYLAND SCHOOL OF PHARMACY CENTER FOR TRANSLATIONAL MEDICINE

- Dr Gobburu is co-founder of Vivpro Corp. which commercializes R&D Intelligence Assistant tool. (www.vivpro.ai)

- Dr Gobburu is co-founder of Pumas-AI Inc. which commercializes Pumas and Lyv. (www.pumas.ai)

Accelerating LAI Generic Drug Development using Model-Integrated BE

Donald Lee, Joga Gobburu
University of Maryland



Research made possible via a Grant from Center for Research on Complex Generics

CENTER FOR RESEARCH ON COMPLEX GENERICS
at the University of Maryland, Baltimore and the University of Michigan

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY
CENTER FOR TRANSLATIONAL MEDICINE

FDA U.S. FOOD & DRUG ADMINISTRATION

Mr Donald Lee

Graduate Student

UNIVERSITY of MARYLAND
SCHOOL OF PHARMACY
CENTER FOR TRANSLATIONAL MEDICINE

Long-Acting Injectables

Vivitrol®
(naltrexone for extended-release injectable suspension) 380 mg/vial

Probuphine®
(buprenorphine) implant

Sandostatin® LAR Depot
(octreotide acetate) for injectable suspension
10mg · 20mg · 30mg

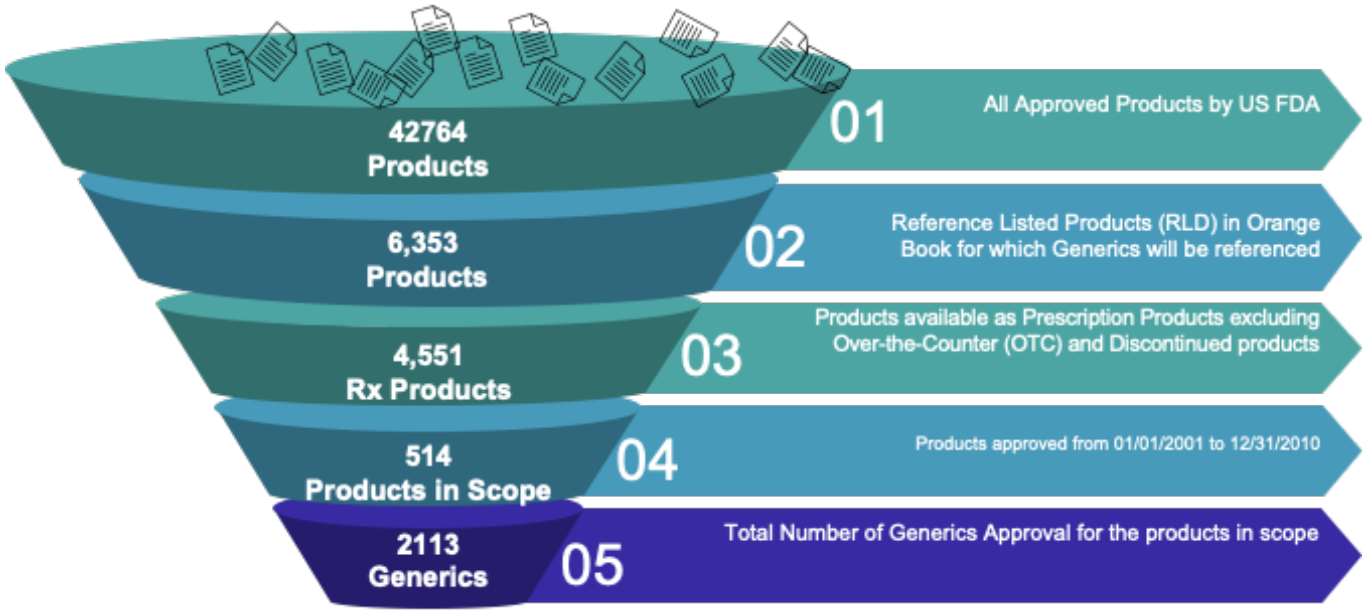
Lupron Depot®
(leuprolide acetate for depot suspension)

TRELSTAR®
(triptorelin pamoate for injectable suspension)

Lupaneta Pack™
leuprolide acetate for depot suspension and norethindrone acetate tablets

Triptodur®
(triptorelin)
for extended release injectable suspension

R&D Intelligence



https://vivproadmin.medium.com/there-are-six-generics-per-branded-oral-product-308171be40b3

6 Generics Per Brand Product Immediate-Release

Results from Vivpro R&D Intelligence Assistant (www.vivpro.ai)

<1 Generics Per Brand Product Long-Acting Injectables

https://vivproadmin.medium.com/there-are-six-generics-per-branded-oral-product-308171be40b3

Lack of Generics is a National Concern

LAI Generic Development: Challenges

Testing in patients

- Recruitment slow
- Variability inflated
- Washout impossible

Long Duration

- Steady-state impractical
- Discontinuations high
- Rich sampling infeasible

Rigid Designs

- Rich sampling impractical
- Parallel design needs larger sample sizes
- Additional BE endpoints
- Conventional BE analysis inefficient

Can LAI generics be developed in half the time, at half the cost?

STATE OF THE ART

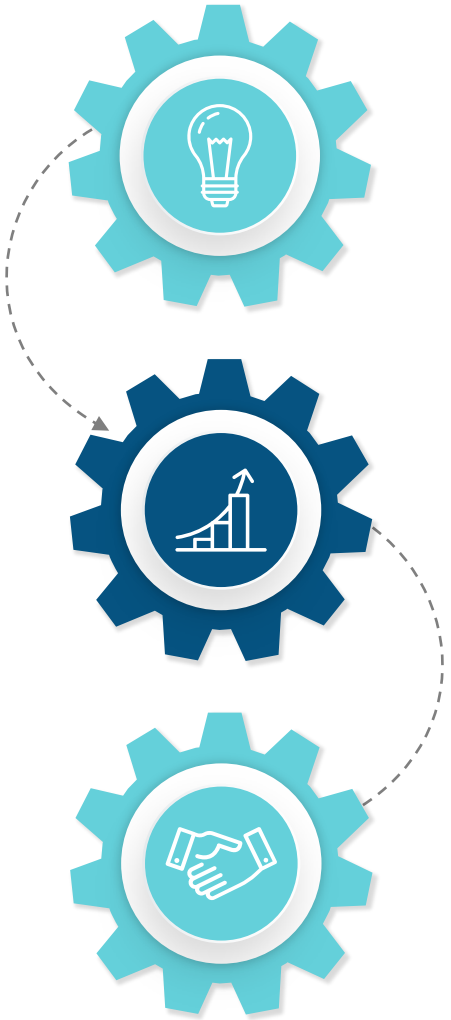
Generating Model Integrated Evidence for Generic Drug Development and Assessment

Liang Zhao[1], Myong-Jin Kim[1], Lei Zhang[2] and Robert Lionberger[2]

Quantitative methods and modeling (QMM) covers a broad spectrum of tool sets, of which physiologically based models and quantitative clinical pharmacology are most critical for generic drugs. QMM has been increasingly applied by the US Food and Drug Administration (FDA) to facilitating generic drug development and review, and has played a critical role in the modernization of bioequivalence (BE) assessment, especially for locally acting drug products, complex products of other types, and modified-release solid oral dosage forms. QMM has aided the development of novel BE methods, *in vitro*–only BE approaches, and risk-based evaluations. The future of QMM is model integrated evidence or virtual BE studies that can potentially provide pivotal information for generic drug approval. In summary, QMM is indispensable in modernizing generic drug development, BE assessment, and regulatory decision makings. Regulatory examples demonstrate how QMM can be used in modernizing generic drug development, addressing challenges in BE assessment, and supporting regulatory decision making.

CLINICAL PHARMACOLOGY & THERAPEUTICS | VOLUME 105 NUMBER 2 | FEBRUARY 2019

LAI Generic Development: Disruption



01

Learn-Apply Paradigm

Learn from Abbreviated BE Study
Apply to Full BE study

02

Scientific Evidence

Learn-Apply Paradigm evaluated thoroughly

03

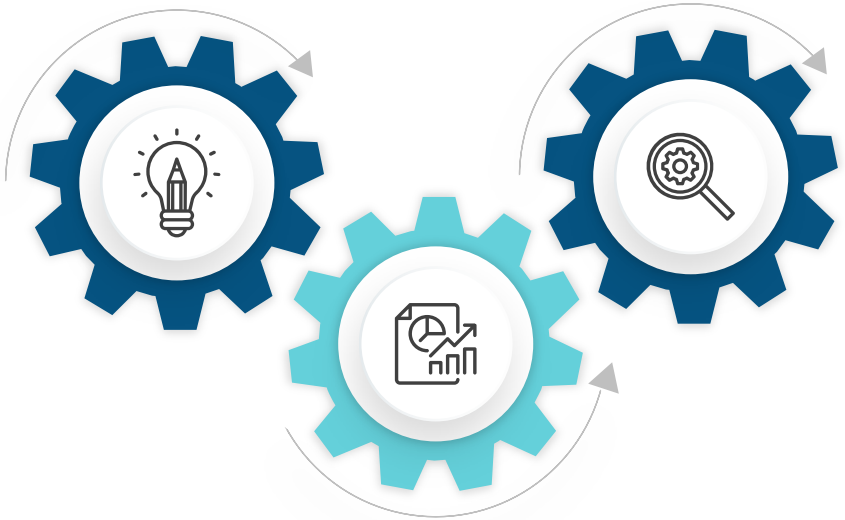
Implementation

Development and Regulatory Strategy

Learn-Apply Paradigm to LAI Generic Development

Abbreviated BE (ABE) Study

Shorter, Smaller, Single-dose BE Trial



Model-integrated Full BE (FBE) Study

Simulate FBE study using ABE model

Model-based Analysis

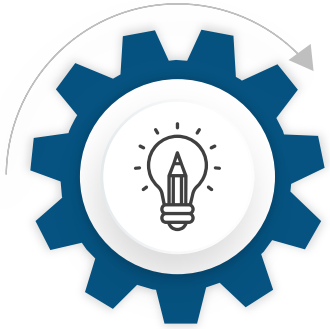
Analyze ABE using population PK modeling

Scientific Evidence

Historically, all Generic policies have been developed using modeling and simulation techniques.

Research Design

Abbreviated BE (ABE) Study

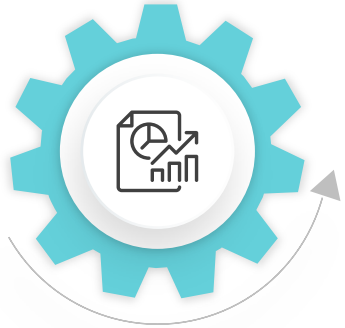


LAI Q1MO
Patients

N	50/arm
Samples	100-25%

T/R	1, 0.8
BSV	10-20%
WSV	10-20%

Model-based Analysis



Pop PK Modeling
NCA

Model-integrated Full BE (FBE) Study

Simulate Full BE
NCA

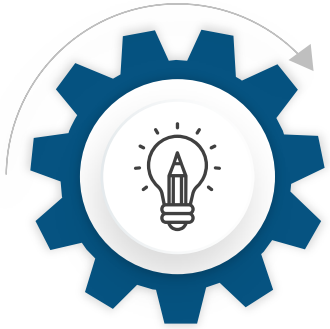
N	200/arm
Samples	100%

Modeling and simulation performed using Pumas software (www.pumas.ai)

Research Design

UNIVERSITY of MARYLAND SCHOOL OF PHARMACY CENTER FOR TRANSLATIONAL MEDICINE

Abbreviated BE (ABE) Study



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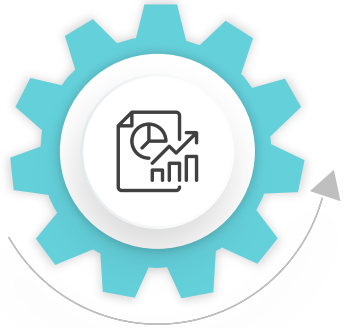

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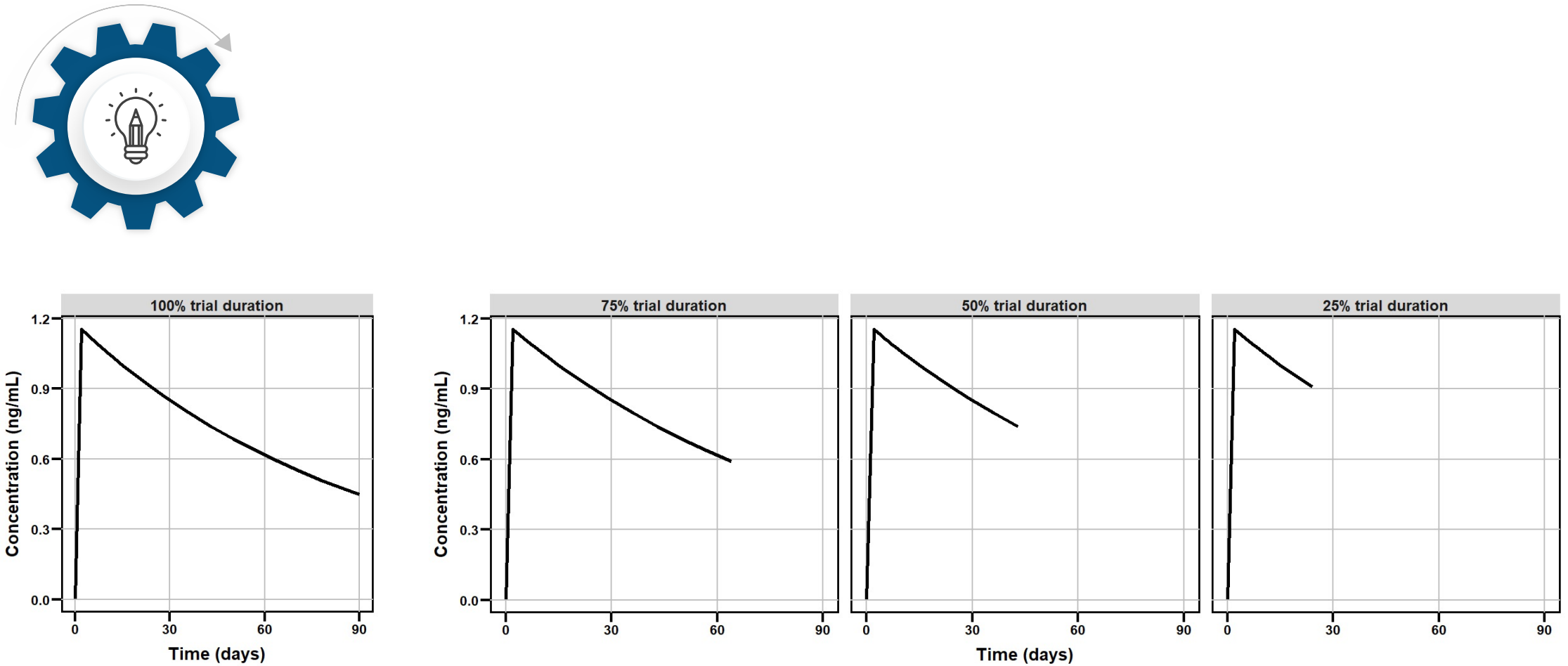

Research Design

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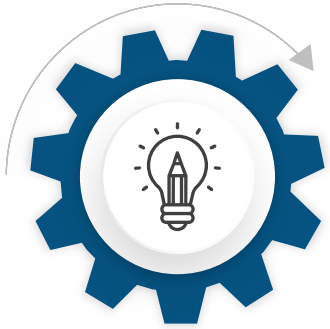

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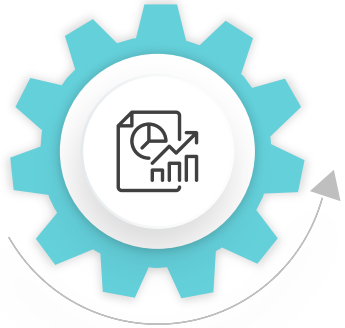

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Simulate Full BE
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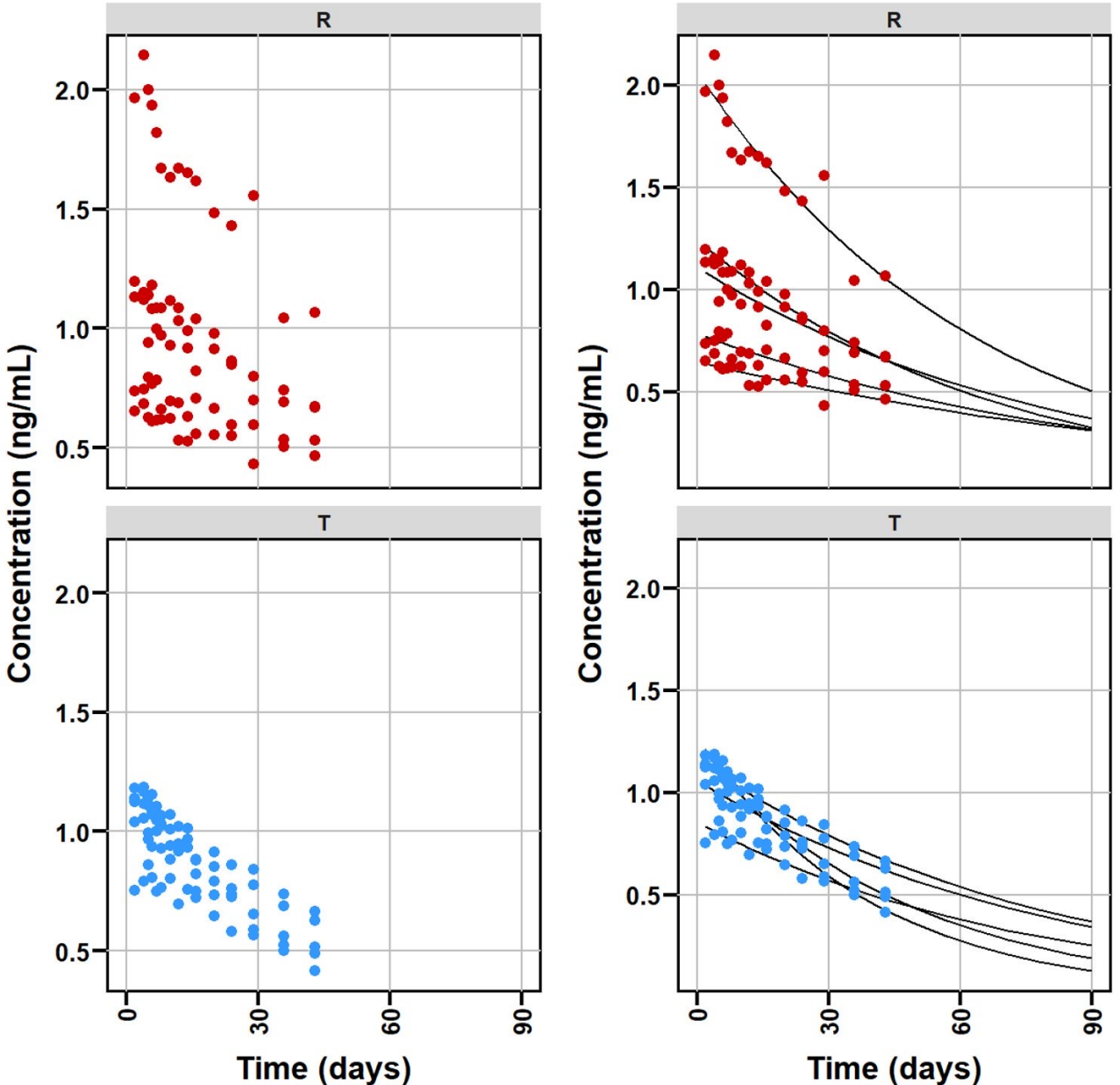
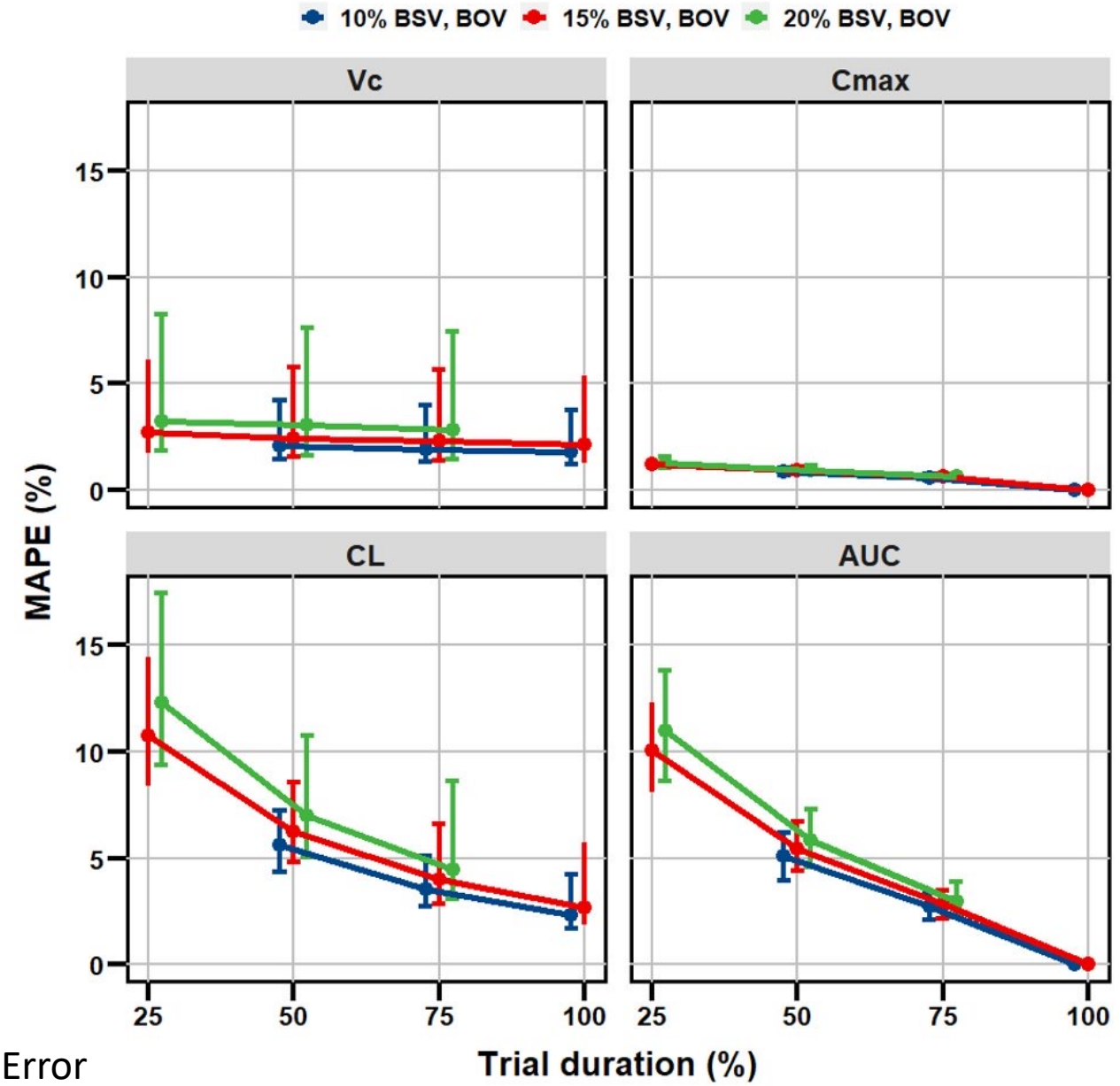
Modeling of ABE



Subject	CL	Vc
1	10	100
2	8	80
3	12	110

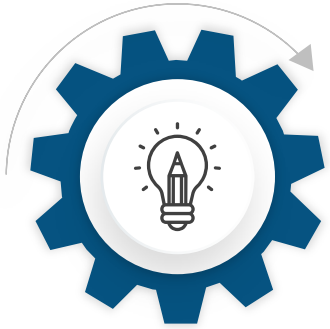
Modeling of ABE



MAPE = Mean Absolute Prediction Error

Research Design

Abbreviated BE (ABE) Study



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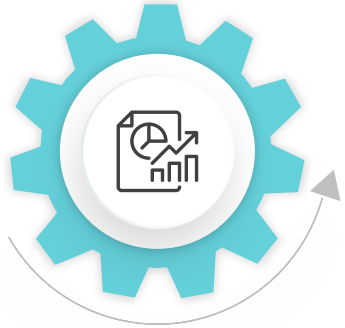

Pop PK Modeling
NCA

Model-integrated Full BE (FBE) Study

Simulate Full BE
NCA

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Samples	100%

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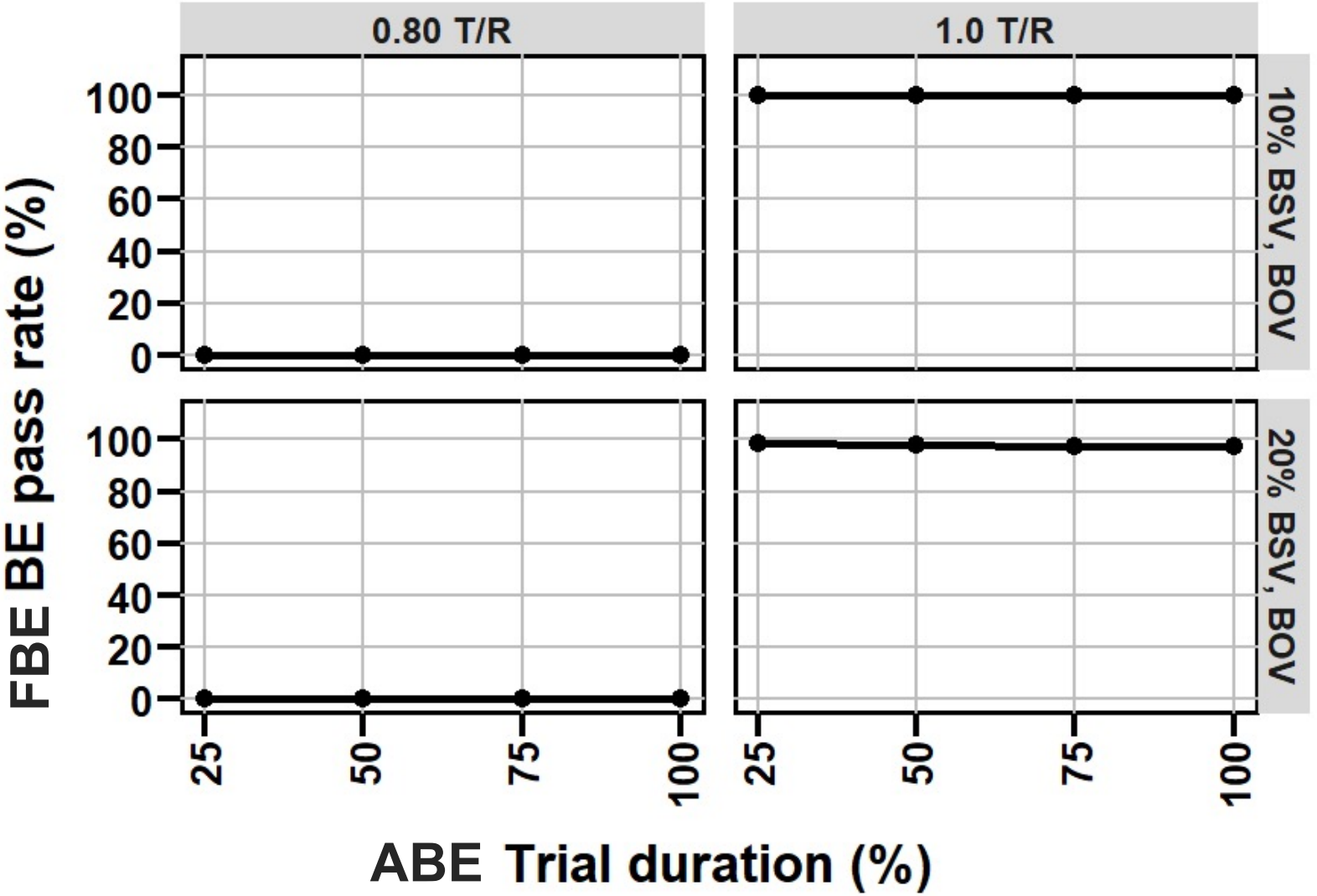
Model-integrated Full BE Study Preserves Type I Error & High Power



Pharmacokinetic-Based Criteria for Supporting Alternative Dosing Regimens of Programmed Cell Death Receptor-1 (PD-1) or Programmed Cell Death-Ligand 1 (PD-L1) Blocking Antibodies for Treatment of Patients with Cancer

Guidance for Industry

A PK-based approach relying on population-PK (Pop-PK) modeling and simulation can be applied to support the approval of alternative dosing regimens for a PD-1 or PD-L1 blocking antibody that is already approved based on clinical efficacy and safety trials. The Pop-PK model should be established with sufficient PK data from all indicated patient populations over a wide range of dosing regimens (i.e., different from the alternative dosing regimens). The model itself should be well validated and determined to be fit for the purpose. Refer to the FDA Pop-PK draft guidance for recommendations about Pop-PK models.[2] Simulation can be performed to derive the PK profiles and parameters following the alternative dosing regimens.

https://www.fda.gov/media/151745/download

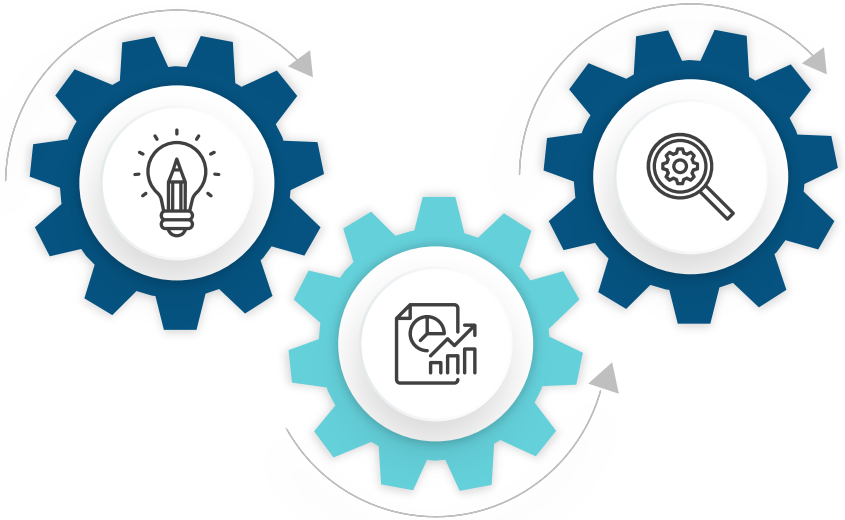
Further Research

- Evaluation of Model Qualification Methodology
- Evaluation of Different Model Estimation Methods
- Expansion to More Complex Absorption Products

Learn-Apply Paradigm to LAI Generic Development

Abbreviated BE (ABE) Study

Shorter, Smaller, Single-dose BE Trial



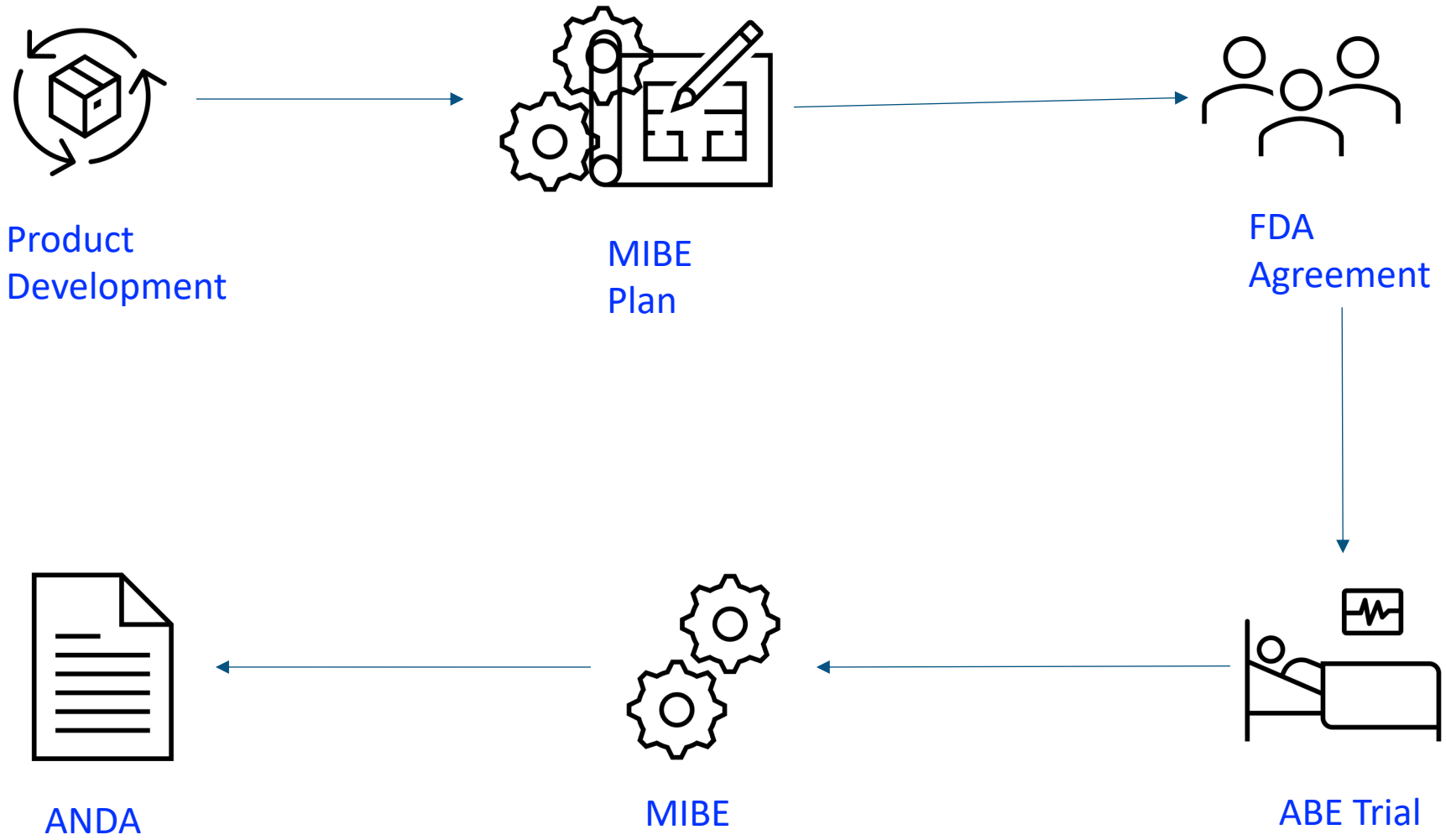
Model-integrated Full BE (FBE) Study

Simulate FBE study using ABE model

Model-based Analysis

Analyze ABE using population PK modeling

Learn-Apply Paradigm to LAI Generics
2x Faster, 50% Smaller



Thank You

Email Address
jgobburu@rx.umaryland.edu