Concepts of model-based quantitative decision making

ECP 8506 Clinical Trial Simulation
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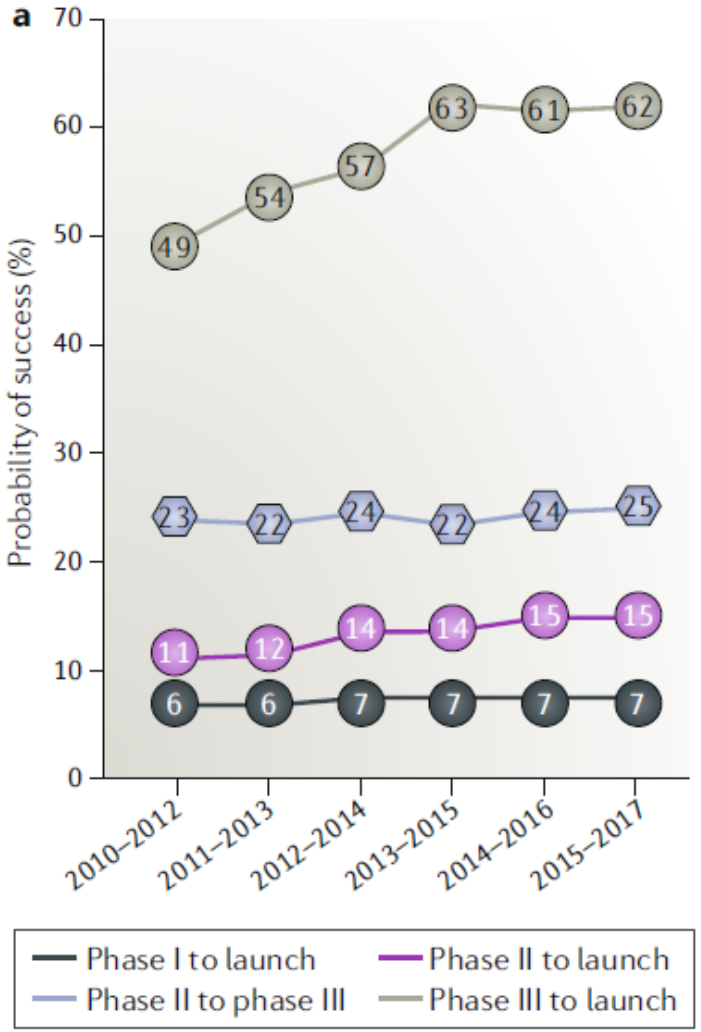
Learning Objectives

- Review drug development processes and reasons for drug attrition
- Understand different quantitative medicine approaches
- Utilize credibility assessment framework in model-informed drug development
- Examples of model-informed drug development

About 90% of clinical drug development fails



Dowden H, Munro J. Trends in clinical success rates and therapeutic focus. *Nat Rev Drug Discov*. 2019;18(7):495-496

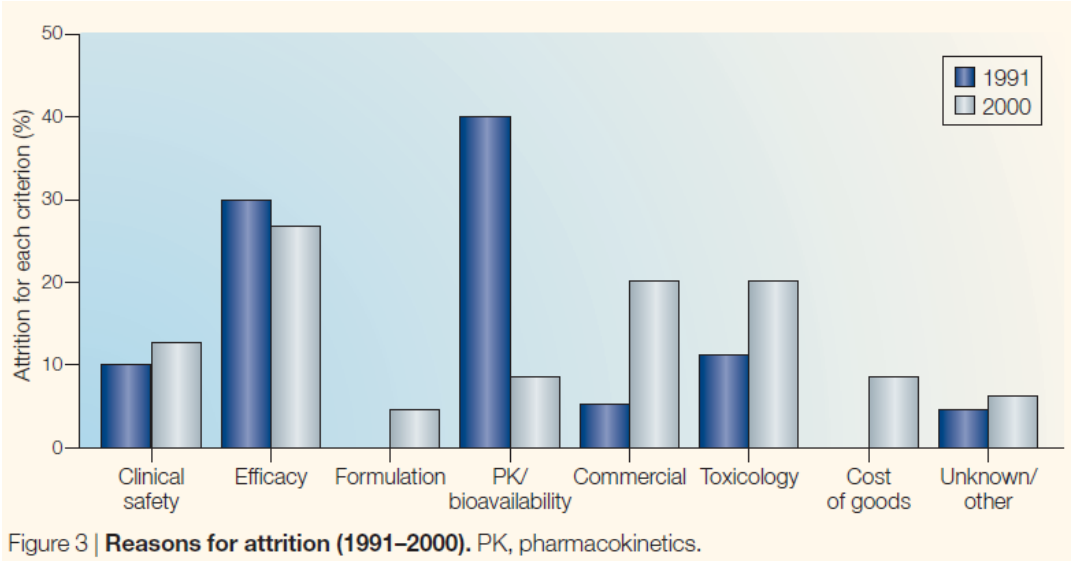
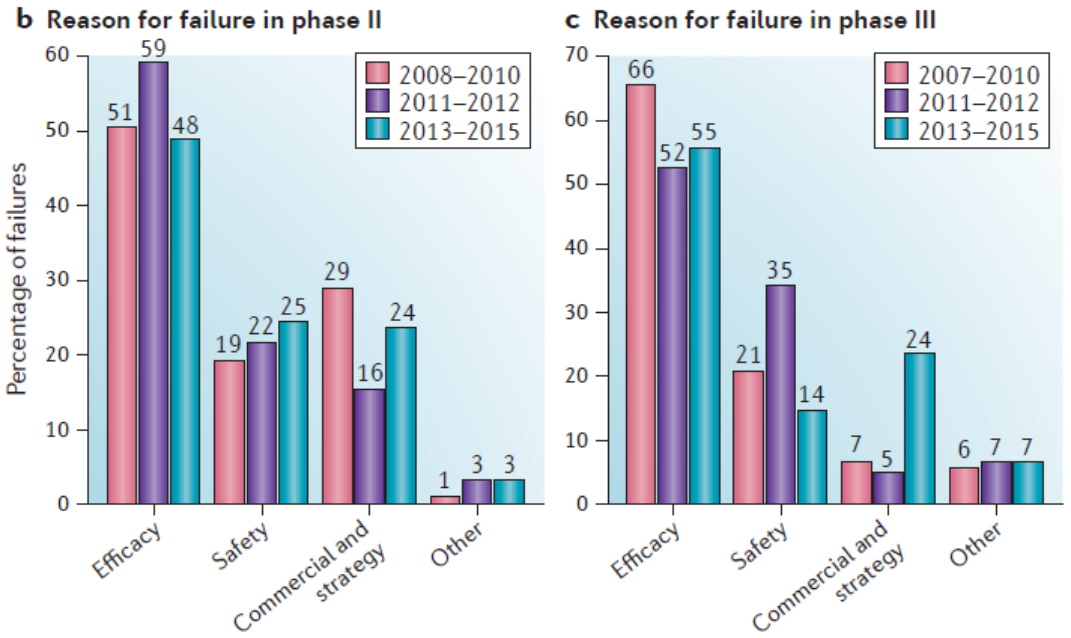


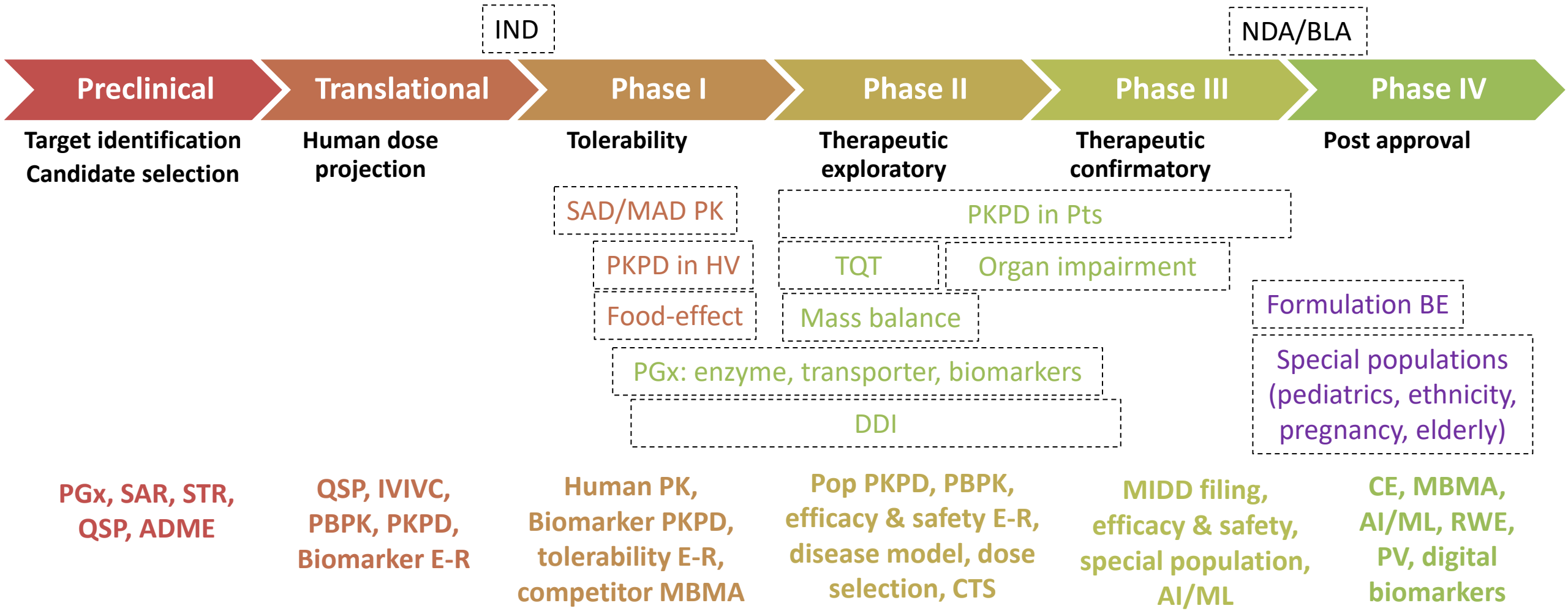
Figure 3 | **Reasons for attrition (1991–2000).** PK, pharmacokinetics.

Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates?. *Nat Rev Drug Discov*. 2004;3(8):711-715.



Harrison RK. Phase II and phase III failures: 2013-2015. *Nat Rev Drug Discov*. 2016;15(12):817-818.

Various tools can be used to support drug development



CE, comparative effectiveness; CTS, clinical trial simulation; E-R, exposure-response; IVIVC, in vitro-in vivo correlation; MBMA, model-based meta-analysis; PBPK, Physiologically based pharmacokinetic; PKPD, pharmacokinetic—pharmacodynamic; PV, pharmacovigilance; QSP, quantitative system pharmacology; RWE, real-world evidence; SAR, structure–activity relationship; STR, structure–tissue exposure/selectivity relationship

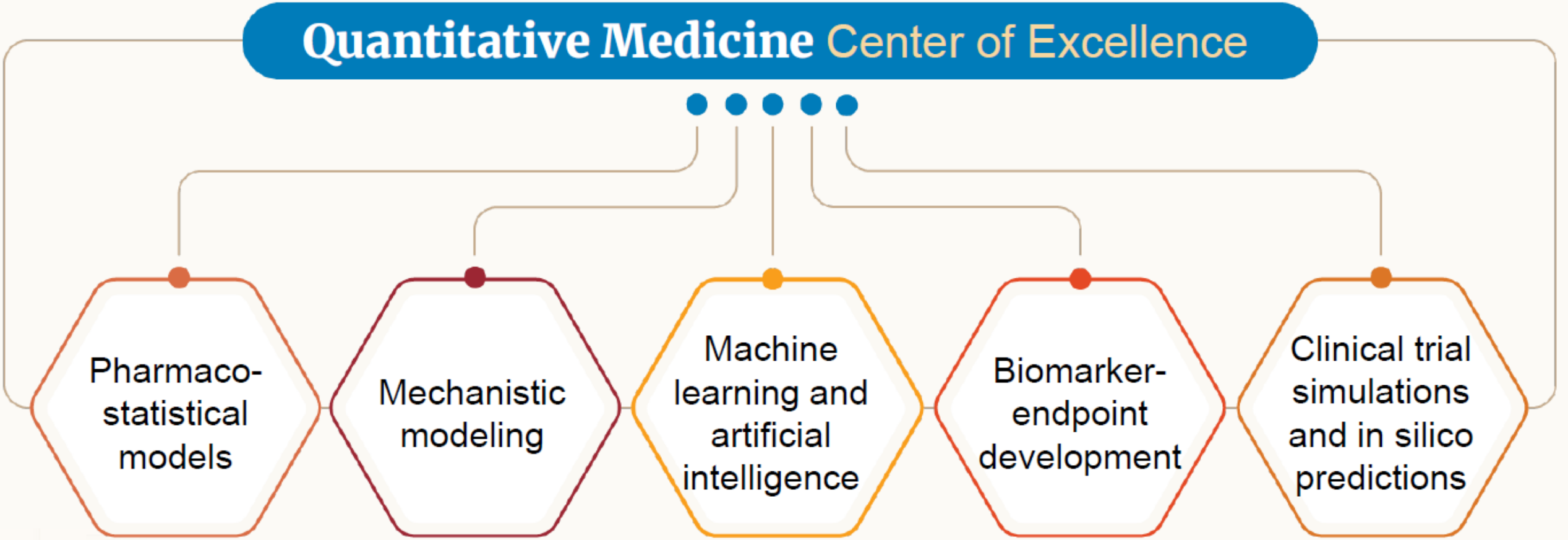
Adapted from Dr. Mark Gastonguay. Model-Informed Decision Making in Drug Development. C-Path MIDD Training Course.

Using Quantitative Medicine approach has the potential to maximize patient and societal benefit

- On 03/25/2024, FDA's Center for Drug Evaluation and Research (CDER) launched the new CDER Quantitative Medicine (QM) Center of Excellence (CoE)
  - The development and application of **exposure-based**, **biological**, and **quantitative modeling and simulation** approaches derived from nonclinical, clinical, and real-world sources to inform drug development, regulatory decision-making, and patient care
  - Model-informed drug development (MIDD)
  - Complex innovative trial design (CID)
  - Fit-for-purpose initiative (FFP)
  - Model integrated evidence (MIE)
  - Physiology based biopharmaceutics modeling (PBBM)

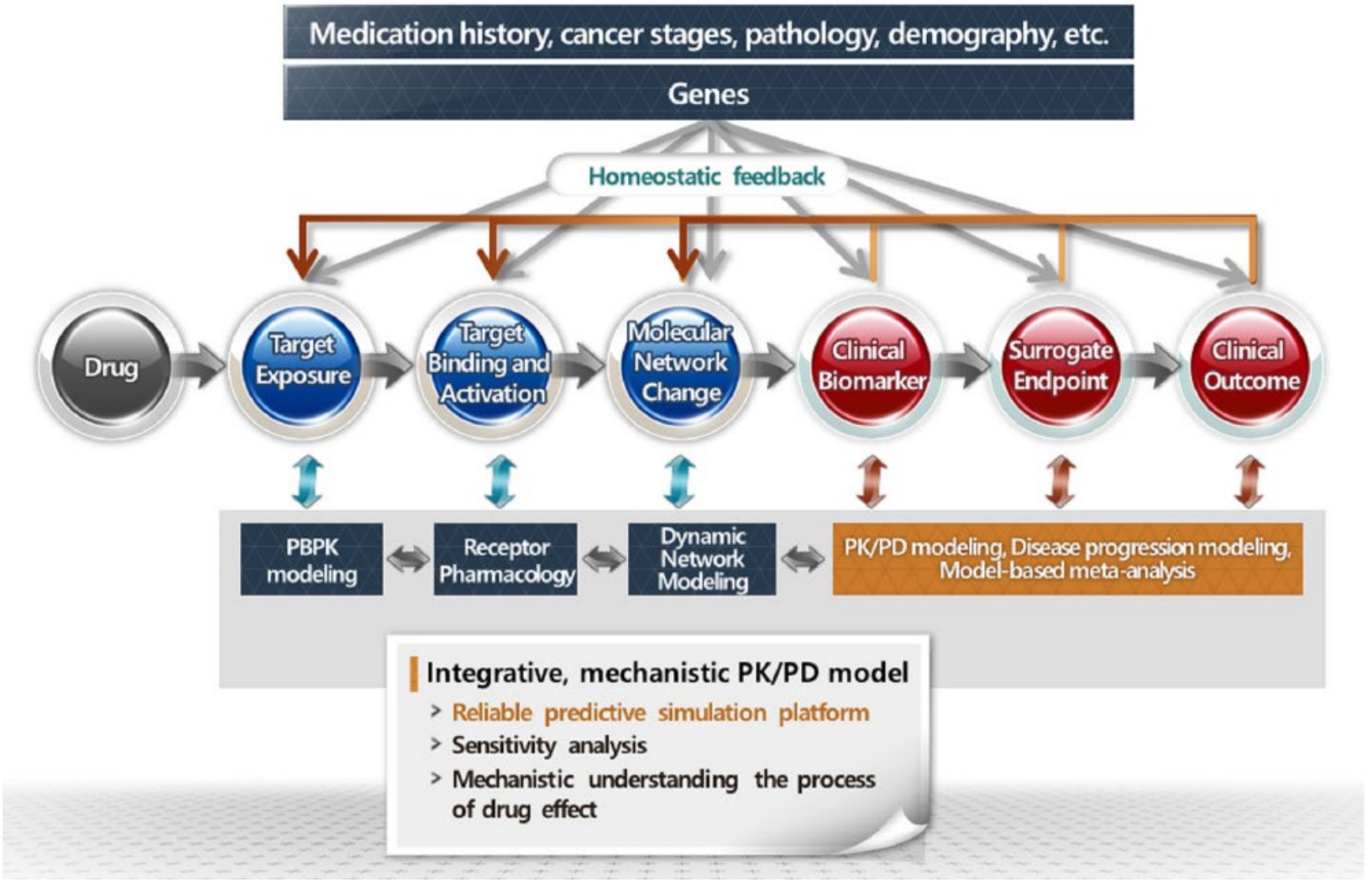
https://www.fda.gov/drugs/drug-safety-and-availability/cder-establishes-new-quantitative-medicine-center-excellence

Scope of CDER QM CoE



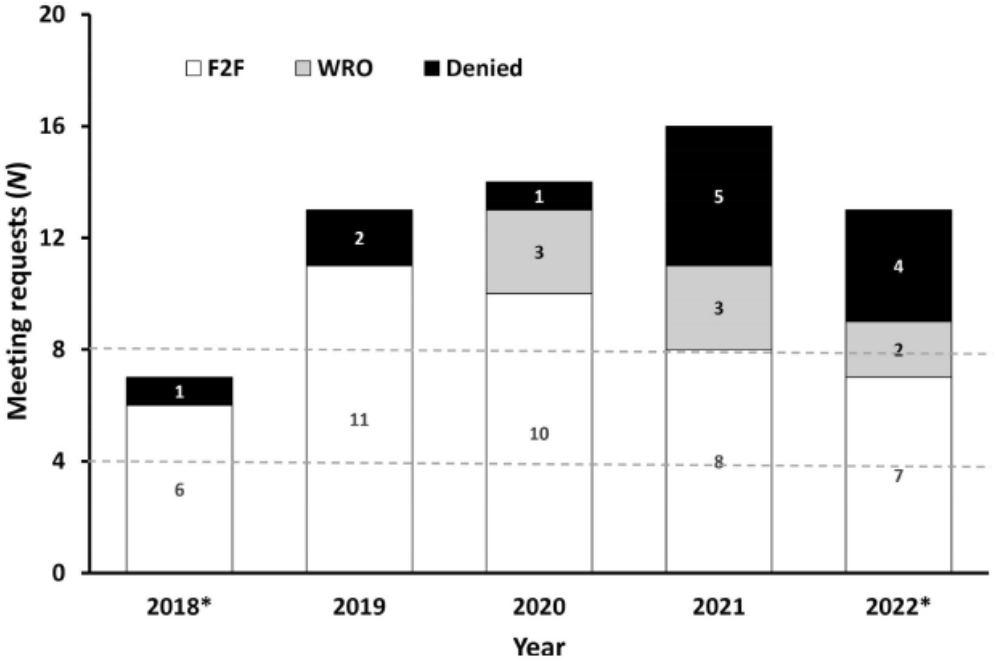
FDA Workshop. Streamlining Drug Development and Improving Public Health through Quantitative Medicine. APRIL 25, 2024

Integrative models encompassing the whole mechanistic processes of drug action

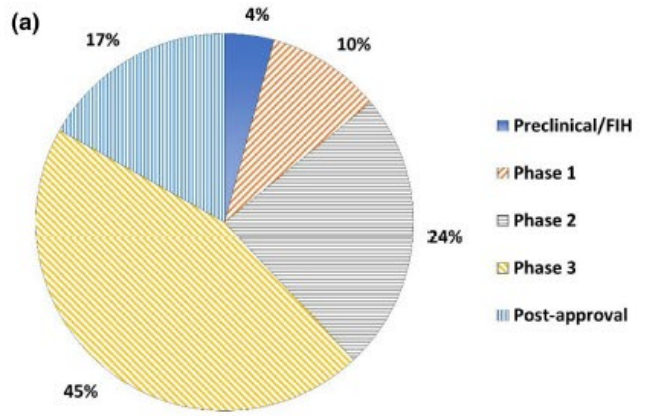


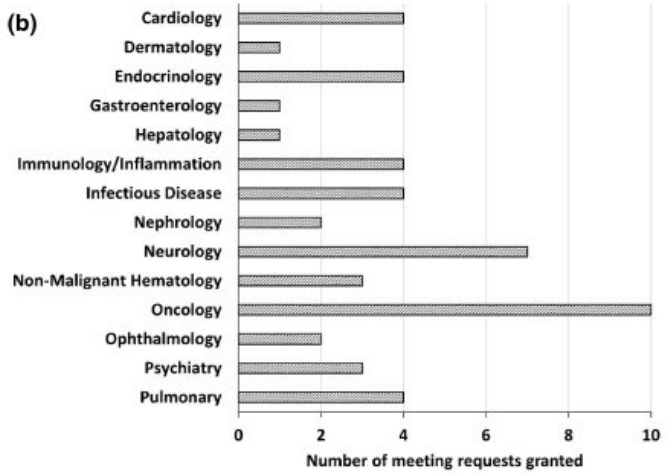
Lim HS. Evolving role of modeling and simulation in drug development. *Transl Clin Pharmacol*. 2019;27(1):19-23.

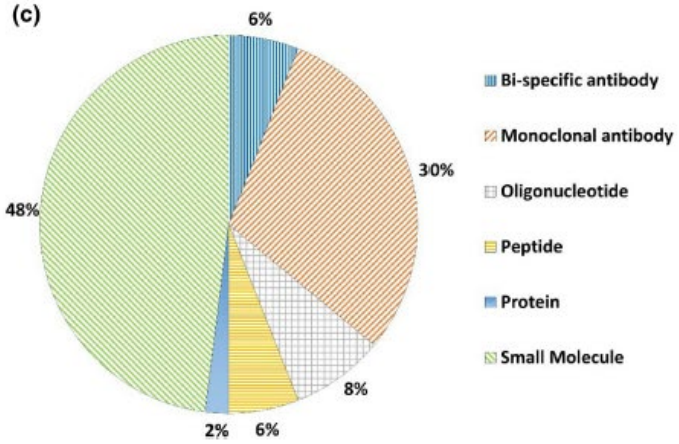
Increasing numbers of MIDD meeting requests with FDA

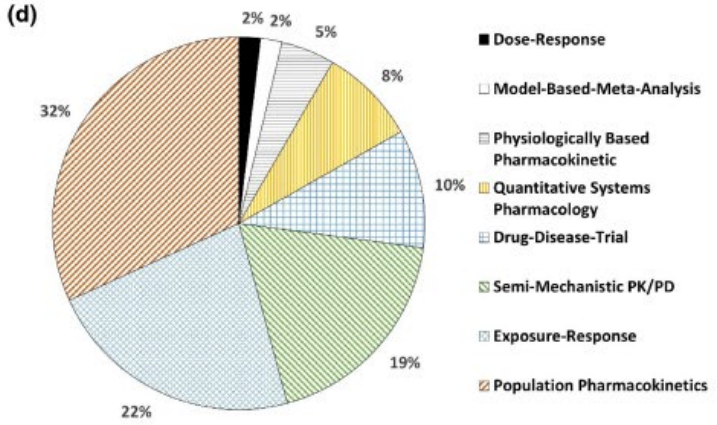


A total of 50 meeting requests (~ 10/year) between July 2018-Sep 2022









Madabushi R, et al. The US Food and Drug Administration's Model-Informed Drug Development Meeting Program: From Pilot to Pathway. *Clin Pharmacol Ther*. 2024;116(2):278-281.

Examples of MIDD to support drug development

Disease Area	Modeling Approach	Application
Schizophrenia (13)	Item Response Theory Method and Concordance Analysis	Support the use of a modified alternative endpoint and shorter clinical trials for demonstration of efficacy
Non-Small Cell Lung Cancer (14)	Disease Progression Model	Use early biomarker changes to predict long-term clinical benefit (overall survival)
Duchenne Muscular Dystrophy (15)	Disease Progression Model	Support the use of genetic mutation for patient enrichment, stratified randomization, and patient matching strategy for clinical efficacy and safety trials
Pediatrics (16)	Exposure-matching with popPK or PBPK modeling	Identify dose(s) to be tested in pediatric clinical efficacy and safety trials
Various Disease Areas (17)	Exposure-Response Modeling	Dose selection for clinical trials
Pediatrics (18)	Pharmacokinetic Modeling	Sample size determination
Various Disease Areas (19)	Machine Learning Modeling	Patient enrichment
Various Disease Areas (20)	QSP Modeling	Predict safety risks

Drug Name (Brand Name)	Modeling Approach	Regulatory Action
Aripiprazole Lauroxil (21) (Aristada ®)	Exposure-response and popPK modeling and simulation	Support the approval of a new strength and a new dosing regimen without additional clinical trial
Adalimumab (22) (Humira ®)	popPK modeling and simulation	Support the pediatric extrapolation and dose determination in patients with Hidradenitis Suppurativa.
Hydroxychloroquine (23)	PBPK modeling in combination with pharmacodynamics evaluation	Assess the potential effectiveness of a compound.
Paliperidone Palmitate (24) (Invega Sustena®)	popPK modeling and simulation	Support approval of a loading dose, dosing window, re-initiation strategy and dosage adjustment in patient subgroups without clinical trials.
Pembrolizumab (25) (Keytruda®)	popPK modeling and simulation	Support the approval of patient-friendly dosing (less frequent dosing) regimen.
Sotalol injection (26)	popPK and exposure-response modeling and simulation	Support the approval of loading doses for treatment initiation and up-titration.
Remdesivir (Veklury®) Baricitinib (Olumiant ®) Bamlanivimab and etesevimab (27)	popPK modeling and simulation	Support the use of the drugs in pediatric patients.

Madabushi R, et al. Review: Role of Model-Informed Drug Development Approaches in the Lifecycle of Drug Development and Regulatory Decision-Making. *Pharm Res.* 2022;39(8):1669-1680.

Examples of disease models to support drug development

No	Disease Model	Use
1	Non-small cell lung cancer model	Late phase clinical trial design
2	Parkinson's disease model	Endpoint selection and clinical trial design
3	Alzheimer's disease model	Endpoint selection and clinical trial design
4	Diabetes disease model	Clinical trial design
5	Huntington's disease model	Patient enrichment and clinical trial design
6	Duchenne muscular dystrophy disease model	Patient enrichment and clinical trial design
7	Human immunodeficiency virus model	Clinical trial design
8	Schizophrenia model	Pediatric extrapolation
9	Bipolar I disorder model	Pediatric extrapolation
10	Weight loss model	Clinical trial design
11	Bone density model	Clinical trial design
12	Idiopathic pulmonary fibrosis model	Patient enrichment and clinical trial design
13	Rheumatoid arthritis model	Endpoint selection and clinical trial design
14	Pulmonary arterial hypertension model	Endpoint selection and clinical trial design

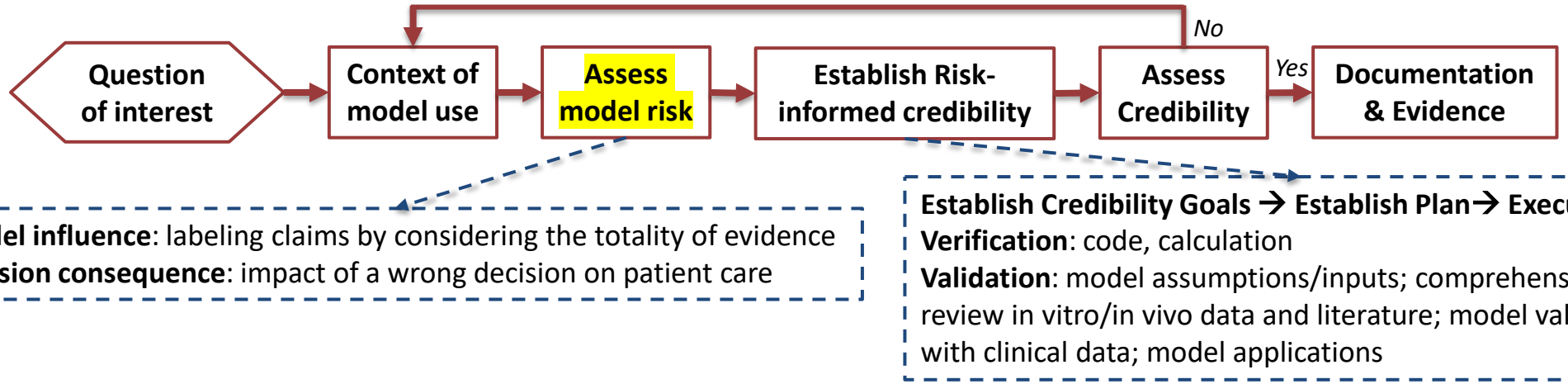
https://www.fda.gov/about-fda/cder-offices-and-divisions/division-pharmacometrics

Examples of fit-for-purpose initiative

Disease Area	Submitter	Tool	Trial Component	Issuance Date and Supporting Information
Alzheimer's disease	The Coalition Against Major Diseases (CAMD)	Disease Model: Placebo/Disease Progression	Demographics, Drop-out	Issued June 12, 2013 • Determination Letter
Multiple	Janssen Pharmaceuticals and Novartis Pharmaceuticals	Statistical Method: MCP-Mod	Dose-Finding	Issued May 26, 2016 • Determination Letter • Statistical Review • Pharmacometric Review
Multiple	Ying Yuan, PhD The University of Texas MD Anderson Cancer Center Department of Biostatistics	Statistical Method: Bayesian Optimal Interval (BOIN) design	Dose-Finding	Issued: December 10, 2021 • Determination Letter • Statistical Review • Publication Erratum
Multiple	Pfizer	Statistical Method: Empirically Based Bayesian Emax Models	Dose-Finding	Issued: August 5, 2022 • Determination Letter • Multidisciplinary Review

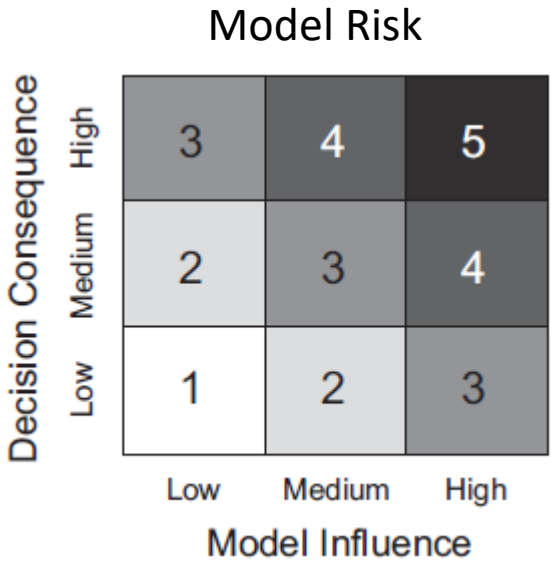
https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tools-fit-purpose-initiative

Credibility assessment framework in MIDD



Model influence	Description
Low	Model provides minor evidence; substantial nonclinical and clinical data are available to inform the decision
Medium	Model provides supportive evidence; some clinical trial data are available to inform the decision
High	Model provides substantial evidence; no clinical trial data relevant to the context of use or limited clinical trial data from similar scenarios are available to inform the decision

Decision consequence	Description
Low	Incorrect decision would not result in adverse outcomes in patient safety or efficacy
Medium	Incorrect decision could result in minor to moderate adverse outcomes in patient safety or efficacy
High	Incorrect decision could result in severe adverse outcomes in patient safety or efficacy



Kuemmel C, et al. Consideration of a Credibility Assessment Framework in Model-Informed Drug Development: Potential Application to Physiologically-Based Pharmacokinetic Modeling and Simulation. *CPT Pharmacometrics Syst Pharmacol*. 2020;9(1):21-28.

Example of credibility assessment framework

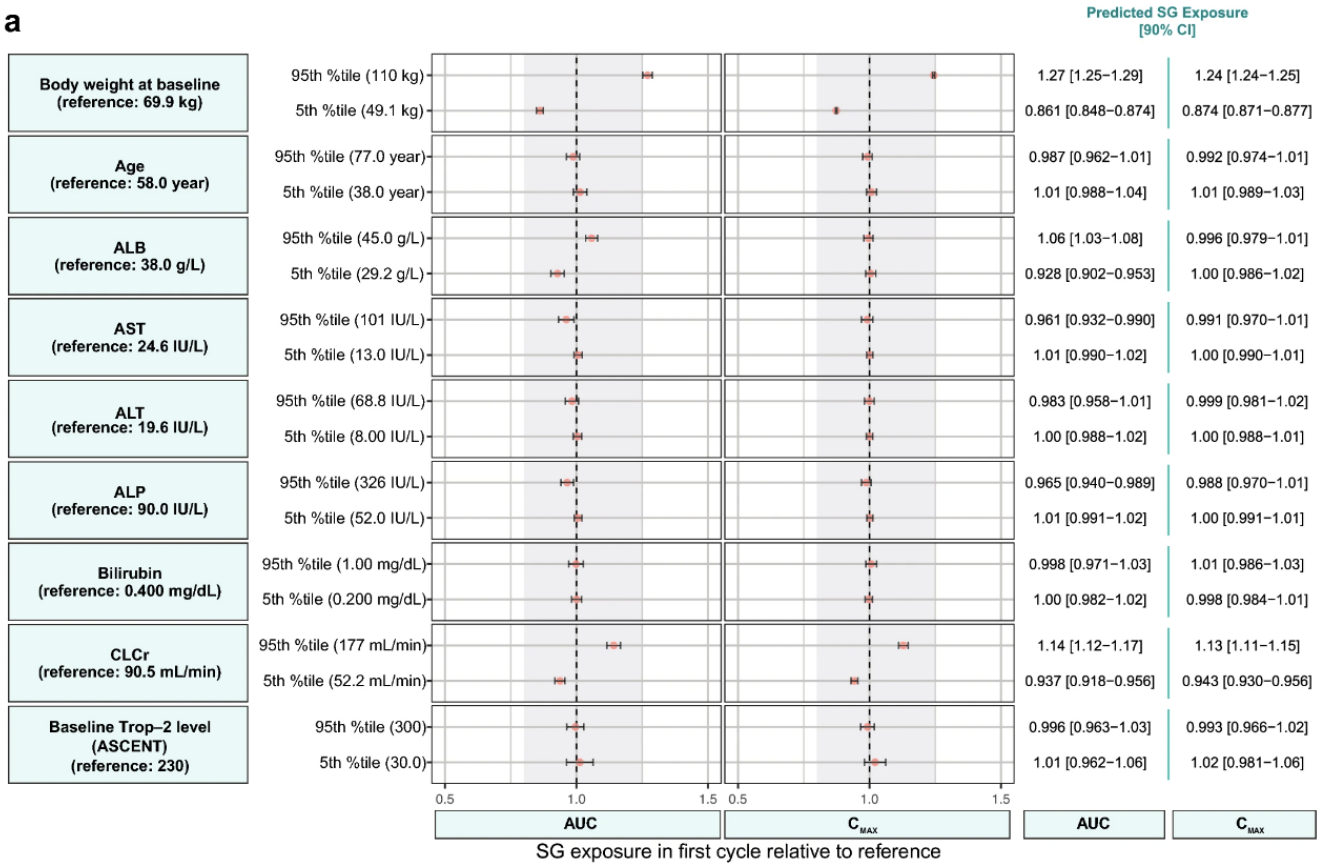
Category	Context of use
Question of interest	How should the investigational drug be dosed when coadministered with CYP3A4 modulators?
Context of use	• Simulation to predict effects of weak and moderate CYP3A4 modulators on investigational drug PK • Predictions will be used for dosing recommendations in label • No DDI studies proposed with weak and moderate CYP3A4 modulators; have clinical data with strong CYP3A4 modulators
Model risk	**High**
Model influence	*High* • Model provides substantial evidence • Limited clinical data from similar scenarios to support the decision
Decision consequence	*Medium* • Incorrect decision could result in minor to moderate adverse patient outcomes
Validation plan	• Ensure model reproduces clinical PK data at different doses from healthy volunteers • Reproduce clinical PK data when dosed with strong CYP3A4 modulators • Reproduce effects observed for other CYP3A4 substrates with weak and moderate modulators

Kuemmel C, et al. Consideration of a Credibility Assessment Framework in Model-Informed Drug Development: Potential Application to Physiologically-Based Pharmacokinetic Modeling and Simulation. *CPT Pharmacometrics Syst Pharmacol*. 2020;9(1):21-28.

Interpret covariate effects using PopPK modeling

Question: Sacituzumab govitecan (Trodelvy) is approved for locally advanced and metastatic breast cancer. Does sacituzumab govitecan dose need to be adjusted for intrinsic or extrinsic factors?

Context of use: Use PopPK to examine the impact of covariates.



Hepatotoxicity according to NCI common toxicity criteria

Grade	1	2	3	4
AST, ALT (IU/L)	≤2.5xULN	>2.5-5xULN	>5-20xULN	>20xULN
Total bilirubin (mg/dL)		<1.5xULN	>1.5-3xULN	>3xULN

USPI: *No adjustment to the starting dosage is required when administering TRODELVY to patients with mild hepatic impairment [see Clinical Pharmacology (12.3)].*

Sathe AG, et al. Population Pharmacokinetics of Sacituzumab Govitecan in Patients with Metastatic Triple-Negative Breast Cancer and Other Solid Tumors. *Clin Pharmacokinet.* 2024;63(5):669-681.

Predicting survival using tumor growth model

Question: Tumor size-based end points, such objective response rates (ORRs) or even progression-free survival (PFS), often demonstrated a weak correlation with overall survival (OS). Is there a better surrogate endpoints that can better forecast OS and to quantify drug effect in patients with cancer?

Context of use: Use the tumor growth inhibition (TGI) – OS model to predict OS and then to bridge the gap between early and late phase drug development.

TGI model

Wang's Model

$$TS_i(t) = TS_i(0) \bullet e^{-SR_i \bullet t} + PR_i \bullet t$$

TS, tumor size (sum of the longest diameters)
SR, tumor shrinkage rate
PR, tumor progression rate

Chan's Model

$$TS_i(t) = TS_i(0) \bullet \left(e^{-KS_i \bullet t} + e^{KG_i \bullet t} - 1\right)$$

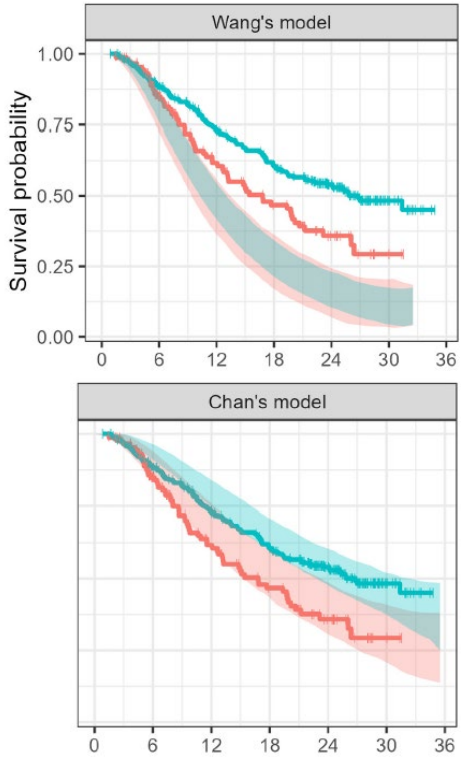
KS, tumor shrinkage rate
KG, tumor growth rate

Survival model

Cox regression model with:

- TGI metrics
- Baseline characteristics
  - Wang's model: ECOG, baseline tumor size, % tumor reduction from baseline at wk 8
  - Chan's model: log (KG), CRP, # metastatic sties, race, Alb, LDH, IC or TC > 0 vs. IC and TC = 0, Neutrophil-to-Lymphocyte ratio, lines of therapy, liver metastasis, time-to-tumor growth

OS prediction



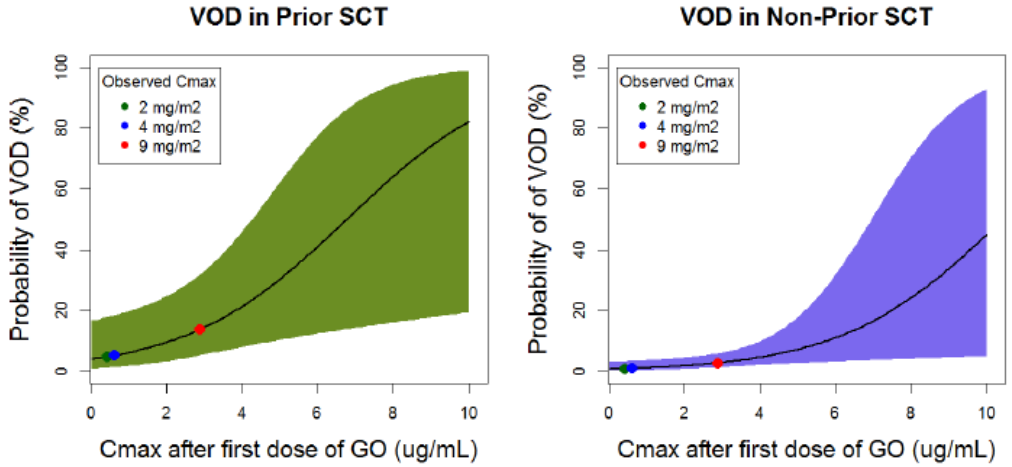
Sheng Y, et al. Tumor growth inhibition-overall survival modeling in non-small cell lung cancer: A case study from GEMSTONE-302. *CPT Pharmacometrics Syst Pharmacol*. 2024;13(3):437-448.

Support a lower fractionated dose of Mylotarg using ER analysis

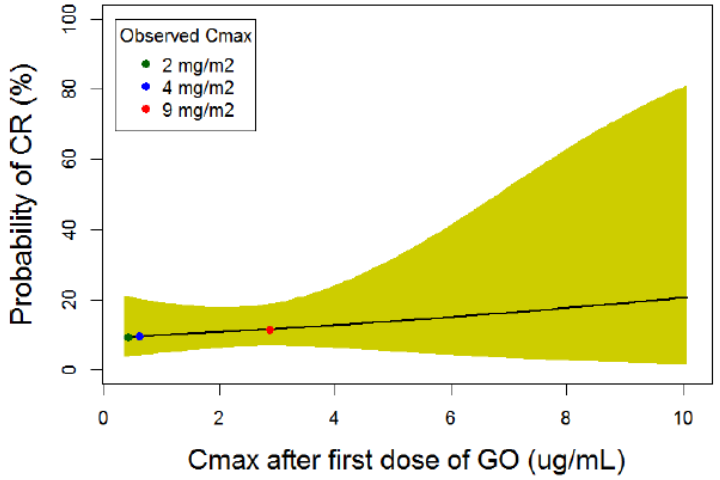
Question: Gemtuzumab ozogamicin (Mylotarg) received accelerated approval in 2000, but a Phase 3 study (SWOGS106) failed to confirm benefit with higher rate of hepatic veno-occlusive disease (VOD) which has substantial morbidity and mortality. Does changing induction dose from 9 mg/m^2 on Day 1/15 to 3 mg/m^2 on Day 1/4/7 maintain the same efficacy but reduce safety?

Context of use: Use ER analyses to support lower fractionated dose.

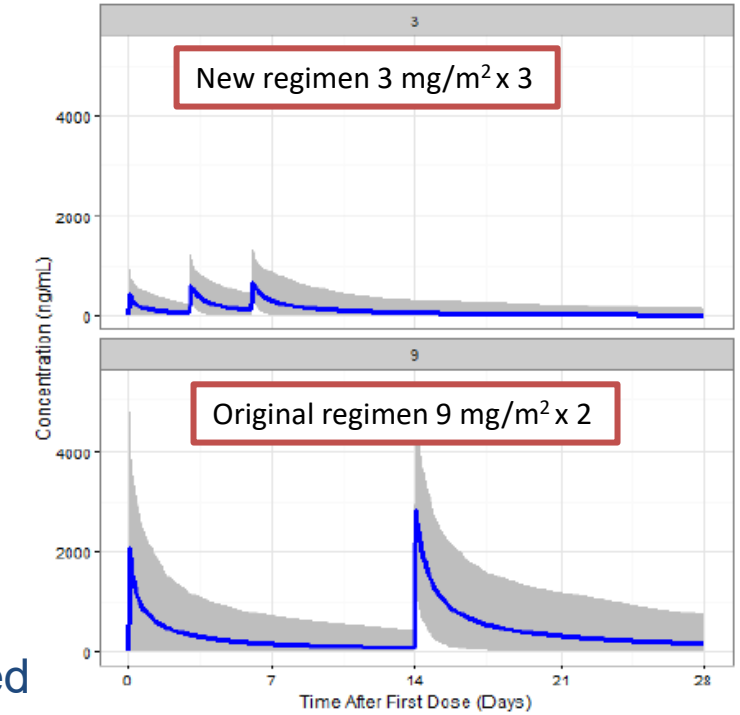
Significant ER safety



Flat ER efficacy



CD33 site saturation achieved at Dose > 2 mg/m^2

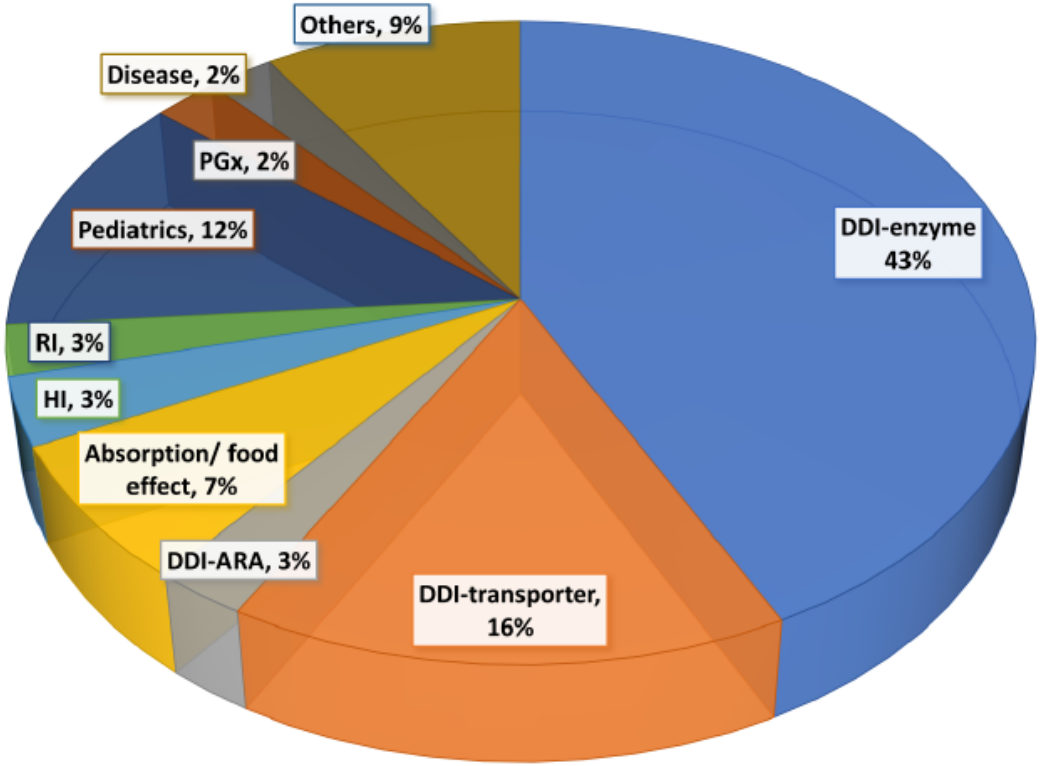


Cmax reduced by ~75%

FDA Clinical Pharmacology and Biopharmaceutics Reviews. 761060Orig1s000 and 761060Orig2s000

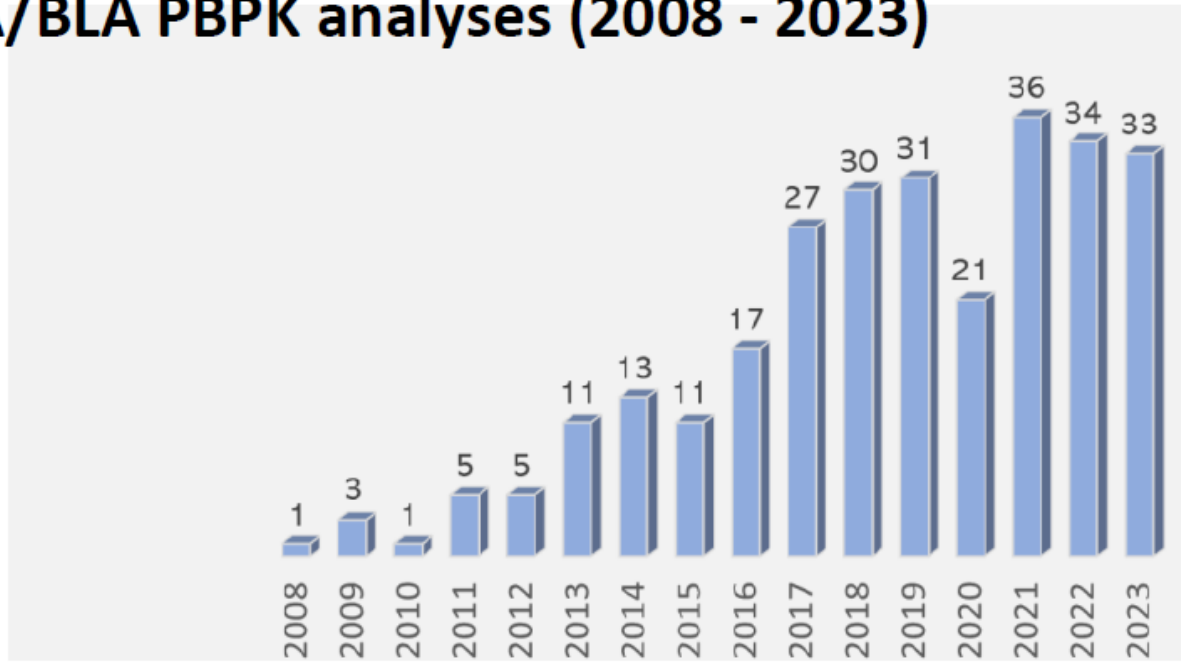
Increased use of PBPK to support NDA/BLA

Areas of Application in IND/NDA/BLA N=368, NDA=137 (2018- 2022)



- DDI applications constitute 60%
- Many analyses were submitted as INDs

NDA/BLA PBPK analyses (2008 - 2023)

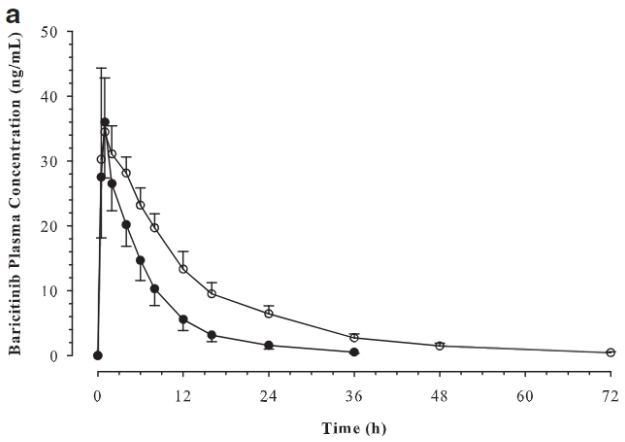


Previously presented in 'Current practice in model evaluation and assessment for PBPK models' reusability in new drug development ' May 3, 2024. MCERSI/FDA MMF meeting

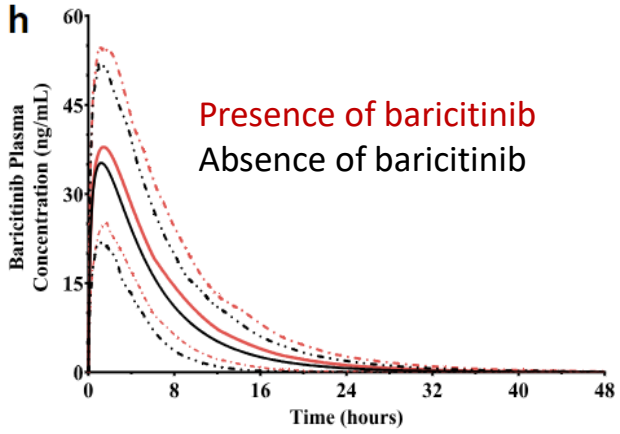
Predicting OAT3 mediated DDI using PBPK

Question: Baricitinib is a JAK inhibitor to treat adults with severe alopecia areata and with moderately to severely active rheumatoid arthritis after treatment with 1 or more TNF inhibitors. Baricitinib is a substrate for OAT3 MATE2-K, P-gp, and BCRP. What is the effect of ibuprofen (OAT3 inhibitor) on baricitinib PK?

Context of use: Use PBPK models based on probenecid (OAT3 inhibitor) and baricitinib to predict the effect of ibuprofen on baricitinib.



Impact of probenecid on baricitinib (geo ratio and 90% CI):
Cmax: 1.03 (0.94, 1.13)
AUC0-inf: 2.03 (1.91, 2.16)



PBPK prediction (geo ratio and 90% CI):
Cmax: 1.17 (1.15–1.7)
AUCo-inf: 1.95 (1.84–2.07)

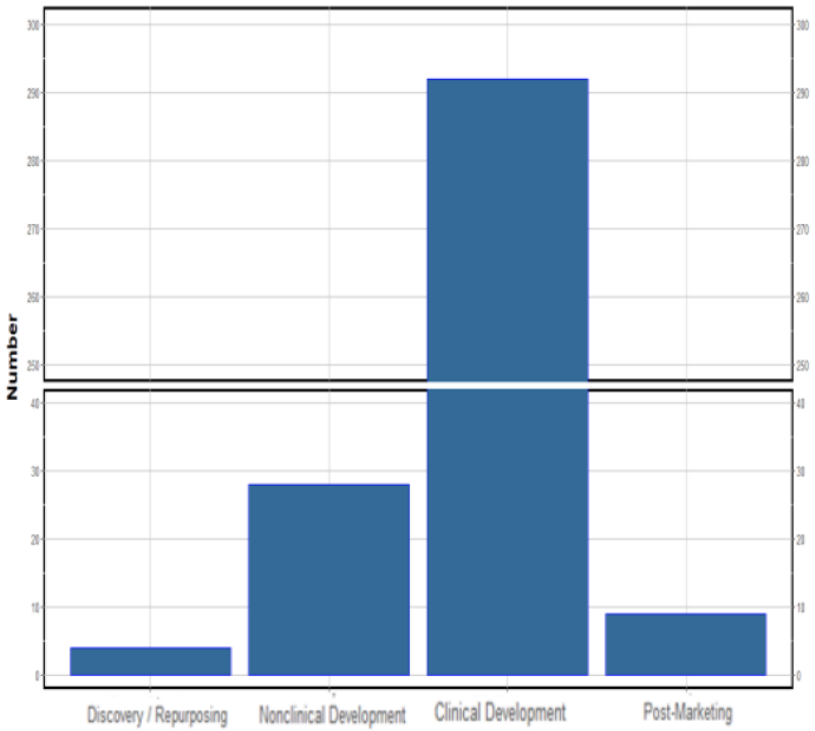
Table 4 Observed and predicted AUC and C_{max} for baricitinib, probenecid, ibuprofen and diclofenac.

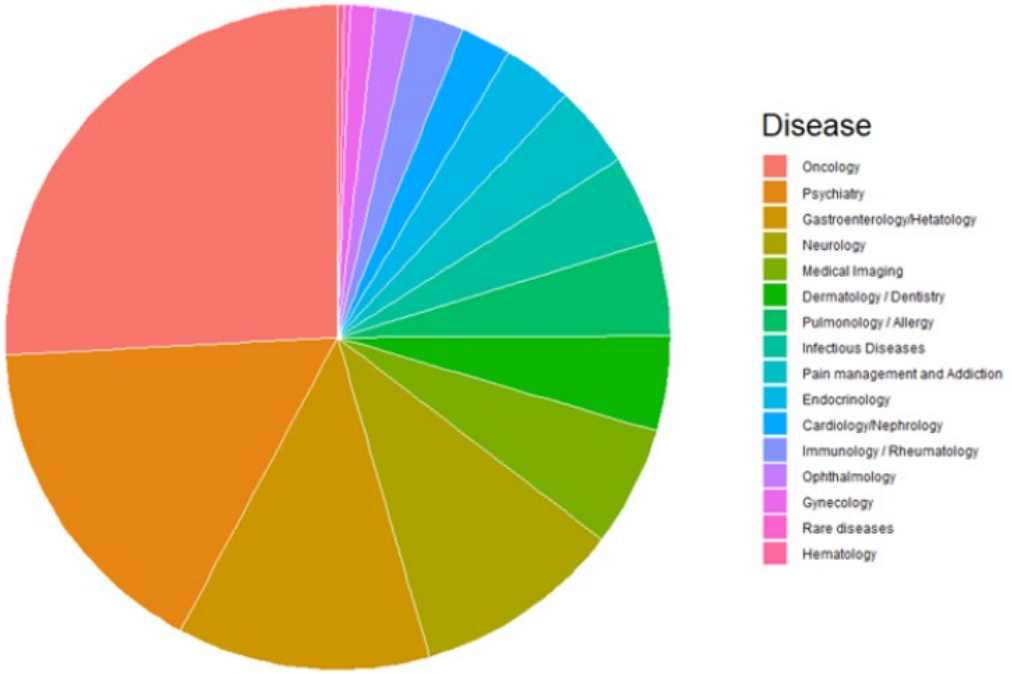
Compound	Parameter	Observed Mean (CV)	Predicted Geometric Mean (5-95% CI)	Observed/ Predicted
Baricitinib	C_{max} (ng/mL)	36.2 (22)	34.9 (33.3 – 36.7)	1.0
	AUC(0-∞) (ng·h/mL)	236 (22)	230 (215 – 247)	1.0
Probenecid (1,000 mg BID)	C_{max} (μg/mL)	145	160 (150 – 169)	0.9
	$C_{ss,ave}$ (μg/mL)	115	116 (94 – 139)	1.0
Ibuprofen (800 mg QID)	C_{max} (μg/mL)	55.6 (24)[a]	52.8 (50.1 – 55.6)	1.1
	AUC (μg·h /mL)	218 (23)[a]	183 (170 – 196)	1.2
Diclofenac(100 mg BID)	C_{max} (μg/mL)	1.2 – 3.6[b]	2.7	–
	AUC (μg·h/mL)	2.7 – 4.4[b]	3.0	–
Baricitinib (+/- Probenecid)	AUC ratio(90% CI)[c]	2.03(1.91-2.16)	1.95 (1.84-2.07)	1.0
Baricitinib (+/- Probenecid))	C_{max} ratio(90% CI)[d]	1.03 (0.940, 1.13)	1.17 (1.15-1.7)	0.9
Baricitinib (+/- Ibuprofen)	AUC ratio(90% CI)[c]	NA	1.24 (1.22-1.26)	NA
Baricitinib (+/- Ibuprofen)	C_{max} ratio(90% CI)[d]	NA	1.07 (1.06-1.08)	NA
Baricitinib (+/-Diclofenac)	AUC ratio (90% CI)[c]	NA	1.00 (1.00-1.00)	NA
Baricitinib (+/- Diclofenac)	C_{max} ratio(90% CI)[d]	NA	1.00 (1.00-1.00)	NA

USPI: *"…ibuprofen (OAT3 inhibitors with less inhibition potential) predicted minimal effect on the PK of baricitinb"*

Posada MM, et al. Prediction of Transporter-Mediated Drug-Drug Interactions for Baricitinib. Clin Transl Sci. 2017;10(6):509-519.

AI/ML submissions by development stage (2016-2022)





Regulatory submissions to the CDER that included AI/ML by stage of the drug development life cycle and therapeutic area in which it was proposed or applied, US FDA from 2016 to 2021.

Common analysis types

- Outcome prediction
- Covariate selection/confounding adjustment
- Pharmacometric modeling
- Dose selection/optimization
- Anomaly detection
- Imaging, video, and voice analysis
- RWD, NLP
- Drug discovery/repurposing
- Drug toxicity prediction
- Enrichment design
- Pt risk stratification
- Adherence
- Synthetic control
- Endpoint/biomarker assessment
- Postmarking surveillance

Liu Q, et al. Landscape Analysis of the Application of Artificial Intelligence and Machine Learning in Regulatory Submissions for Drug Development From 2016 to 2021. *Clin Pharmacol Ther*. 2023;113(4):771-774.

ML-based Patient Population Selection

Question: Patients in the Anakinra Phase 3 trial (SAVE-MORE) were selected based on a biomarker cut-off, soluble urokinase plasminogen activator receptor (suPAR) ≥ 6 ng/mL, intending to enrich the trial with patients at risk for progression to severe respiratory failure. SuPAR test is not commercially available in the United States at the time.

Context of use: Use ML to explore clinical characteristics and/or laboratory tests that could reliably identify the patients with baseline suPAR ≥ 6 ng/mL.

Table 1 Eight criteria in the scoring rule to identify patients with suPAR levels of 6 ng/mL or higher

Age ≥ 75 years
Severe pneumonia by WHO criteria
Current/previous smoking status
Sequential Organ Failure Assessment (SOFA) score ≥ 3
Neutrophil-to-lymphocyte ratio (NLR) ≥ 7
Hemoglobin ≤ 10.5 g/dL
Medical history of ischemic stroke
Blood urea ≥ 50 mg/dL and/or medical history of renal disease

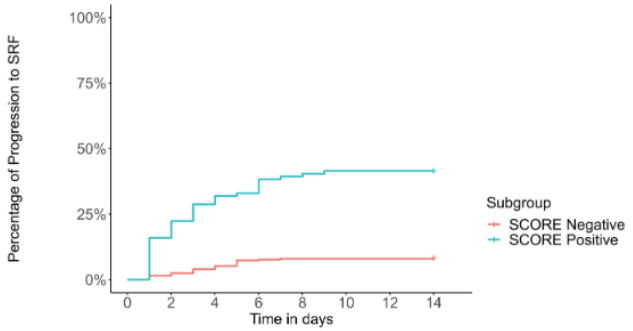
suPAR, soluble urokinase plasminogen activator receptor; WHO, World Health Organization.

The elastic net regression was used to select contributing feature(s) and a neural network-based model was applied to independently select feature(s) and the related cutoff value(s).

Table 2 Performance of the scoring rule to identify patients with suPAR levels of 6 ng/mL or higher in both the training dataset (SAVEMORE trial) and the external validation dataset (SAVE trial)

Training dataset (SAVEMORE trial)				External validation dataset (SAVE trial)			
	suPAR ≥ 6	suPAR < 6	Total		suPAR ≥ 6	suPAR < 6	Total
SCORE (+)	231	12	243	SCORE (+)	95	6	101
	(PPV = 0.95, sensitivity = 0.41)	(FPR = 0.04)			(PPV = 0.94, sensitivity = 0.37)	(FPR = 0.07)	
SCORE (–)	338	256	594	SCORE (–)	159	76	235
		(NPV = 0.43, specificity = 0.96)				(NPV = 0.32, specificity = 0.93)	
Total	569	268	837	Total	254	82	336

FPR, false positive rate; NPV, negative predictive value; PPV, positive predictive value; suPAR, soluble urokinase plasminogen activator receptor.



Clinical scoring rule had high positive predictive value, high specificity, reasonable sensitivity, and biological relevance. It is expected to identify patients who are likely to have an elevated suPAR level ≥ 6 ng/mL at baseline.

Liu Q, et al. Using Machine Learning to Determine a Suitable Patient Population for Anakinra for the Treatment of COVID-19 Under the Emergency Use Authorization. *Clin Pharmacol Ther*. 2024;115(4):890-895.

Concepts of model-based quantitative decision making

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