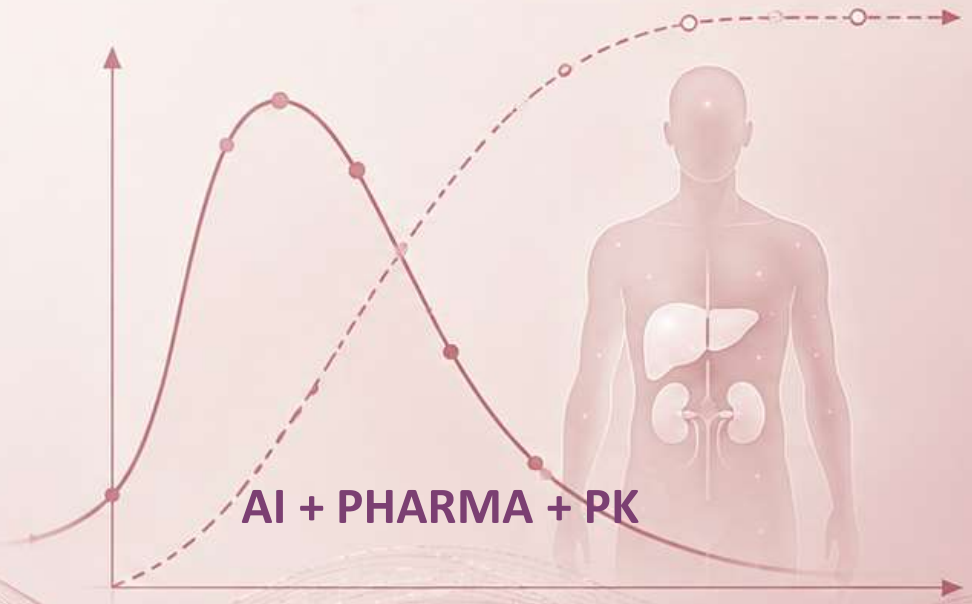
# AI-ENABLED BIOEQUIVALENCE

Smarter study design, pharmacokinetic evidence and regulatory decisions

Dr.MOJTABA SARKANDI

SCIENTIFIC WORKSHOP DECK

Bioequivalence • Pharmacokinetics • Artificial Intelligence



# BE turns pharmacokinetic similarity into a regulatory bridge

**Test product**

TEST / GENERIC

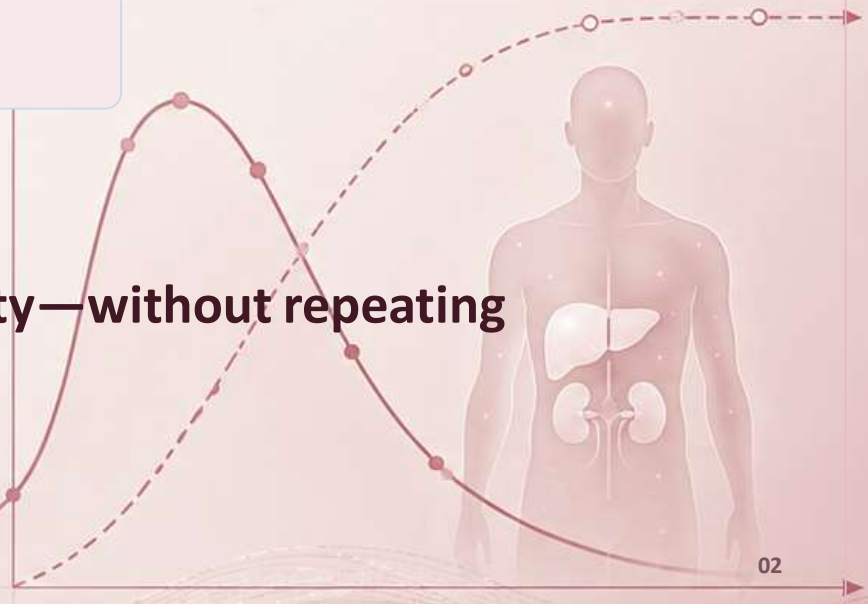
NO MEANINGFUL DIFFERENCE

**Rate** + **Extent**

of systemic absorption under comparable conditions

**Reference**

REFERENCE / ORIGINATOR



**PK equivalence supports comparable efficacy and safety—without repeating large Phase III trials.**

# One principle supports every major development decision

### GENERIC APPROVAL

Demonstrates interchangeability with the reference product.

### FORMULATION BRIDGING

Connects early clinical formulations to the marketed product.

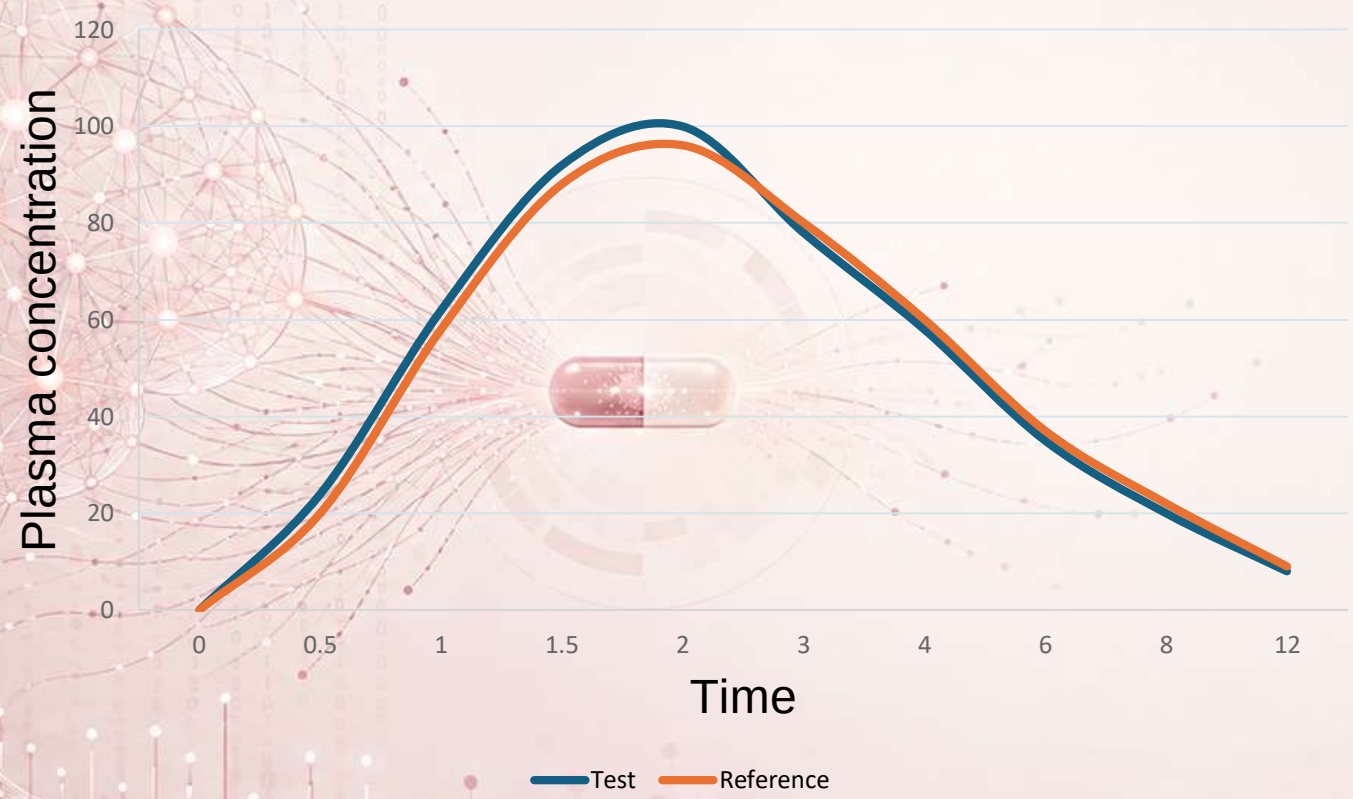
### POST-APPROVAL CHANGE

Supports changes in process, manufacturing site or composition.

### GLOBAL ACCESS

Enables WHO prequalification and reliance-based procurement.

# Cmax, Tmax and AUC capture distinct dimensions of exposure




**Cmax** — **Peak exposure**

Absorption rate

**Tmax** — **Time to peak**

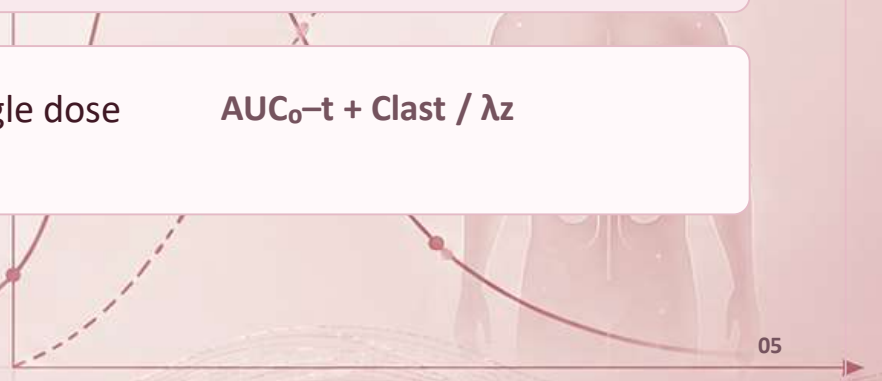
Descriptive rate

**AUC** — **Total exposure**

Extent absorbed

# Primary PK endpoints answer three different clinical questions

| ENDPOINT | DEFINITION | INTERPRETATION | DERIVATION / REPORTING |
|---|---|---|---|
| **Cmax** | Highest observed plasma concentration | Peak exposure and absorption rate | Observed directly |
| **Tmax** | Time at which Cmax occurs | Timing of peak / onset context | Median + range; usually descriptive |
| **$AUC_{0}–t$** | Exposure from dosing to last measurable sample | Observed extent of absorption | Linear-up/log-down trapezoidal NCA |
| **$AUC_{0}–\infty$** | $AUC_{0}–t$ plus the extrapolated terminal tail | Total exposure after a single dose | **$AUC_{0}–t + Clast / \lambda z$** |

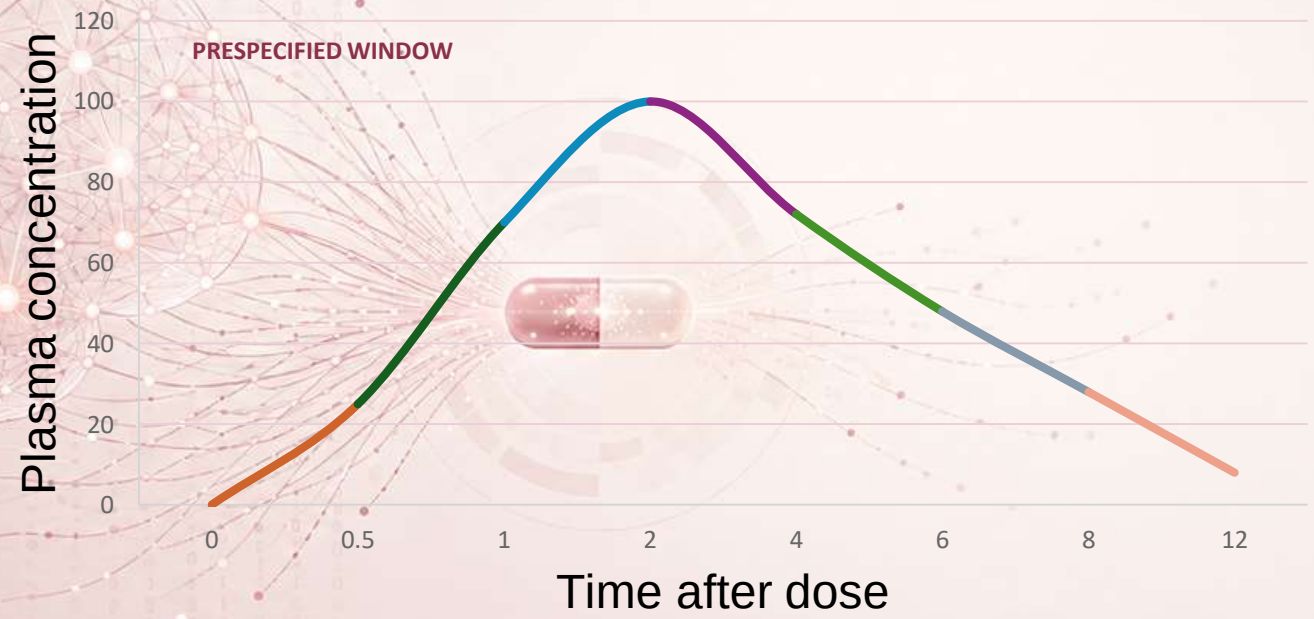


# Supporting NCA parameters test whether exposure is reliable

| | | |
|---|---|---|
| **Clast** | **Last quantifiable concentration** | Anchors terminal-tail extrapolation |
| **λz** | **Terminal elimination rate constant** | Slope of the log-linear terminal phase |
| **t½** | **Terminal half-life** | ln(2) / λz; informs sampling duration and washout |
| **AUCextrap (%)** | **Fraction of $AUC_0$–∞ beyond the last sample** | A quality check on terminal coverage |
| **$AUC_0$–72h** | **Truncated exposure to 72 hours** | May replace $AUC_0$–t for long half-life IR drugs |

**Sampling should capture ≥80% of $AUC_0$–∞; otherwise the terminal exposure estimate is less dependable.**

# Partial AUC isolates a clinically relevant exposure window




## Definition

AUC calculated only between two prespecified time points.

$$pAUC(t_1–t_2) = \int C(t)\, dt$$

## Why it matters

It measures early, middle or late exposure that Cmax and total AUC can conceal.

**The cutoff must be clinically justified and specified before analysis.**

# pAUC exposes differences that total AUC can hide

**EARLY EXPOSURE**

## Rapid-onset products

Tests whether clinically important initial exposure is reproduced.

**MODIFIED RELEASE**

## Extended or delayed release

Separates early, middle and late release behavior; can detect dose dumping.

**LONG-ACTING INJECTABLES**

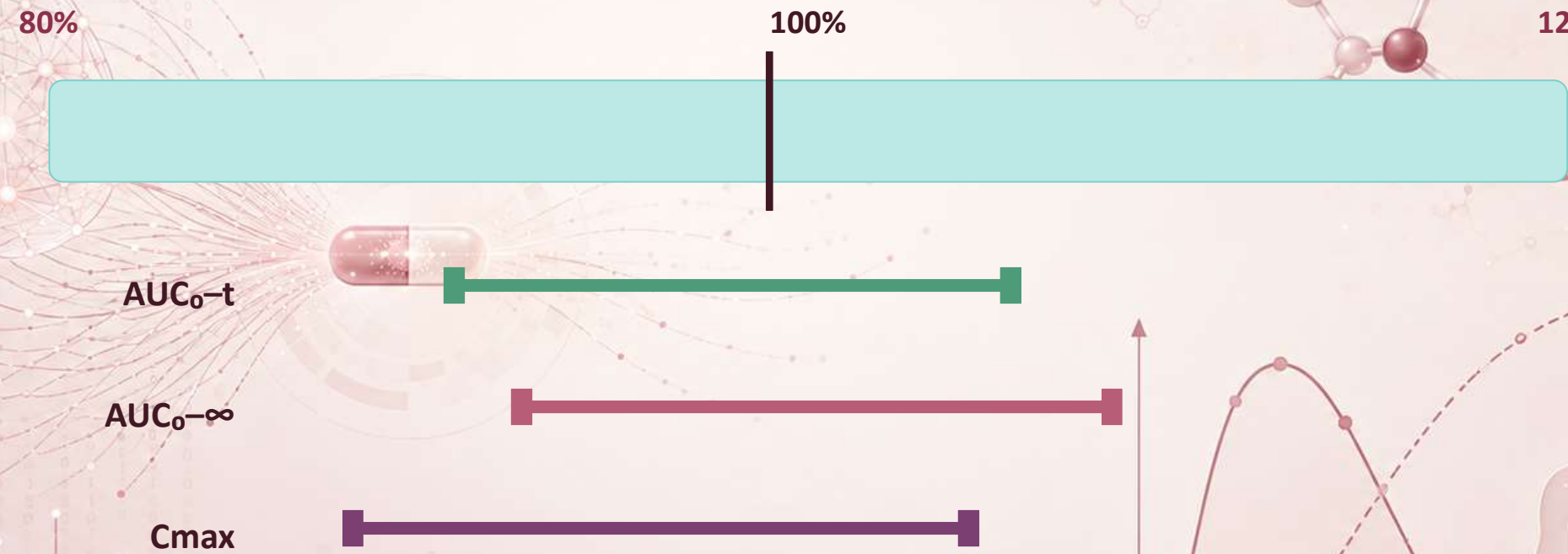
## Multiphasic depot release

Distinguishes initial burst from sustained exposure over later intervals.

**Regulatory interpretation**

pAUC is an additional, product-specific endpoint—not a universal replacement for Cmax or total AUC.

# The entire 90% CI must remain within 80–125%




TOST on log-transformed PK endpoints • geometric mean ratio (Test / Reference)

# Study design should match half-life, variability and safety

**DEFAULT**

## 2×2 CROSSOVER

Each participant receives Test and Reference; within-subject comparison improves precision.

**T → washout → R**

**LONG HALF-LIFE / CARRYOVER**

## PARALLEL

Different groups receive one treatment; simpler exposure, larger sample.

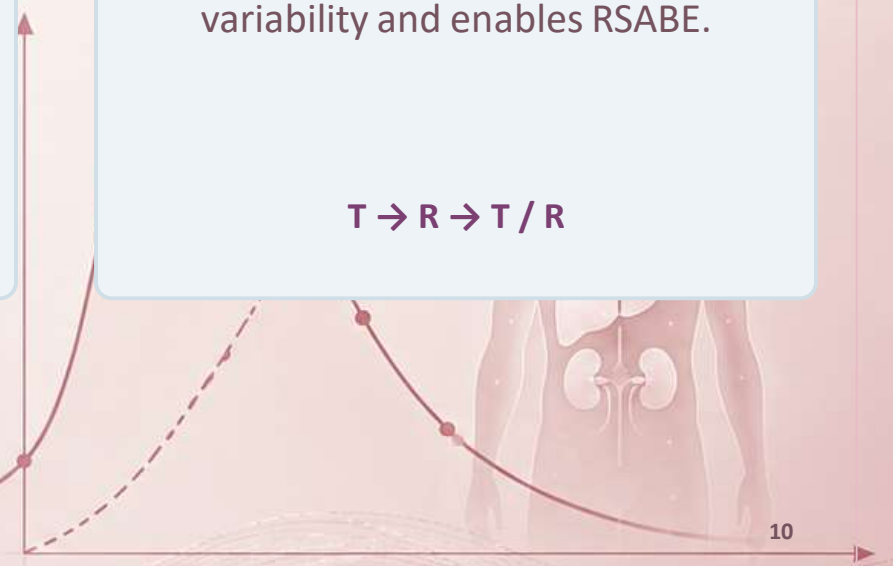
**T | R**

**HIGHLY VARIABLE DRUGS**

## REPLICATE

Repeated dosing estimates within-subject reference variability and enables RSABE.

**T → R → T / R**



# Food-effect strategy is now explicitly risk based

**Does food have a meaningful risk of changing the relative performance of Test vs Reference?**

**LOWER RISK**

**One scientifically sensitive condition may be sufficient**

**HIGHER RISK**

**Both fasting and fed studies may be needed**

Risk depends on formulation behavior—not merely on whether food changes absolute exposure.



# Good BE science begins with ethical, informative participation

**18–55**

Typical healthy adult age range

**12–36**

Common sample-size range

**≥80%**

Target statistical power

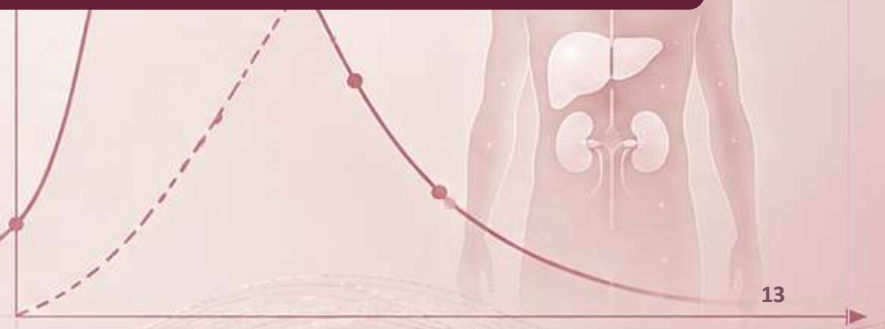
- Ethics approval and informed consent
- GCP-compliant dosing, sampling and safety monitoring
- Validated bioanalytical assay—typically LC–MS/MS

# BCS biowaivers require tightly controlled formulation risk

| PERMEABILITY | High | Low |
|---|---|---|
| **High solubility** | **CLASS I**<br>Primary biowaiver candidate | **CLASS III**<br>Possible with strict excipient controls |
| **Low solubility** | **CLASS II**<br>Dissolution-limited | **CLASS IV**<br>Highest formulation risk |

## Evidence package

- Rapid, similar dissolution
- Immediate-release dosage form
- Excipient risk assessment
- ICH M9 / WHO criteria



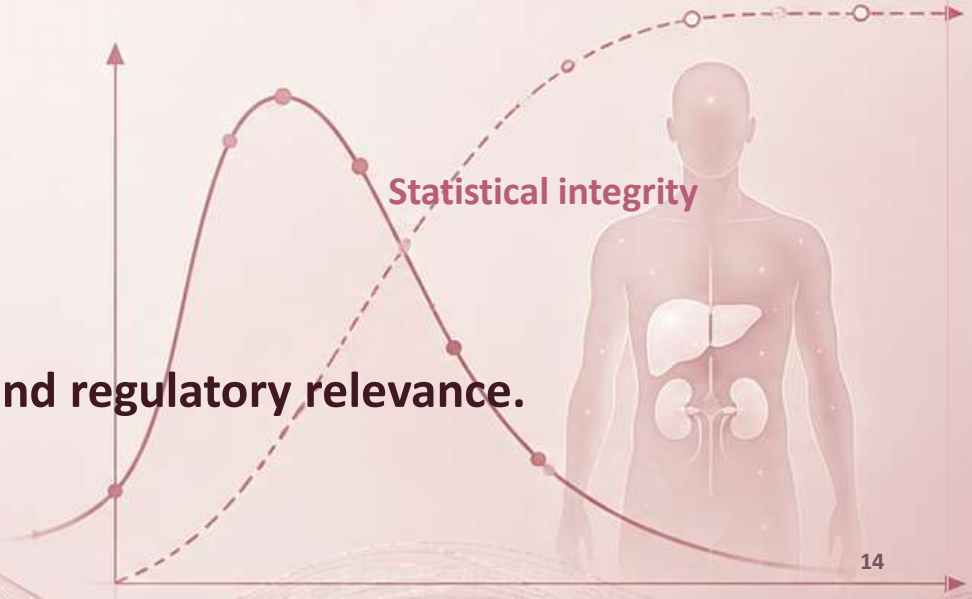
# A defensible BE conclusion needs an unbroken evidence chain

01 Protocol → 02 Reference → 03 Ethics → 04 Clinical → 05 Assay → 06 NCA → 07 TOST → 08 Report

Design sensitivity

Analytical validity

Statistical integrity



**Every handoff must preserve traceability, quality and regulatory relevance.**

# ICH M13 is converging global BE expectations

**M13A** — FINAL — Immediate-release solid oral dosage forms

**M13B** — DRAFT — Additional-strength biowaivers

**M13C** — IN DEVELOPMENT — Other BE design topics

**Alignment reduces duplication—but comparator selection and local requirements still matter.**

# Complex products often need more than standard PK endpoints

INHALATION | TRANSDERMAL | LIPOSOMAL | LONG-ACTING INJECTABLES

## Why complexity matters

- Local delivery may not track systemic exposure
- Release profiles can require partial AUC
- PK may need PD or clinical endpoint support
- Interchangeability rules remain jurisdiction-specific

**Evidence becomes multimodal**

**PK + dissolution + imaging + device performance + model-informed evidence**

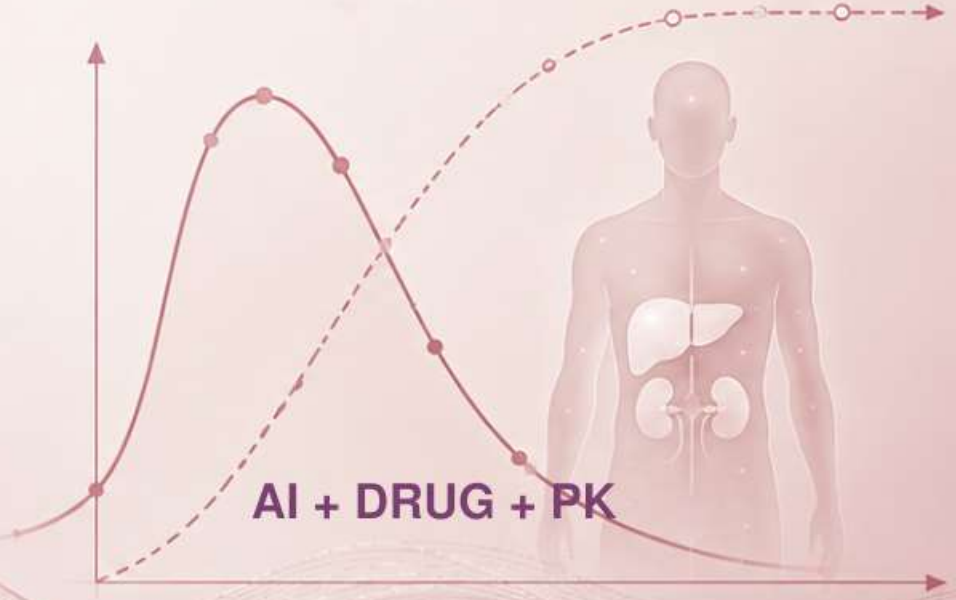


# AI-ASSISTED BIOEQUIVALENCE STUDY DESIGN

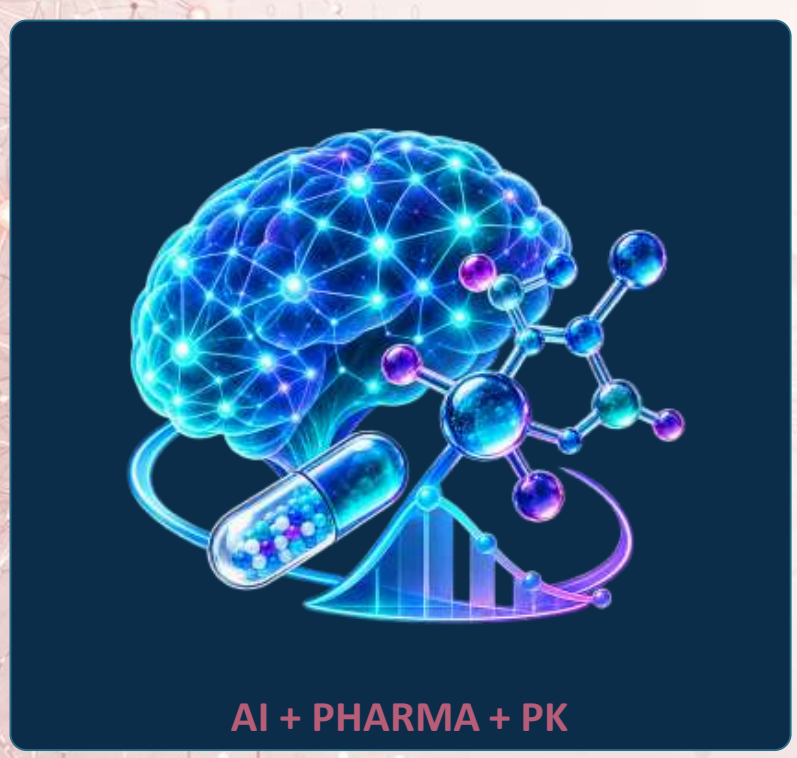
Smarter formulation selection, robust trial design and defensible virtual evidence

**SCIENTIFIC CONTINUATION DECK**

**Experimental data • PBPK/PBBM • Statistics • Explainable ML**



# AI strengthens every stage of bioequivalence development




| | |
|---|---|
| **SMARTER DESIGN** | Predict variability and optimize sampling windows. |
| **FORMULATION INTELLIGENCE** | Learn dissolution–PK relationships and prioritize prototypes. |
| **TRUSTED DECISIONS** | Integrate data with validation, explainability and human oversight. |

**Validated AI supports evidence—it never substitutes for it.**

# AI should augment—not redefine—bioequivalence

## NOT AI BY ITSELF

- PBPK and PBBM
- Monte Carlo simulation
- Classical statistical analysis
- Noncompartmental PK

## AI-ENABLED LAYER

- Machine learning and deep learning
- Data-driven optimization
- NLP evidence extraction
- Hybrid mechanistic–ML models

**The most accurate description is advanced modeling and simulation augmented by AI.**

# AI can strengthen every design decision before dosing begins

### EVIDENCE

Extract product, PK and regulatory knowledge

### FORMULATION

Rank candidates and identify failure drivers

### DESIGN

Compare crossover, parallel and replicate options

### SAMPLING

Optimize time points and washout

### SIMULATION

Run virtual populations and stress scenarios

### GOVERNANCE

Lock protocol, audit models and preserve human review



**The value is prospective: reduce avoidable uncertainty before the pivotal study.**

# Structured evidence is the first design input

## INPUTS

- Physicochemistry and BCS
- Dissolution and composition
- Pilot and published PK
- Within-subject variability
- Food and population effects
- Guidelines and PSGs

## NLP + HUMAN VERIFICATION

| | |
|---|---|
| **EXTRACT** | Entities, values, study conditions and source links |
| **NORMALIZE** | Units, terminology and product-specific context |
| **VERIFY** | PK and regulatory experts confirm every critical claim |
| **OUTPUT** | A traceable evidence table for design decisions |

**Language models accelerate review; they do not validate regulatory truth.**

# Machine learning can screen formulation risk

**API + EXCIPIENTS + PROCESS + DISSOLUTION**

↓

**Random Forest • Gradient Boosting • Gaussian Process • Neural Networks • Bayesian Optimization**

↓

**P(BE PASS)**

Probability of meeting BE criteria

**PK OUTPUTS**

Predicted Cmax and AUC

**DISSOLUTION**

Expected Test–Reference distance



**Use the model to prioritize pilot candidates—not to declare BE independently.**

# Product risk determines the study architecture

| | |
|---|---|
| Typical oral product | 2×2 crossover |
| Very long half-life | **Parallel or long-washout crossover** |
| **High within-subject variability** | Full or partial replicate |
| **Narrow therapeutic index** | **Product-specific design and limits** |
| Complex or locally acting product | Totality of evidence + modeling |
| BCS-biowaiver candidate | **Assess eligibility under ICH M9** |

**AI compares scenarios; the regulatory question still defines the admissible design.**

# Sample size depends on variability, ratio and design

### EXPECTED GMR

Likely Test/Reference ratio

### CVw

Within-subject coefficient of variation

### POWER

Usually 80% or 90%

### BE LIMITS

Commonly 80.00–125.00%

### DESIGN

Crossover, parallel or replicate

### ATTRITION

Non-evaluable and dropout allowance

$$\sigma w^2 = \ln(1 + CVw^2)$$

# A 25% CVw example requires about 42–44 enrollments

## ASSUMPTIONS

- CVw = 25%
- Expected GMR = 0.95
- BE limits = 80–125%
- Power = 90%
- 2×2 crossover
- Attrition = 15%

$$\sigma w^2 = \ln(1 + 0.25^2) = 0.0606$$

Approximate analyzable N

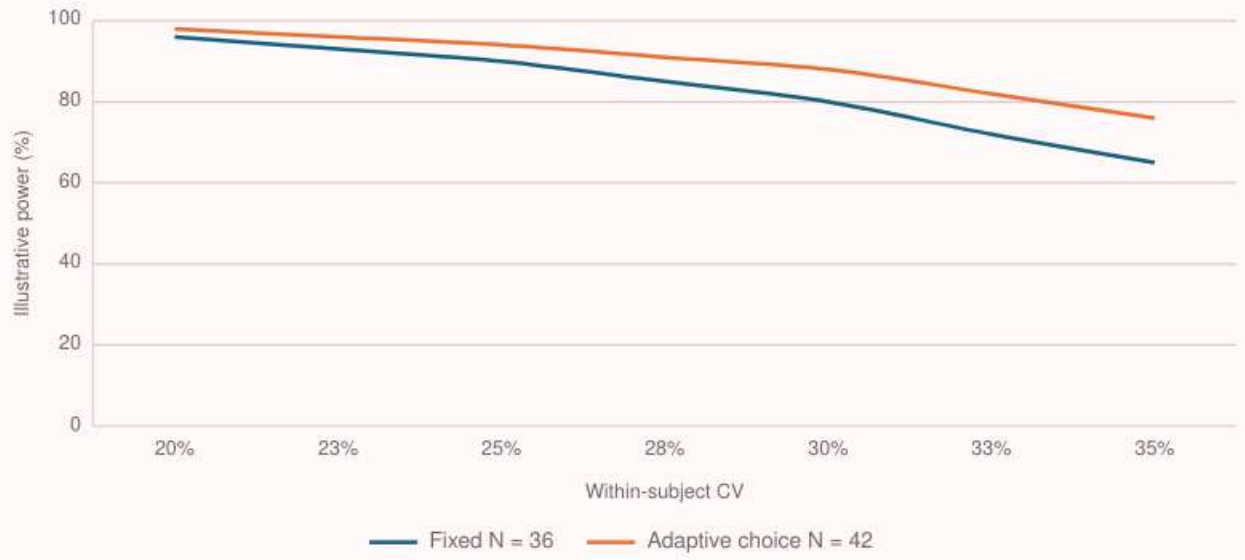
$$\approx 36$$

$$36 \div (1 - 0.15) = 42.4$$

**ENROLL 42–44 PARTICIPANTS**

**Educational approximation—protocol N must be reproduced with a validated method.**

# Uncertainty in CVw should be designed—not ignored




## AI-ASSISTED STRESS TEST

- Treat CVw as a distribution
- Simulate thousands of trials
- Measure underpower risk
- Compare sample-size options
- Select a defensible margin

**Illustrative curves show the design principle—not observed clinical performance.**

# Sampling density should protect Cmax and AUC

**Early dense sampling**

**Peak protection**

**Terminal coverage**

**Expected Tmax ≈ 2 h**

0 | 0.25 | 0.5 | 0.75 | 1 | 1.25 | **1.5** | **2** | **2.5** | **3** | 4 | 6 | 8 | 12 | 16 | 24 | 36 h

- Capture the ascending limb and peak
- Preserve adequate $AUC_{0–t}$ coverage
- Estimate the terminal phase reliably
- Remove only demonstrably redundant samples



# Washout should protect the slowest plausible eliminators

## COMMON RULE

**5 half-lives**

Remaining fraction = $(½)^5$

**= 3.125%**

## POPULATION-AWARE RULE

- Model the half-life distribution
- Use an upper percentile—not only the mean
- Confirm negligible pre-dose exposure
- Stress-test carryover scenarios

**AI adds value when elimination variability is wide or incompletely observed.**

# Food effects emerge from interacting physiological changes

**GASTRIC**
pH and emptying

→

**INTESTINAL**
Fluid volume and bile

→

**DRUG**
Dissolution and precipitation

→

**SYSTEMIC**
Splanchnic blood flow

→

**BIOLOGY**
Enzymes and transporters



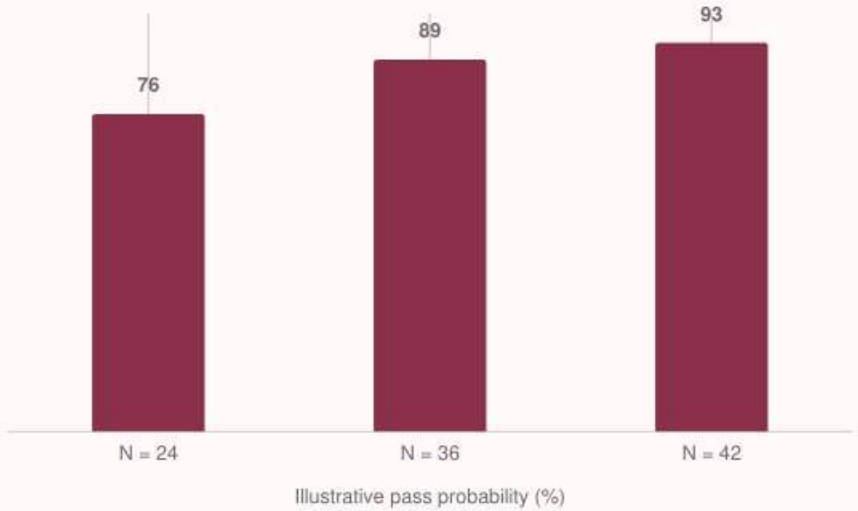
**PBPK/PBBM simulates mechanism; ML can learn response patterns across related compounds.**

**The decision to require a fed study must remain aligned with ICH, FDA/EMA guidance and the PSG.**

# Virtual BE converts design choices into pass probabilities

## VIRTUAL SUBJECT LOOP

- Generate Test and Reference profiles
- Compute AUC and Cmax
- Analyze log-scale T/R ratios
- Repeat across virtual trials
- Identify the dominant failure driver




**Failure driver: gastric emptying variability**

**This example supports N = 42 and denser sampling around Tmax.**

REAL FDA CASE • ANDA 211253

# Diclofenac gel demonstrates regulatory-grade virtual BE

## THE CHALLENGE

- Local skin exposure matters
- Plasma PK may be incomplete
- Clinical endpoint studies are costly
- Formulation sensitivity is essential

## TOTALITY OF EVIDENCE

- Q1/Q2 sameness and physical-structural similarity
- In vitro product characterization
- In vivo PK evidence
- Dermal PBPK for Test and Reference
- Virtual BE plus sensitivity analysis

**FDA accepted the package without a comparative clinical endpoint study.**

# Credibility came from multilevel validation and sensitivity

## PRODUCT-LEVEL VALIDATION

Published single- and multiple-dose data, different application amounts and sites, plus an independent ANDA PK dataset.

## PLATFORM-LEVEL VALIDATION

The mechanistic dermal absorption platform was evaluated with additional topical active ingredients.

**SENSITIVITY TEST**

**Reasonable changes in influential parameters did not overturn the BE conclusion.**

**A good fit is insufficient unless assumptions, uncertainty and discriminatory ability are tested.**

# A defensible AI-enabled workflow has six locked gates

01

Define the regulatory question

02

Pre-specify data splits and leakage controls

03

Build the mechanistic PBPK/PBBM core

04

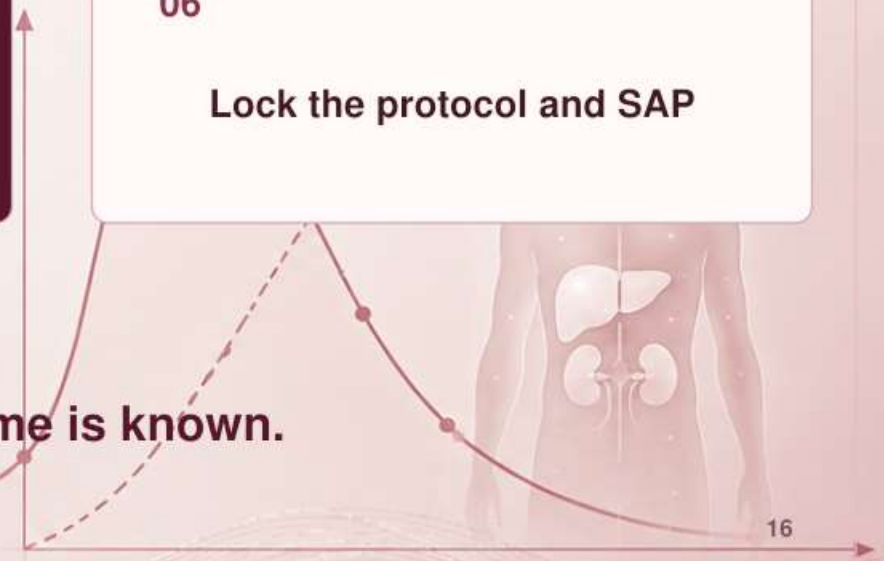
Validate for the exact context of use

05

Simulate design and stress scenarios

06

Lock the protocol and SAP



**No post hoc redesign after the pivotal outcome is known.**

# Credible AI requires controls beyond predictive accuracy

| | |
|---|---|
| **LIMITED DATA** | Sparse complete formulation–dissolution–PK datasets |
| **BIAS** | Successful studies are more visible than failures |
| **LEAKAGE** | Subject or batch records crossing train/test splits |
| **GENERALIZATION** | Performance may not transfer across products |
| **AUDITABILITY** | Data, code, version, seed and decisions must be traceable |
| **HUMAN CONTROL** | Outliers and regulatory conclusions require expert judgment |

**Regulatory acceptance is earned through evidence, explainability and reproducibility—not the AI label.**

# The strongest design combines five forms of evidence

01

**EXPERIMENTAL DATA**

Anchors biological reality

02

**PBPK / PBBM**

Preserves mechanistic causality

03

**CLASSICAL STATISTICS**

Defines the BE decision

04

**EXPLAINABLE ML**

Targets uncertainty and accelerates prediction

05

**EXPERT JUDGMENT**

Protects regulatory and clinical relevance

**Validated hybrid evidence can reduce uncertainty—and sometimes reduce human study burden.**

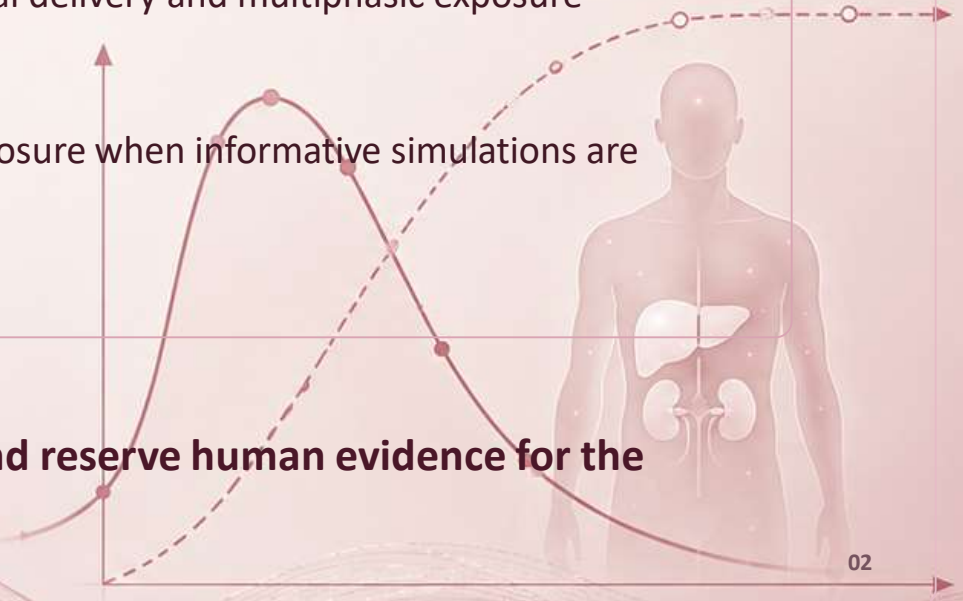
**AI assists the decision; accountable scientists remain responsible for it.**

# AI is reshaping BE as product complexity grows

**500+**

**FDA drug and biologic submissions containing AI components since 2016**

| | |
|---|---|
| **COST** | Human crossover studies, dense sampling and bioanalysis |
| **TIME** | Iterative formulation development and failed pivotal studies |
| **COMPLEXITY** | Modified release, local delivery and multiphasic exposure |
| **ETHICS** | Repeated human exposure when informative simulations are possible |



**The strategic shift: use models to learn earlier, design smarter and reserve human evidence for the questions that truly require it.**

# FDA and EMA are converging on good AI practice

## EMA • 2024

**AI across discovery, nonclinical, clinical, manufacturing and post-authorisation use**

GxP alignment • ethics • traceability • patient safety • result integrity

## FDA + EMA • 2026

**Ten guiding principles for good AI practice in drug development**

Human-centric • risk-based • clear context of use • data governance • lifecycle management

**Regulatory convergence is moving from “Can AI be used?” to “What makes its evidence credible for this decision?”**

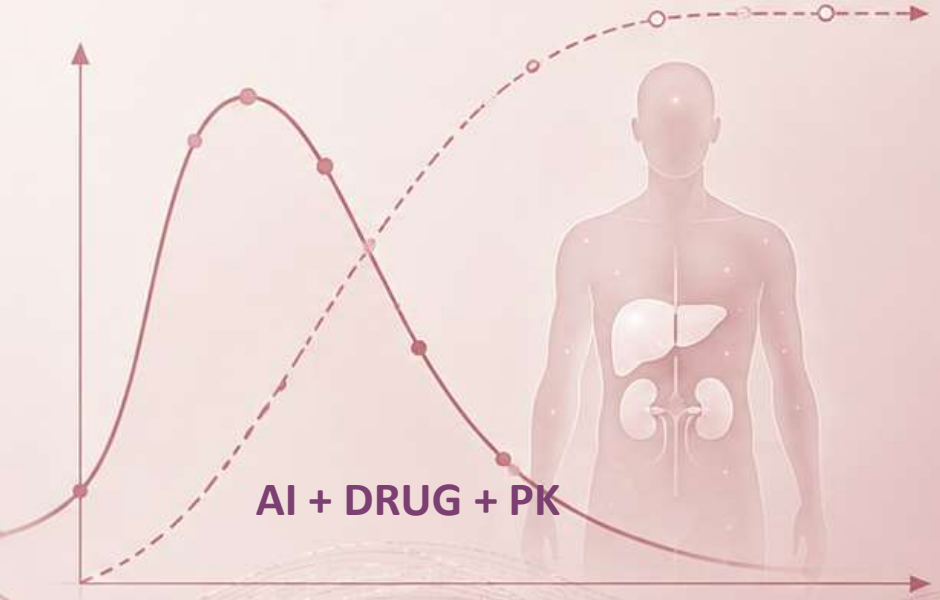
# AI PLATFORMS

# FOR BIOEQUIVALENCE

From PBPK/PBBM and virtual trials to intelligent data operations

**SCIENTIFIC CONTINUATION DECK**

**Simcyp • GastroPlus • PK-Sim • Phoenix • Medidata • Saama**



# The platform landscape has two distinct layers

## SCIENTIFIC / MECHANISTIC

**Directly informs BE risk**

- PBPK and PBBM
- Virtual bioequivalence
- Formulation bridging
- Dissolution safe space
- NCA and statistical BE

## OPERATIONAL / DATA

**Improves study execution**

- Clinical data integration
- AI-assisted quality checks
- Workflow orchestration
- Risk-based monitoring
- Traceable review and reporting

**The first layer predicts exposure; the second protects data flow and decision quality.**

HOW THE STACK FITS TOGETHER

# A modern BE workflow combines—not substitutes—platforms

01

## FORMULATION

**GastroPlus / Simcyp**

Dissolution, particle size, food effect

02

## VIRTUAL TRIAL

**Simcyp / GastroPlus / PK-Sim**

Population PK profiles and BE probability

03

## PK ANALYSIS

**Phoenix WinNonlin / R**

NCA, Cmax, AUC and statistical BE

04

## TRIAL DATA

**Medidata / Saama**

Collection, cleaning, oversight and auditability

**Platform value comes from a validated handoff of assumptions, data, parameters and uncertainty.**

# SIMCYP

## PBPK PLATFORM

Virtual populations, regulatory applications and bioequivalence decisions

**SCIENTIFIC CONTINUATION DECK**

**MECHANISTIC PBPK, VBE AND AI-ENABLED SUPPORT**



# Simcyp models drug exposure in virtual patients

## PHYSIOLOGICALLY BASED PHARMACOKINETICS

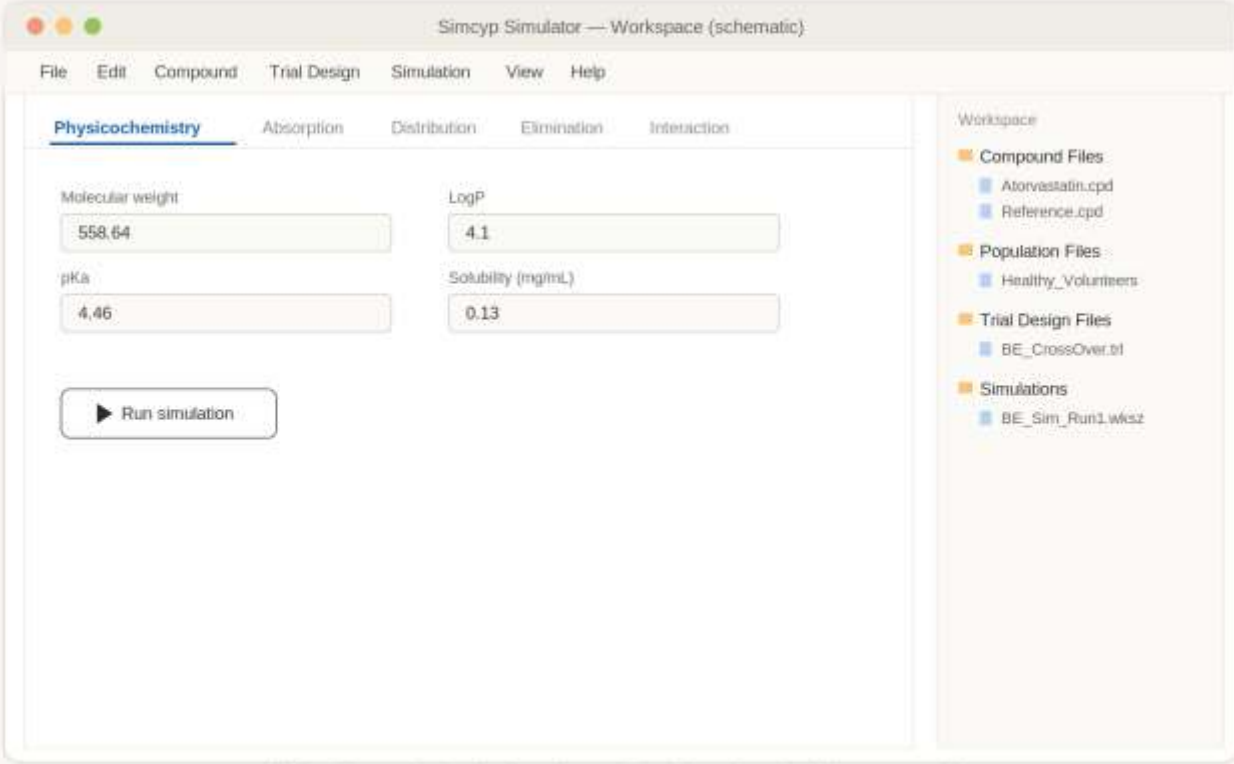
- Organ volumes and blood flows
- Enzyme and transporter activity
- Absorption, distribution and clearance
- Population variability and covariates

## MODEL OUTPUTS

| | |
|---|---|
| PLASMA | Concentration-time profiles |
| TISSUES | Local and organ exposure |
| POPULATION | Variability across individuals |
| DECISIONS | Dose, trial and formulation questions |

**Simcyp combines drug-specific data with system and population knowledge.**

# The workspace connects four evidence layers




**COMPOUND** Physicochemistry, binding, permeability and clearance

**SYSTEM** Organ physiology, enzymes and transporters

**POPULATION** Demographics, genetics and disease states

**TRIAL** Dose, regimen, sampling and comparator design

**The model links these layers before the virtual trial begins.**

A CORE SIMCYP CAPABILITY

# Validated virtual populations represent human variability

**DEMOGRAPHY**

Age, sex, body size and ethnicity

**PHYSIOLOGY**

Organ size, blood flow and protein abundance

**ONTOGENY**

Developmental changes in enzymes and transporters

**DISEASE**

Renal, hepatic and cardiovascular changes

**Population libraries allow correlated virtual individuals instead of isolated average values.**

# Virtual bioequivalence estimates the probability of a BE outcome

**STEP 1**

Create virtual Test and Reference products

**STEP 2**

Define the crossover or replicate design

**STEP 3**

Generate virtual subjects and concentration profiles

**STEP 4**

Calculate Cmax, AUC and confidence intervals

**STEP 5**

Repeat trials and estimate probability of success

**VBE supports formulation selection, trial planning and model-informed alternatives when regulators accept the context of use.**

**The model requires product-specific verification and validation before regulatory use.**

# Special-population models extend predictions beyond healthy adults

## CLINICAL POPULATIONS

- Renal impairment
- Hepatic impairment
- Reduced cardiac output
- Paediatric age groups
- Pregnancy and lactation

## MECHANISTIC DETAIL

- Developmental physiology and enzyme ontogeny
- Kidney, brain and cardiac submodels
- Changes in binding, blood flow and clearance
- Population-specific variability distributions

**Predictions remain limited to populations and scenarios supported by credible inputs and validation.**

# Mechanistic dermal modeling links formulation to local exposure

| | |
|---|---|
| **FORMULATION** | Release and partitioning |
| **STRATUM CORNEUM** | Diffusion barrier |
| **VIABLE SKIN** | Dermal distribution |
| **SYSTEMIC CIRCULATION** | Plasma exposure |

## MULTI-PHASE, MULTI-LAYER MODEL

- Local and systemic exposure
- Sensitivity to formulation differences
- Integration of in vitro product data
- Virtual BE assessment



**Dermal PBPK can support a totality-of-evidence strategy for complex topical generics.**

FDA CASE: ANDA 211253

# Diclofenac gel demonstrates a regulatory-grade VBE application

## THE QUESTION

- Complex topical product
- Local and systemic exposure
- Clinical endpoint study burden
- Need for formulation sensitivity

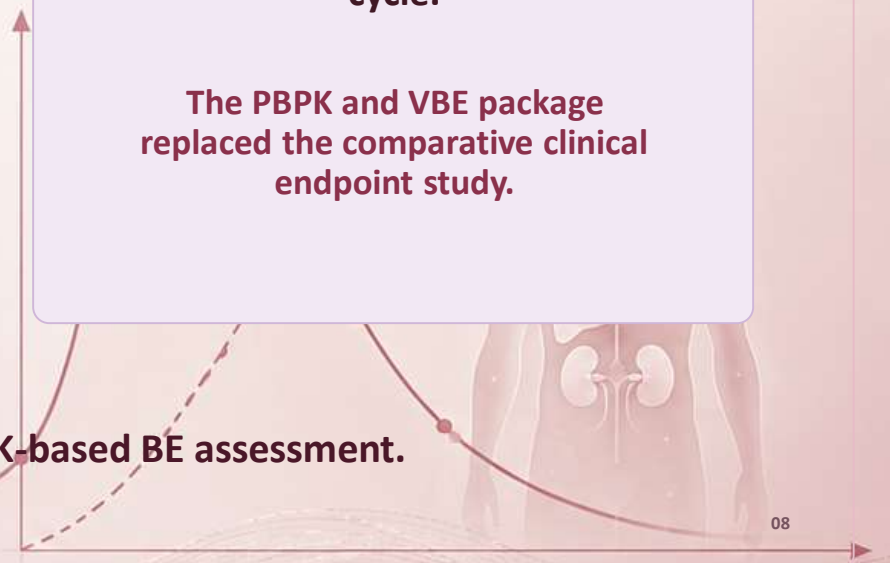
## THE EVIDENCE

- Product sameness and characterization
- In vivo PK evidence
- Dermal PBPK model validation
- Virtual BE analysis

## THE OUTCOME

**FDA approved the generic diclofenac sodium topical gel, 1%, during the first review cycle.**

**The PBPK and VBE package replaced the comparative clinical endpoint study.**



**FDA described this as the first ANDA approval supported by a PBPK-based BE assessment.**

# Regulatory credibility comes from documented performance




## CURRENT EVIDENCE

| | |
|---|---|
| 120+ | novel drugs supported according to Certara |
| 25 years | of consortium development |
| 37 | participating pharmaceutical companies |
| 11 | regulatory agencies licensing the platform |

**EMA qualified Simcyp V19 for defined CYP-mediated drug-drug interaction contexts in 2025. Qualification does not validate every model or application automatically.**

# One platform addresses questions across development

### FIRST-IN-HUMAN

Estimate exposure and support starting-dose selection

### DRUG INTERACTIONS

Predict CYP and transporter-mediated interaction risk

### FORMULATION

Assess food effects, absorption and product performance

### SPECIAL POPULATIONS

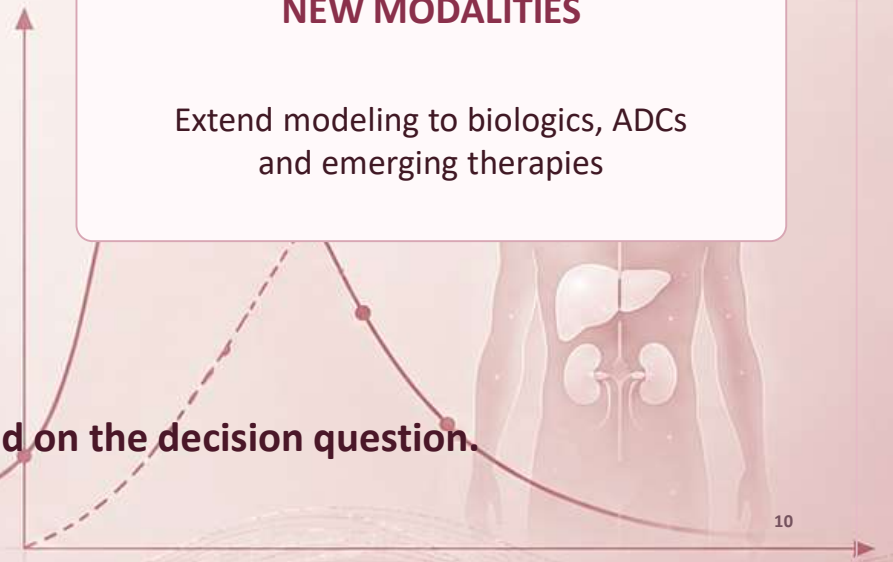
Explore unstudied physiology and dosing scenarios

### VIRTUAL BE

Compare Test and Reference products in simulated trials

### NEW MODALITIES

Extend modeling to biologics, ADCs and emerging therapies



**The appropriate module, evidence burden and validation plan depend on the decision question.**

# Version 25 expands modeling and user support

### BIOPHARMACEUTICS

More emphasis on formulation and virtual BE workflows

### BIOLOGICS AND TMDD

Improved representation of membrane targets and target shedding

### COMPUTING

Modern interface and cloud-enabled execution

### AI SUPPORT

Ask Simcyp help chat and structure-based parameter predictors

**AI features assist navigation and parameter estimation. The core simulator remains a mechanistic PBPK platform.**

# PBPK simulation and artificial intelligence play different roles

## MECHANISTIC PBPK

- Uses physiological and biochemical equations
- Represents organs, enzymes and transporters
- Simulates virtual individuals from specified distributions
- Tests scenarios through explicit model structure

## AI-ENABLED SUPPORT

- Learns patterns from data
- Predicts parameters from chemical structure
- Supports search, assistance and workflow efficiency
- Can augment hybrid mechanistic and data-driven models

**Simcyp becomes AI-enabled when machine learning contributes to prediction or workflow decisions.**

# A credible bioequivalence workflow follows six controlled stages

**01 QUESTION**

Define the product risk and regulatory objective

**02 INPUTS**

Characterize drug, formulation and physiology

**03 MODEL**

Build the absorption and PBPK structure

**04 VERIFY**

Confirm implementation and parameter traceability

**05 VALIDATE**

Test prediction against relevant observed data

**06 APPLY**

Run VBE scenarios and quantify uncertainty



**Each regulatory conclusion remains tied to a prespecified context of use and documented uncertainty.**

TAKE-HOME MESSAGE

# Simcyp is strongest when the decision and evidence are explicit

| | | |
|---|---|---|
| 01 | MECHANISTIC FOUNDATION | Drug and physiology models explain why exposure changes |
| 02 | POPULATION REALISM | Virtual populations quantify variability and special-population effects |
| 03 | REGULATORY TRACK RECORD | Documented use supports confidence, within defined contexts |
| 04 | AI AUGMENTATION | New AI functions improve assistance and selected predictions |

**For bioequivalence, the platform can connect formulation behavior, patient variability and probability of success.**

# GASTROPLUS

## PBBM AND PBPK

Mechanistic absorption, formulation development and virtual bioequivalence

**SCIENTIFIC CONTINUATION DECK**

**ACAT, FORMULATION, VBE AND AI-ENABLED SUPPORT**



# GastroPlus connects formulation behavior to systemic exposure

## MECHANISTIC MODELING

- Physiologically based biopharmaceutics modeling
- Whole-body PBPK and pharmacodynamics
- Oral and non-oral absorption routes
- Human and animal simulations

## QUESTIONS IT ANSWERS

| | |
|---|---|
| **ABSORPTION** | What limits oral bioavailability? |
| **FORMULATION** | Which product attributes control exposure? |
| **POPULATION** | How does variability affect PK? |
| **STUDY** | Will Test and Reference meet BE criteria? |

**The platform integrates compound, formulation, physiology and observed PK data.**

# A GastroPlus model begins with decision-relevant inputs

| | | |
|---|---|---|
| 01 | **COMPOUND** | Solubility by pH, pKa, logP or logD, permeability and binding |
| 02 | **FORMULATION** | Particle size, dissolution, dosage form, release profile and strength |
| 03 | **PHYSIOLOGY** | GI transit, fluid volumes, bile salts, enzymes, transporters and organ data |
| 04 | **TRIAL** | Dose, route, fed or fasted condition, sampling and observed concentration data |

**MODEL OUTPUT: concentration-time profiles, tissue exposure, PK endpoints and uncertainty**

# ACAT is the mechanistic core of oral absorption modeling

| STOMACH | DUODENUM | JEJUNUM | ILEUM | COLON |
|---|---|---|---|---|
| Release and dissolution | Rapid transit and absorption | Major absorptive region | Late absorption and precipitation | Residual absorption |

**Within each region, ACAT calculates dissolution, precipitation, degradation, transit, permeability and first-pass loss over time.**

**The model links API properties, formulation performance and gastrointestinal physiology.**

# ACATPlus extends the absorption framework for complex products

## ACAT FOUNDATION

- Regional GI physiology
- Dynamic dissolution and precipitation
- Permeability and intestinal metabolism
- Transporter and first-pass effects

## ACATPLUS EXTENSION

- Greater mechanistic detail
- More flexible process definitions
- Support for difficult formulation questions
- Expanded PBBM applications

**This depth makes GastroPlus particularly useful for poorly soluble drugs and formulation-sensitive exposure.**

# Oral exposure emerges from interacting physiological processes

## DISSOLUTION

Particle size, solubility, salt form and release rate

## GI ENVIRONMENT

Regional pH, bile salts, fluid volume and transit

## MEMBRANE

Permeability, uptake, efflux and saturable absorption

## PRESYSTEMIC LOSS

Luminal degradation, gut metabolism and hepatic first pass

## MEAL STATE

Gastric emptying, bile secretion and altered dissolution

**GastroPlus can isolate the process that limits exposure and test formulation changes before clinical evaluation.**

**The largest value appears when dissolution, permeability and physiology interact.**

# Whole-body PBPK predicts distribution beyond the gastrointestinal tract

## PHYSIOLOGICAL SYSTEM

- Organ volumes and blood flows
- Tissue partition coefficients
- Plasma protein binding
- Renal and hepatic clearance
- Enzymes and transporters

## APPLICATIONS

- Human PK prediction from preclinical data
- First-in-human dose assessment
- Tissue concentration prediction
- Renal or hepatic impairment
- Age, body size and disease effects

**PBPKPlus connects the absorption model to systemic distribution and elimination.**

# Virtual formulation experiments reduce unnecessary prototypes

### PARTICLE ATTRIBUTES

Size distribution, crystal form, salt and amorphous fraction

### DISSOLUTION

Rate, profile, precipitation and supersaturation

### DOSAGE FORM

Immediate, delayed, enteric or controlled release

### PRODUCT DESIGN

Dose strength, excipients, release location and timing

**Simulation screens plausible designs before manufacturing a large number of experimental batches.**

# IVIVCPlus links laboratory dissolution to in vivo performance

| | | |
|---|---|---|
| 01 | **OBSERVED PK** | Deconvolution estimates the in vivo absorption profile |
| 02 | **IN VITRO DISSOLUTION** | Profiles describe formulation release under selected conditions |
| 03 | **LEVEL A IVIVC** | Point-to-point relationship connects dissolution and absorption |
| 04 | **PREDICTION** | Convolution predicts plasma concentration-time profiles |
| 05 | **ACCEPTANCE** | Internal and external predictability support the model |

**The resulting model can define dissolution ranges that preserve product performance.**

# Virtual bioequivalence evaluates Test and Reference across simulated trials

### Cmax

Peak systemic exposure

### AUC0-t

Observed exposure through the last quantifiable sample

### AUC0-inf

Total exposure extrapolated to infinity

### Tmax

Time to peak concentration

### PARTIAL AUC

Exposure within a prespecified clinically relevant time window

**For each virtual trial, the model can calculate the Test-to-Reference geometric mean ratio and its 90% confidence interval.**

**The pAUC interval and interpretation must be justified before the analysis.**

# VBE estimates how design and product uncertainty affect success

**PRODUCT MODELS**

Create mechanistic Test and Reference formulations

**VIRTUAL SUBJECTS**

Sample physiological and product variability

**STUDY DESIGN**

Specify crossover, replicate, dose and sampling schedule

**STATISTICAL ANALYSIS**

Calculate endpoint ratios and confidence intervals

**REPEATED TRIALS**

Estimate the probability of meeting BE criteria

**VBE can support candidate selection, sample-size planning, biowaiver strategy and post-approval change assessment.**

# Food effects arise from simultaneous changes in gastrointestinal physiology

## FASTED STATE

- Lower gastric volume
- Faster or variable gastric emptying
- Lower bile salt concentrations
- Different intestinal fluid conditions

## FED STATE

- Delayed gastric emptying
- Higher bile secretion
- Improved solubilization of lipophilic drugs
- Changed dissolution and precipitation

**The model tests whether food increases, decreases or delays absorption.**

# Drug-interaction models combine enzyme and transporter mechanisms

### REVERSIBLE INHIBITION

Immediate concentration-dependent reduction in activity

### TIME-DEPENDENT INHIBITION

Progressive enzyme inactivation during exposure

### INDUCTION

Increased enzyme or transporter expression

### COMPETITIVE METABOLISM

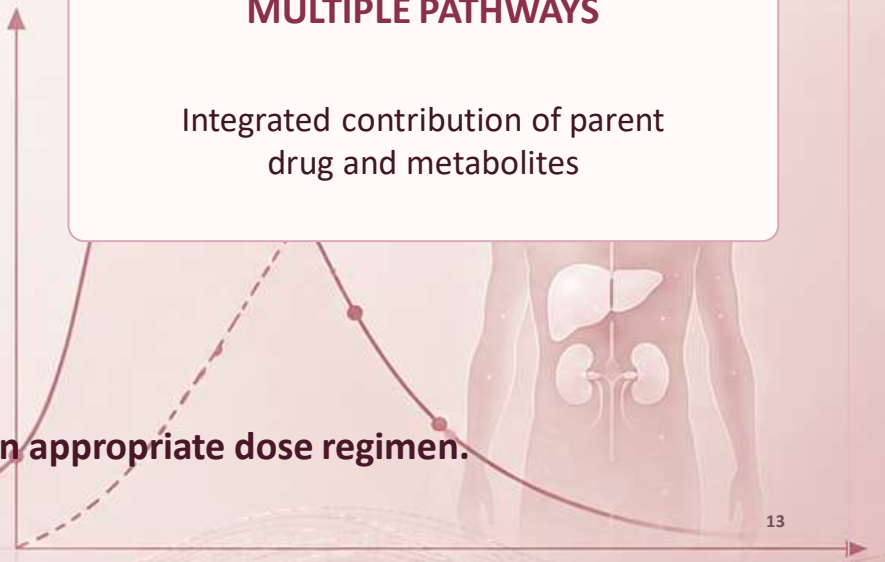
Substrates compete for shared pathways

### TRANSPORTER EFFECTS

Uptake or efflux changes alter exposure

### MULTIPLE PATHWAYS

Integrated contribution of parent drug and metabolites



**The analysis can inform the need for a clinical DDI study and selection of an appropriate dose regimen.**

# Virtual populations and dosage routes expand the scenario space

## VIRTUAL VARIABILITY

- Age, sex, body size and organ function
- Enzyme and transporter expression
- GI transit, solubility and effective permeability
- Formulation and particle-size variability

## SUPPORTED ROUTES

**Oral and oral cavity**

Intravenous

Subcutaneous and intramuscular

Inhalation

Dermal and ocular

**Available routes and capabilities depend on the licensed modules.**

# AssessmentsPlus and GastroPlusGPT add guided analysis

## ASSESSMENTSPLUS

- Reviews compound properties before modeling
- Evaluates simulation results and observed PK mismatch
- Uses embedded decision logic to flag weak assumptions
- Highlights parameters that need further investigation

## GASTROPLUSGPT

- Answers software and workflow questions
- Guides model construction and troubleshooting
- Explains AssessmentsPlus findings
- Improves access to technical documentation

**These tools assist the modeler. Scientific judgment, verification and validation remain essential.**

# P-PSD and ADMET Predictor improve early model inputs

## P-PSD

**Represents a particle-size distribution rather than a single fixed diameter.**

- Links particle variability to dissolution
- Tests effects on Cmax, AUC and BE probability
- Supports poorly soluble drug products

## ADMET PREDICTOR

**Uses chemical structure to estimate parameters for an initial model.**

- Solubility, pKa and lipophilicity
- Permeability and protein binding
- Distribution and metabolic properties

**Predicted inputs require confirmation as experimental and clinical evidence becomes available.**

# Automation scales sensitivity analysis and formulation exploration

| | | |
|---|---|---|
| 01 | **BATCH SIMULATION** | Run large sets of scenarios with consistent settings |
| 02 | **PARAMETER SPACE** | Explore formulation and physiological combinations |
| 03 | **SENSITIVITY** | Identify the inputs that control exposure and BE risk |
| 04 | **OPTIMIZATION** | Search for product designs that meet target performance |
| 05 | **INTEGRATION** | Connect GastroPlus with enterprise data and workflows |

**Automation increases throughput while preserving traceable models and prespecified analyses.**

PLATFORM COMPARISON

# GastroPlus and Simcyp overlap, but their strongest use cases differ

| | GASTROPLUS | SIMCYP |
|---|---|---|
| PRIMARY EMPHASIS | Oral absorption, PBBM and formulation performance | Population PBPK and regulatory DDI modeling |
| DISTINCTIVE STRENGTH | ACAT, IVIVCPlus and integrated dissolution-to-PK workflows | Validated population libraries and broad consortium history |
| VIRTUAL BE | Strong for oral products and formulation-driven risk | Strong across population PBPK and supported product contexts |
| AI SUPPORT | AssessmentsPlus, GastroPlusGPT and ADMET Predictor integration | Ask Simcyp and structure-based parameter support |

**Platform selection should follow the scientific question, available evidence and regulatory strategy.**

TAKE-HOME MESSAGE

# GastroPlus is strongest when formulation drives exposure

| | | |
|---|---|---|
| 01 | MECHANISTIC ABSORPTION | ACAT connects API, product and GI physiology |
| 02 | FORMULATION SCIENCE | Virtual experiments explain how product attributes affect PK |
| 03 | BIOEQUIVALENCE | VBE quantifies the probability that Test and Reference meet PK criteria |
| 04 | PREDICTIVE DISSOLUTION | IVIVCPlus links laboratory release to in vivo performance |
| 05 | AI AND AUTOMATION | Guided assessment and scalable execution improve workflow efficiency |

**The platform adds most value when its models are verified, validated and tied to a clear decision.**

# PK-SIM®

# AND MOBI®

Open-source whole-body PBPK modeling, virtual populations and model extension

**SCIENTIFIC CONTINUATION DECK**

**PBPK • VBE • AUTOMATION • AI-READY WORKFLOWS**



# PK-Sim turns physiology and drug properties into concentration–time predictions

## WHOLE-BODY PBPK

- Organ-resolved physiology
- Blood-flow-driven distribution
- Enzyme and transporter processes
- Human and laboratory-animal species

## DECISIONS SUPPORTED

- First-in-human translation
- Dose selection and regimen design
- Special-population extrapolation
- Drug–drug interaction assessment
- Exposure and tissue-PK prediction

**PK-Sim is the PBPK-focused component of the Open Systems Pharmacology Suite.**

# Reusable building blocks make model construction systematic

### INDIVIDUALS

Anatomy, physiology and demographics

### POPULATIONS

Distributions of physiological variability

### COMPOUNDS

Physicochemical and ADME properties

### FORMULATIONS

Release and dissolution behavior

### PROTOCOLS

Dose, route, schedule and study conditions

**Building blocks can be exchanged to move from animal to human, individual to population, or single to multiple dosing.**

# A PBPK model links system, drug and trial information

| | | |
|---|---|---|
| 01 | **SYSTEM** | Organ volumes, blood flows, tissue composition and physiology |
| 02 | **DRUG** | pKa, lipophilicity, solubility, permeability and binding |
| 03 | **PROCESSES** | Clearance, enzymes, transporters and renal handling |
| 04 | **FORMULATION** | Dose form, dissolution, particle size and release |
| 05 | **OBSERVATIONS** | Plasma, blood, urine or tissue concentration data |

**Model inputs should be evidence-ranked and linked to their experimental source.**

# Physiology converts a dose into organ and plasma exposure

**ADMINISTRATION**

Dose enters a defined route and formulation

**ABSORPTION**

Release and uptake determine systemic entry

**DISTRIBUTION**

Blood flow and partitioning drive tissue exposure

**METABOLISM**

Enzyme abundance and kinetics remove drug

**EXCRETION**

Renal and other pathways complete elimination

**Mass-balance differential equations connect every compartment over time.**

**OUTPUTS: plasma PK • tissue concentrations • pathway contributions • uncertainty**

# Different structures support small molecules and biologics

## SMALL MOLECULES

- Perfusion- or permeability-limited distribution
- Enzyme and transporter kinetics
- Renal filtration and secretion
- Oral, intravenous and other routes

## LARGE MOLECULES

- Alternative tissue structures
- Lymph and endosomal processes
- Target-mediated disposition extensions
- Model-specific mechanistic detail

**Structure selection must match molecular modality and the intended question.**

# MoBi exposes the equations behind a PK-Sim model

| | | |
|---|---|---|
| 01 | START IN PK-SIM | Build a standard PBPK model efficiently |
| 02 | TRANSFER | Export the model with its full mechanistic structure |
| 03 | CUSTOMIZE IN MOBI | Modify equations, reactions, events and spatial structure |
| 04 | EXTEND | Add pharmacodynamics or systems-pharmacology mechanisms |
| 05 | VERIFY | Compare versions and document every assumption |

**The combination provides an accessible front end and an expert-level modeling environment.**

# Virtual populations propagate biological variability into PK

## VARIABILITY SOURCES

- Age, sex, height and body weight
- Organ size and blood flow
- Enzyme and transporter expression
- Renal and hepatic function
- Disease- or population-specific assumptions

## PREDICTIVE OUTPUTS

- Concentration distributions
- Percentiles and prediction intervals
- Exposure–covariate relationships
- Probability of target attainment
- Between-subject variability

**Population models should represent the target clinical population, not merely generic variability.**

# Parameter identification separates estimation from validation

**1 • PRIOR KNOWLEDGE**

Fix or bound parameters using independent evidence

**2 • IDENTIFICATION**

Estimate only parameters supported by the data

**3 • DIAGNOSTICS**

Inspect residuals, plausibility and parameter correlation

**4 • VERIFICATION**

Confirm implementation and numerical behavior

**5 • VALIDATION**

Test predictions against data not used for fitting



**A visually good fit is not sufficient evidence of predictive performance.**

# Sensitivity analysis identifies the assumptions that control exposure

| | | |
|---|---|---|
| 01 | **LOCAL SENSITIVITY** | Effect of a small parameter change near the nominal model |
| 02 | **GLOBAL EXPLORATION** | Joint influence across plausible parameter ranges |
| 03 | **UNCERTAINTY** | Propagation of imperfect knowledge to model outputs |
| 04 | **IDENTIFIABILITY** | Whether available observations can determine a parameter |
| 05 | **DECISION IMPACT** | Which uncertainty could change the clinical conclusion |

**Prioritize experiments that reduce uncertainty in decision-critical parameters.**

# PK-Sim can support a mechanistic virtual bioequivalence workflow

**REFERENCE MODEL**

Verify absorption, disposition and observed reference PK

**TEST PRODUCT**

Represent formulation or dissolution differences

**VIRTUAL SUBJECTS**

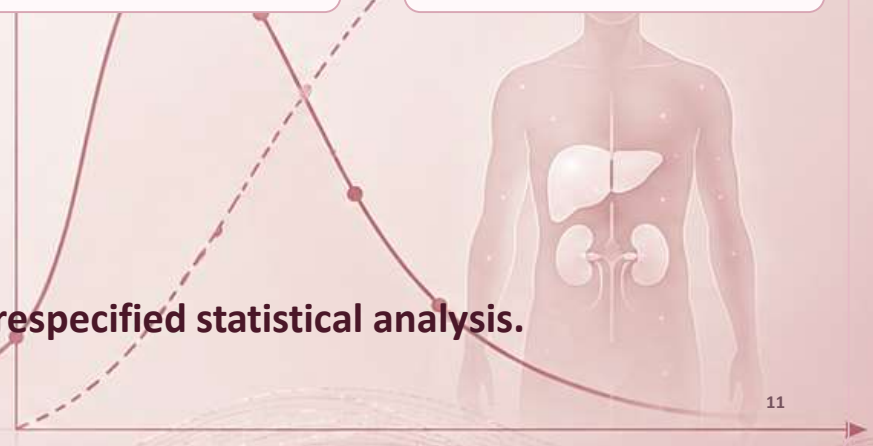
Generate physiological and product variability

**VIRTUAL TRIALS**

Apply dose, sequence, sampling and crossover design

**BE ANALYSIS**

Calculate Cmax and AUC ratios with 90% confidence intervals



**VBE credibility depends on verified product-performance inputs and a prespecified statistical analysis.**

# Bioequivalence endpoints capture rate and extent of exposure

**Cmax**

Maximum observed concentration

**AUC0–t**

Exposure through the last quantifiable sample

**AUC0–∞**

Total exposure extrapolated to infinity

**Tmax**

Time of the observed peak

**PARTIAL AUC**

Exposure within a prespecified time interval

**For conventional average BE, log-transformed Cmax and AUC are typically compared using Test/Reference geometric mean ratios and 90% confidence intervals.**

**The pAUC interval must be clinically and scientifically justified before analysis.**

# Pediatric scaling combines maturation, growth and drug mechanisms

## SYSTEM CHANGES

- Body size and organ growth
- Blood-flow development
- Enzyme ontogeny
- Renal maturation
- Protein-binding differences

## MODEL QUESTIONS

- Is adult clearance scalable?
- Which pathway is age-sensitive?
- What dose achieves matched exposure?
- Where are data gaps largest?
- How uncertain is the proposed regimen?

**Pediatric prediction is mechanistic extrapolation—not simple weight normalization.**

# Mechanistic DDI models connect perpetrators to pathway-level exposure changes

| | | |
|---|---|---|
| 01 | VICTIM MODEL | Establish pathway contributions and baseline PK |
| 02 | PERPETRATOR MODEL | Represent inhibitor, inducer and relevant metabolites |
| 03 | MECHANISM | Competitive inhibition, TDI, induction or transporter effects |
| 04 | REGIMEN | Simulate dose timing, duration and washout |
| 05 | RISK | Predict exposure ratios and identify sensitive scenarios |

**DDI predictions are only as credible as the verified victim and perpetrator models.**

# Open interfaces turn one model into a reproducible analysis pipeline

### OSP SUITE

Graphical model development and review

### OSPSUITE-R

Batch simulations, analysis and reproducible reporting

### SBML

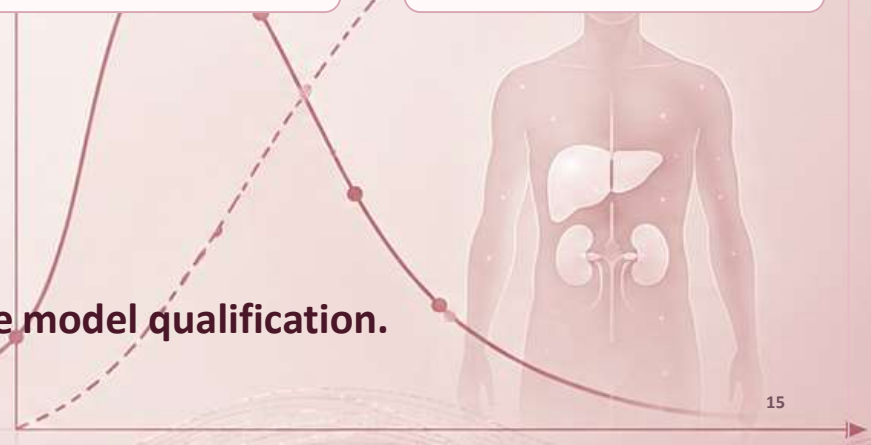
Exchange selected model structures with external tools

### OBSERVED DATA

Import and compare experimental or clinical datasets

### PROJECT HISTORY

Track model changes and document decisions



**Automation improves scale and traceability; it does not replace model qualification.**

# AI can augment PBPK workflows—but PBPK itself is not AI

## MECHANISTIC CORE

- Physiology-based compartments
- Mass-balance differential equations
- Predefined biochemical mechanisms
- Monte Carlo or population simulation

## POSSIBLE AI LAYER

- Predict uncertain molecular inputs
- Emulate computationally intensive simulations
- Detect patterns in residuals
- Prioritize sensitivity scenarios
- Assist literature and model curation

**AI outputs require provenance, external validation and human scientific oversight.**

# The three platforms are complementary rather than interchangeable

| | PK-SIM / MOBI | SIMCYP | GASTROPLUS |
|---|---|---|---|
| ACCESS | Free, open-source | Commercial | Commercial |
| PRIMARY EMPHASIS | Transparent PBPK and model extension | Population PBPK and DDI workflows | PBBM, oral absorption and formulation |
| DISTINCTIVE TOOL | Full PK-Sim ↔ MoBi pathway | Curated population and compound libraries | ACAT and dissolution-to-PK workflow |
| BEST-FIT QUESTION | Can I inspect or extend the model? | How does population variability alter PK? | How does formulation alter absorption? |

**Choose the platform that best matches the scientific question, evidence and regulatory context.**

TAKE-HOME MESSAGE

# PK-Sim is strongest when transparency and extensibility matter

| | | |
|---|---|---|
| 01 | **OPEN SCIENCE** | Free access and inspectable source code support reproducibility |
| 02 | **MECHANISTIC DEPTH** | Whole-body PBPK connects physiology, drug properties and trial design |
| 03 | **MODEL EXTENSION** | MoBi enables equation-level customization and QSP development |
| 04 | **POPULATION PREDICTION** | Virtual subjects support pediatric, DDI and VBE questions |
| 05 | **RESPONSIBLE AI** | AI may assist inputs and analysis, but model credibility remains evidence-based |

Selected sources: Open Systems Pharmacology website, OSP documentation, PK-Sim GitHub repository and the user-supplied review.