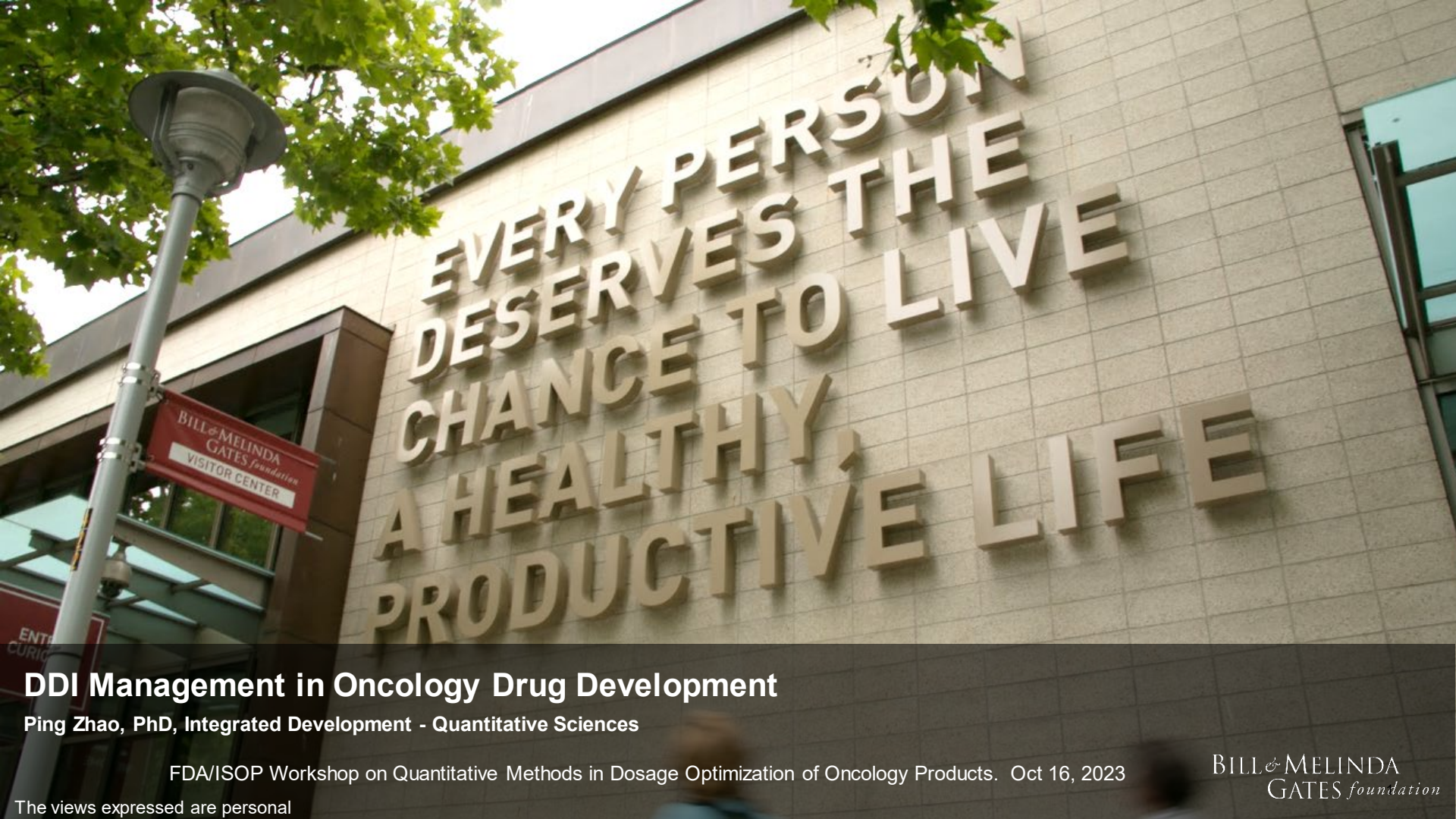

DDI Management in Oncology Drug Development

Ping Zhao, PhD, Integrated Development - Quantitative Sciences

FDA/ISOP Workshop on Quantitative Methods in Dosage Optimization of Oncology Products. Oct 16, 2023

BILL & MELINDA GATES foundation

The views expressed are personal

Draft Panel Questions

Can we use MIDD to assess the doses needed in acute (short-term) DDI vs DDI effects at steady state?

Can we use MIDD to help design better dosing regimens for time-dependent inhibitors over the course of treatment?

Can we use MIDD to simulate/explore better dosing regimens when DDI cannot be avoided (or when we might want to leverage this phenomenon)?

Can we use MIDD to evaluate dosing in clinical scenario that are infeasible to conduct studies?

Outline

Questions	Answers	Rationale
Does technology allow us to answer DDI questions?	Yes	FDA's MIDD definition: "exposure-based, biological, and statistical models derived from preclinical and clinical data sources" Availability and industrialization of user-friendly computational tools
Are we able to address these DDI questions for all drugs with certainty now?	No	Lack of required data to derive the model, both drug or biology /physiology relevant Evolution of science and technology
Are we able to address these DDI questions for all drugs with certainty in the future?	Likely	More efficient knowledge integration Disappearance of barrier between modelers and non-modelers

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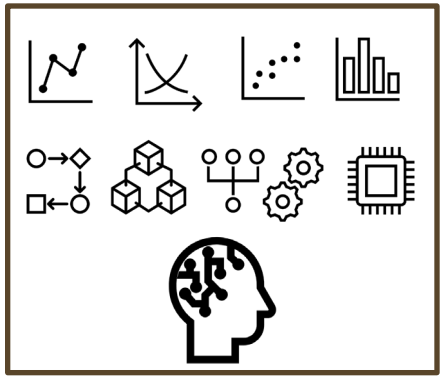
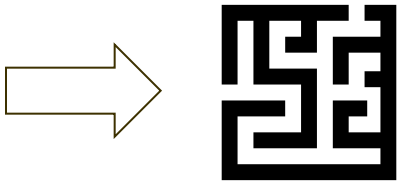
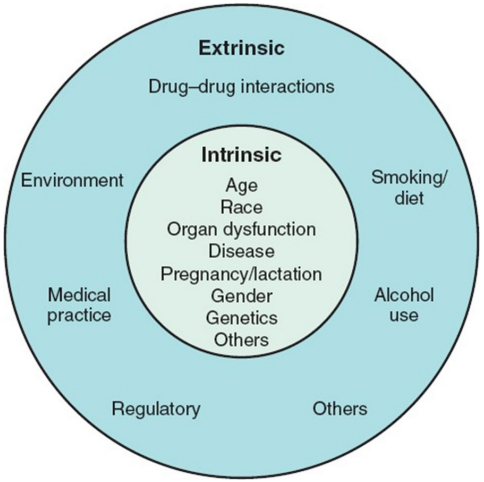
A Complex Problem May Require Complex System to Address



Complex System



Complex Problem

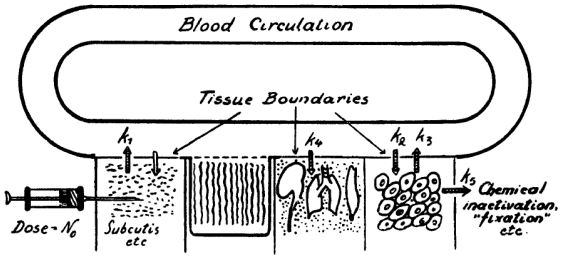


e.g., individualization of medications

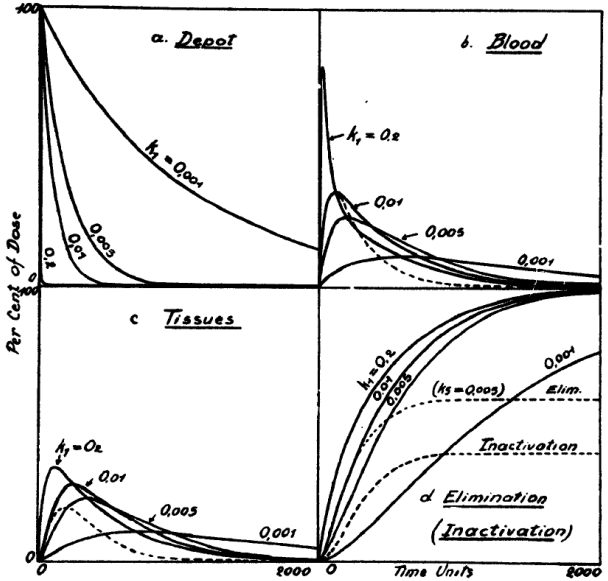
Huang and Temple, Clin Pharmacol Ther, 2008

FDA's MIDD definition: "…exposure-based, biological, and statistical models derived from preclinical and clinical data sources" *PDUFA Commitment Letters*

Pharmacology Is Complex



Local	Drug depot	Blood + equivalent Blood vol	Kidney etc elimination	Tissues	Tissue inactivation
Symbol	D	B	K	T	I
Amount	x	y	u	z	w
Volume	V_1	V_2	–	V_3	–
Concentration	x/V_1	y/V_2	–	z/V_3	–
Perm. coeff	k_1'	–	k_4'	k_2'	–
Velocity constant out	$k_1 = k_1'/V_1$	–	$k_4 = k_4'/V_2$	$k_3 = k_2'/V_3$	k_5
Velocity constant in	neglected	–	not existing	$k_2 = k_2'/V_2$	–
Name of process	Resorption	–	Elimination	Tissue take up -"- output	Inactivation

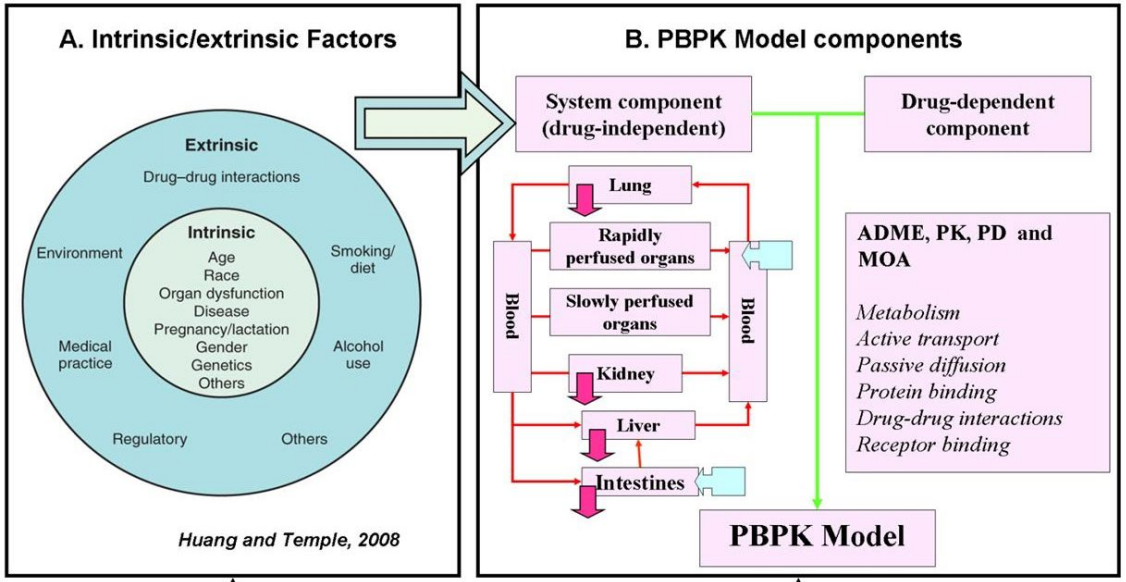


Teorell, Arch Intern Pharmacodyn, 1937

Pharmacology is the science that studies how drugs and medications work in the body, as well as their effects on the body and how they can be used to treat various medical conditions

ChatGPT description to a lay person

Physiologically-based Pharmacokinetic Models (PBPK)

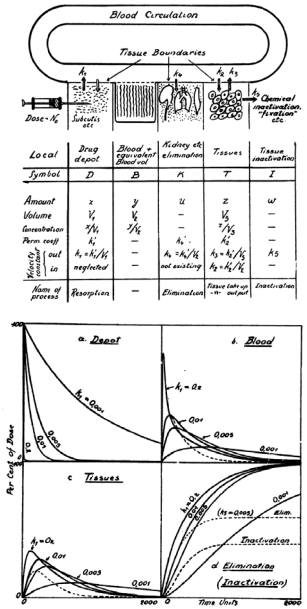


Applications of Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation During Regulatory Review

P Zhao[1], L Zhang[1], JA Grillo[1], Q Liu[1], JM Bullock[1], YJ Moon[1], P Song[1], SS Brar[1], R Madabushi[1], TC Wu[1], BP Booth[1], NA Rahman[1], KS Reynolds[1], E Gil Berglund[2], LJ Lesko[1] and S-M Huang[1]

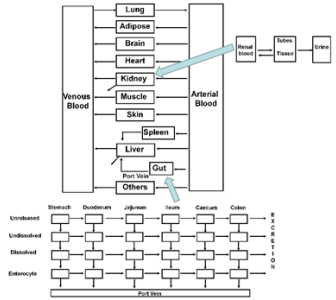
Clin Pharmacol Ther, 2011

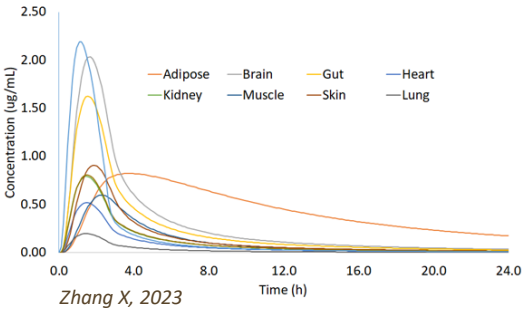
Technology Innovation Realizes A Doctor's Dream



Teorell, Arch Intern Pharmacodyn, 1937

Tech Innovation





Zhang X, 2023

PBPK Industrialization

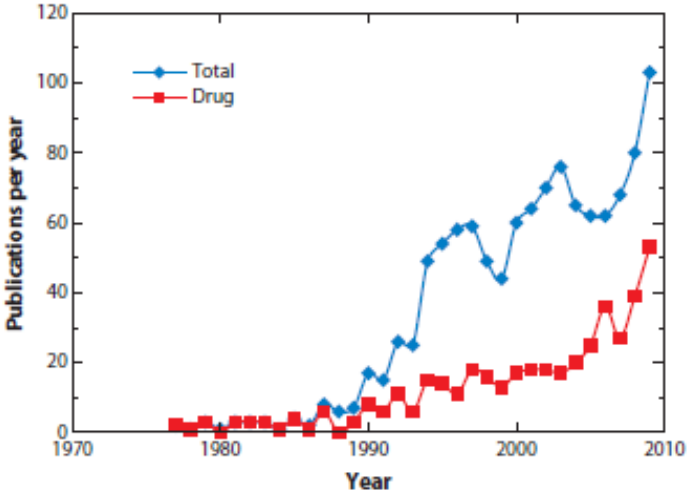
- Routine Applications
- Efficient Analysis
- Efficient Communications
- Powerful Knowledge Integration

Why Software Is Eating the World

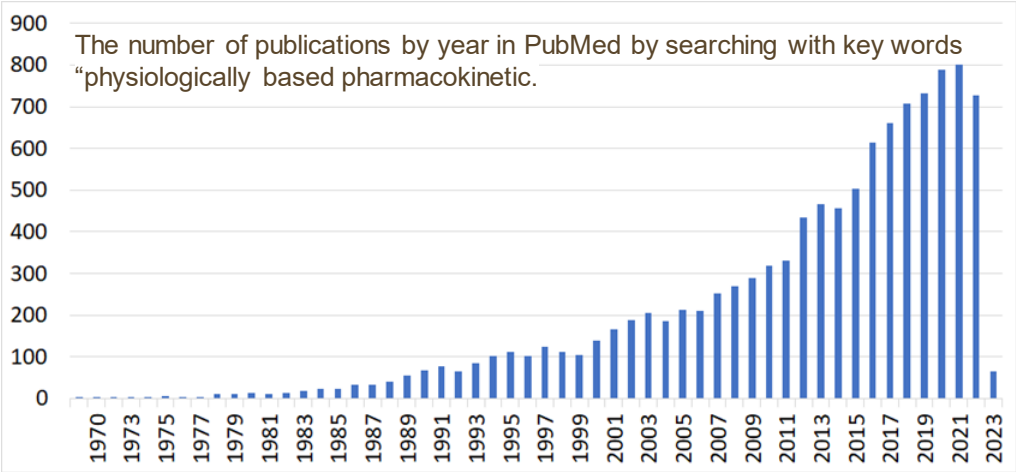
by Marc Andreessen

Industrialization: Common Drivers

PBPK Industrialization: Need, Demand, Efficiency…



Rowland M et al, Ann Rev Pharmacol Toxicol, 2010



Zhang X, 2023

Industrialization: Routine Use in R&D and Registration

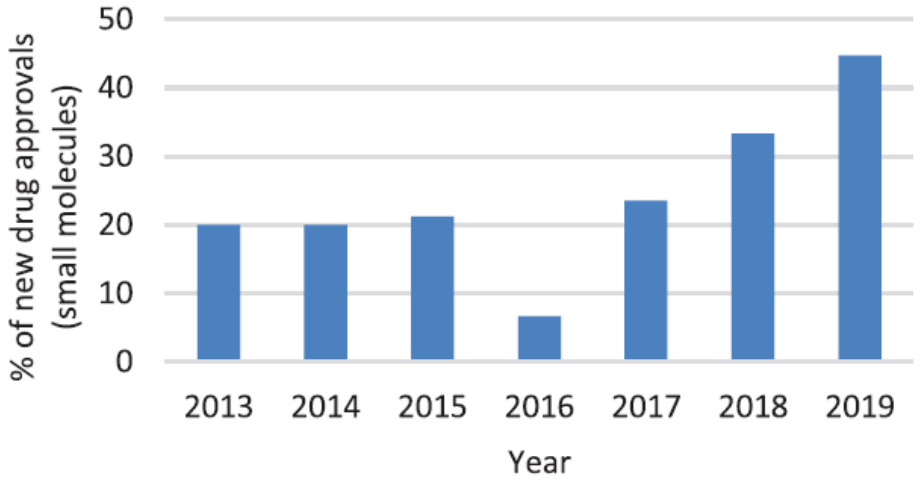


Figure 2. Percentage of new drug approvals containing physiologically based pharmacokinetics (2013-2019).

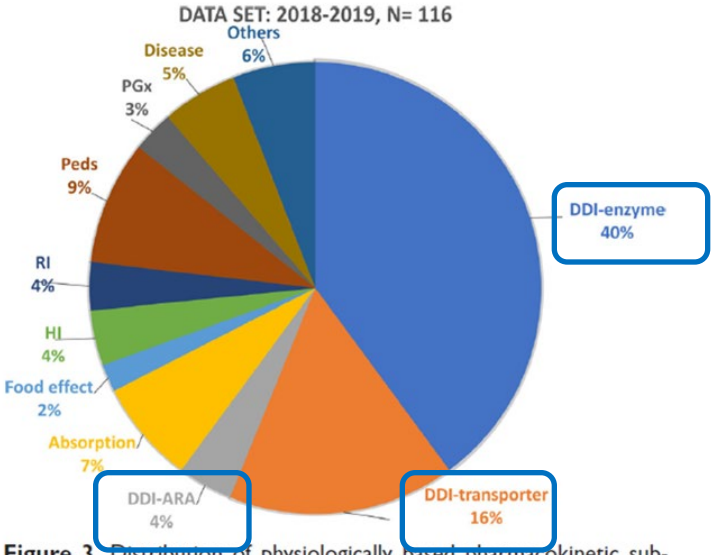
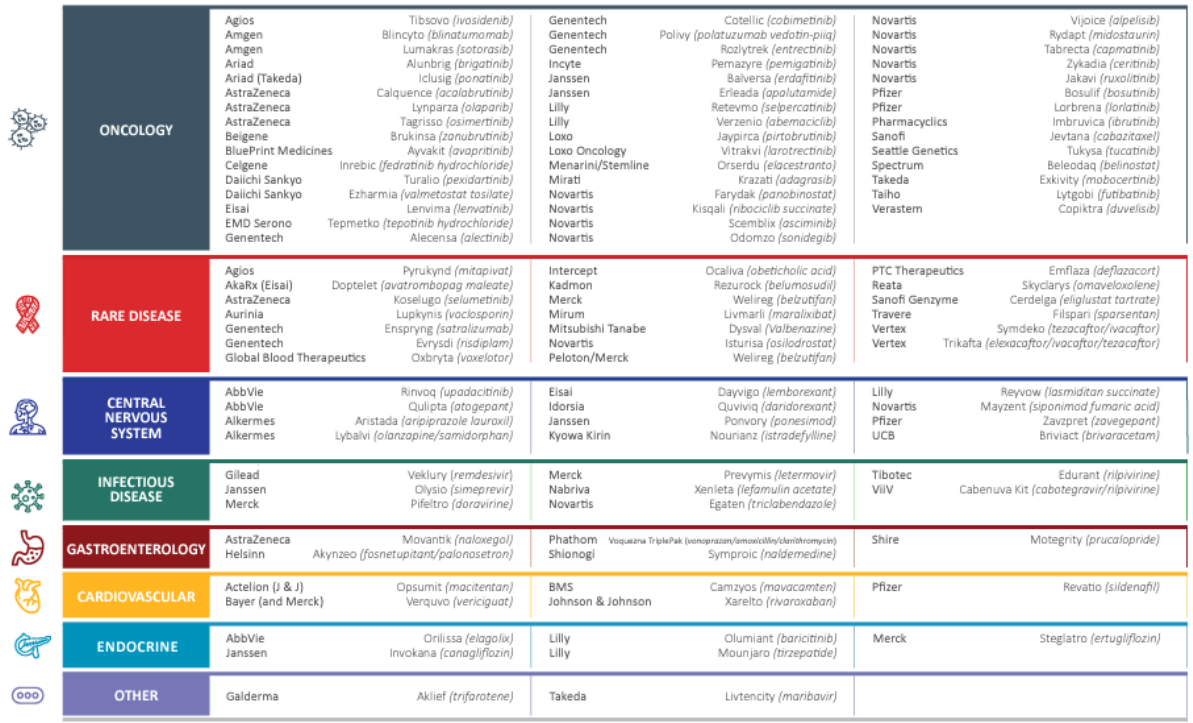


Figure 3. Distribution of physiologically based pharmacokinetic submissions by application areas (2018-2019). DDI-ARA, acid-reducing agent-mediated drug-drug interaction; DDI-enzyme, enzyme-mediated drug-drug interaction; DDI-transporter, transporter-mediated drug-drug interaction; HI, hepatic impairment; peds, pediatrics; PGx, pharmacogenomics; RI, renal impairment.

Prominent use-case is management of drug-drug interactions (DDIs)

Zhang et al, J Clin Pharmacol, 2020

Industrialization of PBPK in Oncology



ONCOLOGY	Agios	Tibsovo *(ivosidenib)*	Genentech	Cotellic *(cobimetinib)*	Novartis	Vijoice *(alpelisib)*
	Amgen	Blincyto *(blinatumomab)*	Genentech	Polivy *(polatuzumab vedotin-piiq)*	Novartis	Rydapt *(midostaurin)*
	Amgen	Lumakras *(sotorasib)*	Genentech	Rozlytrek *(entrectinib)*	Novartis	Tabrecta *(capmatinib)*
	Ariad	Alunbrig *(brigatinib)*	Incyte	Pemazyre *(pemigatinib)*	Novartis	Zykadia *(ceritinib)*
	Ariad (Takeda)	Iclusig *(ponatinib)*	Janssen	Balversa *(erdafitinib)*	Novartis	Jakavi *(ruxolitinib)*
	AstraZeneca	Calquence *(acalabrutinib)*	Janssen	Erleada *(apalutamide)*	Pfizer	Bosulif *(bosutinib)*
	AstraZeneca	Lynparza *(olaparib)*	Lilly	Retevmo *(selpercatinib)*	Pfizer	Lorbrena *(lorlatinib)*
	AstraZeneca	Tagrisso *(osimertinib)*	Lilly	Verzenio *(abemaciclib)*	Pharmacyclics	Imbruvica *(ibrutinib)*
	Beigene	Brukinsa *(zanubrutinib)*	Loxo	Jaypirca *(pirtobrutinib)*	Sanofi	Jevtana *(cabazitaxel)*
	BluePrint Medicines	Ayvakit *(avapritinib)*	Loxo Oncology	Vitrakvi *(larotrectinib)*	Seattle Genetics	Tukysa *(tucatinib)*
	Celgene	Inrebic *(fedratinib hydrochloride)*	Menarini/Stemline	Orserdu *(elacestranto)*	Spectrum	Beleodaq *(belinostat)*
	Daiichi Sankyo	Turalio *(pexidartinib)*	Mirati	Krazati *(adagrasib)*	Takeda	Exkivity *(mobocertinib)*
	Daiichi Sankyo	Ezharmia *(valmetostat tosilate)*	Novartis	Farydak *(panobinostat)*	Taiho	Lytgobi *(futibatinib)*
	Eisai	Lenvima *(lenvatinib)*	Novartis	Kisqali *(ribociclib succinate)*	Verastem	Copiktra *(duvelisib)*
	EMD Serono	Tepmetko *(tepotinib hydrochloride)*	Novartis	Scemblix *(asciminib)*		
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RARE DISEASE	Agios	Pyrukynd *(mitapivat)*	Intercept	Ocaliva *(obeticholic acid)*	PTC Therapeutics	Emflaza *(deflazacort)*
	AkaRx (Eisai)	Doptelet *(avatrombopag maleate)*	Kadmon	Rezurock *(belumosudil)*	Reata	Skyclarys *(omaveloxolone)*
	AstraZeneca	Koselugo *(selumetinib)*	Merck	Welireg *(belzutifan)*	Sanofi Genzyme	Cerdelga *(eliglustat tartrate)*
	Aurinia	Lupkynis *(voclosporin)*	Mirum	Livmarli *(maralixibat)*	Travere	Filspari *(sparsentan)*
	Genentech	Enspryng *(satralizumab)*	Mitsubishi Tanabe	Dysval *(Valbenazine)*	Vertex	Symdeko *(tezacaftor/ivacaftor)*
	Genentech	Evrysdi *(risdiplam)*	Novartis	Isturisa *(asilodrostat)*	Vertex	Trikafta *(elexacaftor/ivacaftor/tezacaftor)*
	Global Blood Therapeutics	Oxbryta *(voxelotor)*	Peloton/Merck	Welireg *(belzutifan)*		
CENTRAL NERVOUS SYSTEM	AbbVie	Rinvoq *(upadacitinib)*	Eisai	Dayvigo *(lemborexant)*	Lilly	Reyvow *(lasmiditan succinate)*
	AbbVie	Qulipta *(atogepant)*	Idorsia	Quviviq *(daridorexant)*	Novartis	Mayzent *(siponimod fumaric acid)*
	Alkermes	Aristada *(aripiprazole lauroxil)*	Janssen	Ponvory *(ponesimod)*	Pfizer	Zavzpret *(zavegepant)*
	Alkermes	Lybalvi *(olanzapine/samidorphan)*	Kyowa Kirin	Nourianz *(istradefylline)*	UCB	Briviact *(brivaracetam)*
INFECTIOUS DISEASE	Gilead	Veklury *(remdesivir)*	Merck	Prevymis *(letermovir)*	Tibotec	Edurant *(rilpivirine)*
	Janssen	Olysio *(simeprevir)*	Nabriva	Xenleta *(lefamulin acetate)*	ViiV	Cabenuva Kit *(cabotegravir/rilpivirine)*
	Merck	Pifeltro *(doravirine)*	Novartis	Egaten *(triclabendazole)*		
GASTROENTEROLOGY	AstraZeneca	Movantik *(naloxegol)*	Phathom	Voquezna TriplePak (vonoprazan/amoxicillin/clarithromycin)	Shire	Motegrity *(prucalopride)*
	Helsinn	Akynzeo *(fosnetupitant/palonosetron)*	Shionogi	Symproic *(naldemedine)*		
CARDIOVASCULAR	Actelion (J & J)	Opsumit *(macitentan)*	BMS	Camzyos *(mavacamten)*	Pfizer	Revatio *(sildenafil)*
	Bayer (and Merck)	Verquvo *(vericiguat)*	Johnson & Johnson	Xarelto *(rivaroxaban)*		
ENDOCRINE	AbbVie	Orilissa *(elagolix)*	Lilly	Olumiant *(baricitinib)*	Merck	Steglatro *(ertugliflozin)*
	Janssen	Invokana *(canagliflozin)*	Lilly	Mounjaro *(tirzepatide)*		
OTHER	Galderma	Aklief *(trifarotene)*	Takeda	Livtencity *(maribavir)*		

Updated July. 2023

- **Multiple Regulatory Authorities**
- **>100 new drugs, 325 label (simulation results in lieu of clinical studies)**

Courtesy, M Jamei

https://www.certara.com/app/uploads/2023/03/Certara_Brochure_Simcyp-PBPK-V22-2023-final-4.pdf

Learning from 2023 FDA Approvals

As of Sep 22, there are 36 NDAs and BLAs with FDA review published

Submissions including PBPK	15 (12 NDAs and 3 BLAs)
Oncology/Hematology	8
DDI	13 Five submissions included multiple applications (DDI as both victim and perpetrator, hepatic and renal impairment)
Label impact	Yes: 8 No, not obvious or not specified: 7
Methods	SimCYP®: 11 Gastroplus®: 1 Not specified: 3

NDA/BLA: 216059, 217639, 216951, 216718, 216386, 217026, 217759, 215887, 216578, 761324, 217188, 215559, 216993, 761342, 761309
Preliminary, non-QC'ed

Outline

Questions	Answers	Rationale
Does technology allow us to answer DDI questions?	Yes	FDA's MIDD definition: "exposure-based, biological, and statistical models derived from preclinical and clinical data sources" Availability and industrialization of user-friendly computational tools
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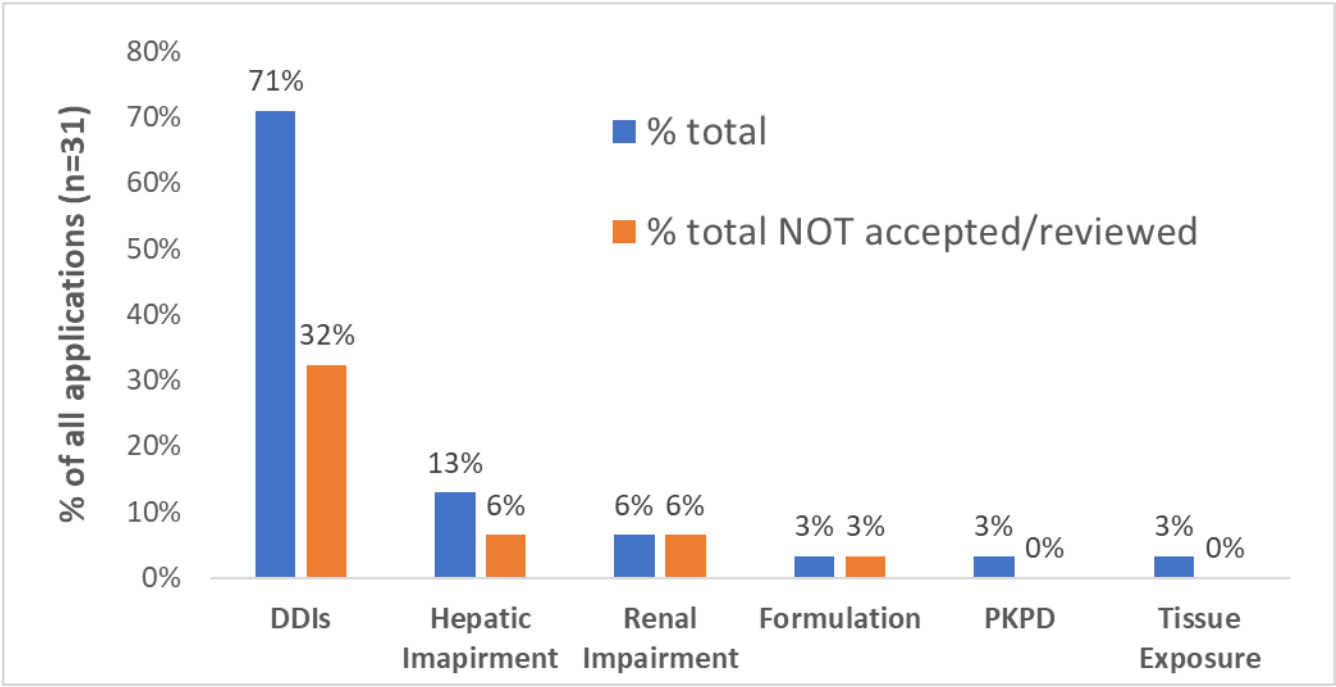
45% of PBPK Applications Not Accepted or Reviewed



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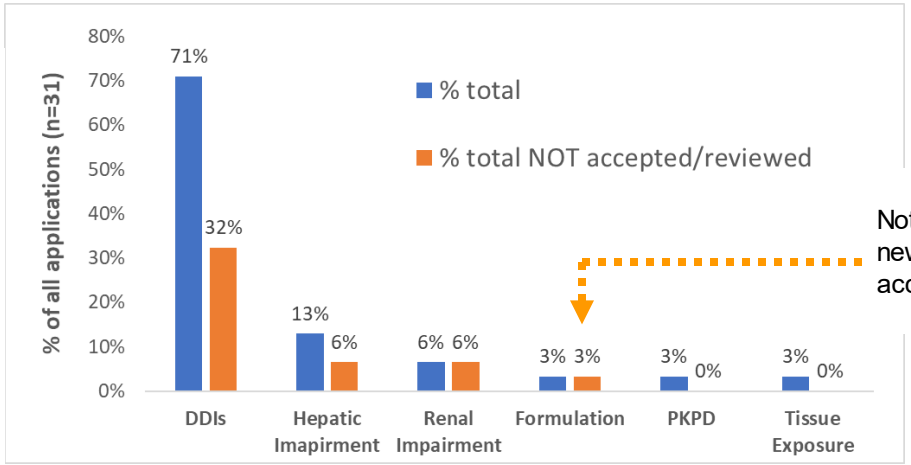
Preliminary, non-QC'ed

Reasons for Not Being Accepted/Reviewed

Not adequate

- CYP contribution uncertain (NDA216718)
- Perpetrator (efavirenz) model not adequate but supportive (NDA217639)
- Rifampin's combined CYP3A induction and OATP1B1/NTCP inhibition not delineated (NDA216386)
- Model for mild CYP3A inducer; effect on CYP1A2 substrate (NDA217759)
- Underpredicted effect of rifampin; pathway not clear for CYP2C8/2C19 to predict effect of these inhibitors and effect of efavirenz (215559)
- Inadequate to predict effects of cytokine change on CYPs (BLA 761342 and 761309)



Not adequate to define new dissolution acceptance criterion

Not adequate because there is no clinical data to verify
Not reviewed because pathway minor

NDA/BLA: 216059, 217639, 216951, 216718, 216386, 217026, 217759, 215887, 216578, 761324, 217188, 215559, 216993, 761342, 761309
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Pragmatism - Living with Uncertainties

Jesduvroqas a CYP2C8 substrate (NDA216951):

DRUG INTERACTIONS

- Moderate CYP2C8 Inhibitors: Reduce starting dose. (7.1)
- CYP2C8 Inducers: Monitor hemoglobin and adjust the dose of JESDUVROQ as appropriate. (7.2)

Daprodustat AUC and C_{max} are expected to increase at least 4-fold and 3-fold, respectively, following concomitant administration of daprodustat with clopidogrel 75 mg once daily (moderate CYP2C8 inhibitor).

'However, the effects of clopidogrel on daprodustat may be underestimated because the clopidogrel PBPK models used by the Applicant were not reliably validated and these clopidogrel models significantly underpredicted the clinically observed interactions between clopidogrel and repaglinide (see Section 14.6 for details). This suggests that the effect of clopidogrel on daprodustat exposure is expected to be no less than the model-predicted effects.' NDA 216951

"All models are wrong, some are useful" G. Box

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216951s000lbl.pdf
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/216951Orig1s000IntegratedR.pdf

Re-usable Models – Efficiency, Generalizability, Predictability

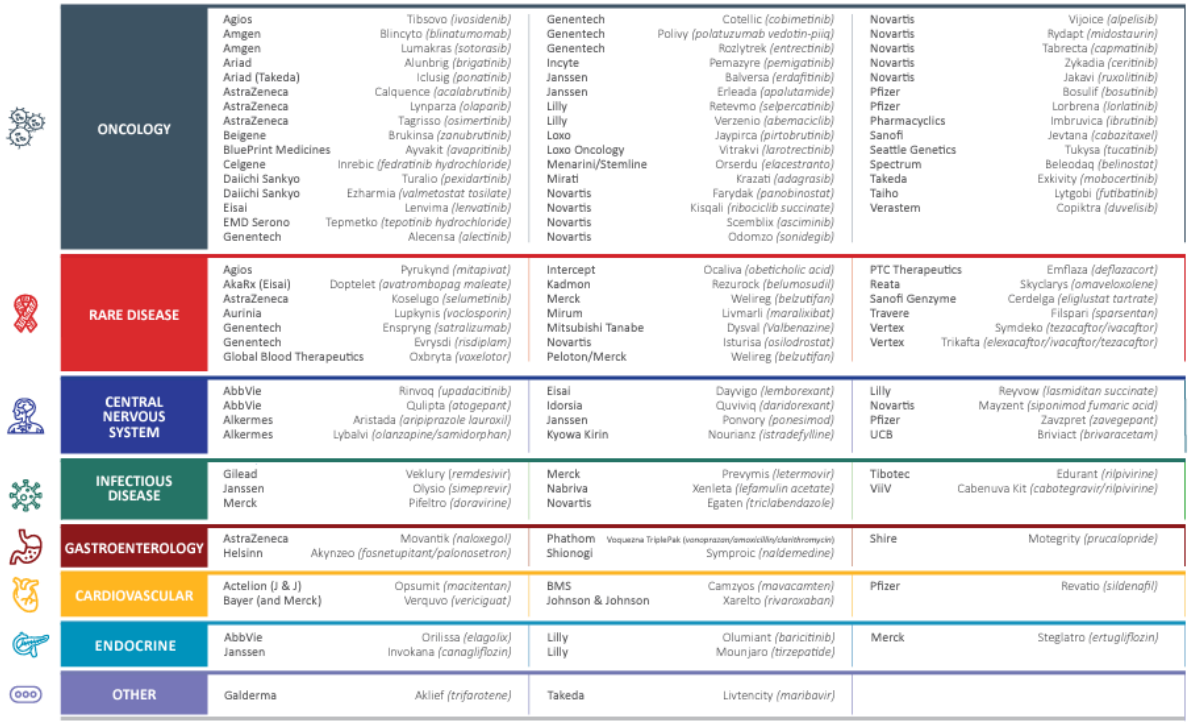
Software library models or **sponsors' models based on publications**

- Sohonos (NDA 215559): 'library files sim-**ketoconazole**-400 mg QD, SV-**rifampin**-MD, SV-**Efavirenz**, SV**Erythromycin**_EC, SV-**Fluconazole**, and SV-**Fluoxetine** were used for DDI simulations without any modification unless otherwise noted' (NDA 215559)

- Jesduvroq (NDA216951): 'The default PBPK models of **gemfibrozil** and **trimethoprim** in Simcyp were used for DDI prediction. The PBPK models of **clopidogrel and its glucuronide** were developed based on published data (Tornio et al. 2014; Shebley et al. 2017; Varma et al. 2019). Simcyp built-in models of **repaglinide** and the PBPK models of **pioglitazone** and **montelukast** built by the Applicant based on were used to qualify the ability of the clopidogrel PBPK model to simulate DDIs with CYP2C8 substrates as well as a CYP3A4 substrate. No modifications were made to the original models'

www.accessdata.fda.gov/drugsatfda_docs/nda/2023/216951Orig1s000IntegratedR.pdf
www.accessdata.fda.gov/drugsatfda_docs/nda/2023/215559Orig1s000IntegratedR.pdf

More Models - Knowledge and Experience



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	Amgen	Lumakras *(sotorasib)*	Genentech	Rozlytrek *(entrectinib)*	Novartis	Tabrecta *(capmatinib)*
	Ariad	Alunbrig *(brigatinib)*	Incyte	Pemazyre *(pemigatinib)*	Novartis	Zykadia *(ceritinib)*
	Ariad (Takeda)	Iclusig *(ponatinib)*	Janssen	Balversa *(erdafitinib)*	Novartis	Jakavi *(ruxolitinib)*
	AstraZeneca	Calquence *(acalabrutinib)*	Janssen	Erleada *(apalutamide)*	Pfizer	Bosulif *(bosutinib)*
	AstraZeneca	Lynparza *(olaparib)*	Lilly	Retevmo *(selpercatinib)*	Pfizer	Lorbrena *(lorlatinib)*
	AstraZeneca	Tagrisso *(osimertinib)*	Lilly	Verzenio *(abemaciclib)*	Pharmacyclics	Imbruvica *(ibrutinib)*
	Beigene	Brukinsa *(zanubrutinib)*	Loxo	Jaypirca *(pirtobrutinib)*	Sanofi	Jevtana *(cabazitaxel)*
	BluePrint Medicines	Ayvakit *(avapritinib)*	Loxo Oncology	Vitrakvi *(larotrectinib)*	Seattle Genetics	Tukysa *(tucatinib)*
	Celgene	Inrebic *(fedratinib hydrochloride)*	Menarini/Stemline	Orserdu *(elacestranto)*	Spectrum	Beleodaq *(belinostat)*
	Daiichi Sankyo	Turalio *(pexidartinib)*	Mirati	Krazati *(adagrasib)*	Takeda	Exkivity *(mobocertinib)*
	Daiichi Sankyo	Ezharmia *(valmetostat tosilate)*	Novartis	Farydak *(panobinostat)*	Taiho	Lytgobi *(futibatinib)*
	Eisai	Lenvima *(lenvatinib)*	Novartis	Kisqali *(ribociclib succinate)*	Verastem	Copiktra *(duvelisib)*
	EMD Serono	Tepmetko *(tepotinib hydrochloride)*	Novartis	Scemblix *(asciminib)*		
	Genentech	Alecensa *(alectinib)*	Novartis	Odomzo *(sonidegib)*		
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	AkaRx (Eisai)	Doptelet *(avatrombopag maleate)*	Kadmon	Rezurock *(belumosudil)*	Reata	Skyclarys *(omaveloxolone)*
	AstraZeneca	Koselugo *(selumetinib)*	Merck	Welireg *(belzutifan)*	Sanofi Genzyme	Cerdelga *(eliglustat tartrate)*
	Aurinia	Lupkynis *(voclosporin)*	Mirum	Livmarli *(maralixibat)*	Travere	Filspari *(sparsentan)*
	Genentech	Enspryng *(satralizumab)*	Mitsubishi Tanabe	Dysval *(Valbenazine)*	Vertex	Symdeko *(tezacaftor/ivacaftor)*
	Genentech	Evrysdi *(risdiplam)*	Novartis	Isturisa *(asilodrostat)*	Vertex	Trikafta *(elexacaftor/ivacaftor/tezacaftor)*
	Global Blood Therapeutics	Oxbryta *(voxelotor)*	Peloton/Merck	Welireg *(belzutifan)*		
CENTRAL NERVOUS SYSTEM	AbbVie	Rinvoq *(upadacitinib)*	Eisai	Dayvigo *(lemborexant)*	Lilly	Reyvow *(lasmiditan succinate)*
	AbbVie	Qulipta *(atogepant)*	Idorsia	Quviviq *(daridorexant)*	Novartis	Mayzent *(siponimod fumaric acid)*
	Alkermes	Aristada *(aripiprazole lauroxil)*	Janssen	Ponvory *(ponesimod)*	Pfizer	Zavzpret *(zavegepant)*
	Alkermes	Lybalvi *(olanzapine/samidorphan)*	Kyowa Kirin	Nourianz *(istradefylline)*	UCB	Briviact *(brivaracetam)*
INFECTIOUS DISEASE	Gilead	Veklury *(remdesivir)*	Merck	Prevymis *(letermovir)*	Tibotec	Edurant *(rilpivirine)*
	Janssen	Olysio *(simeprevir)*	Nabriva	Xenleta *(lefamulin acetate)*	ViiV	Cabenuva Kit *(cabotegravir/rilpivirine)*
	Merck	Pifeltro *(doravirine)*	Novartis	Egaten *(triclabendazole)*		
GASTROENTEROLOGY	AstraZeneca	Movantik *(naloxegol)*	Phathom	Voquezna TriplePak *(vonoprazan/amoxicillin/clarithromycin)*	Shire	Motegrity *(prucalopride)*
	Helsinn	Akynzeo *(fosnetupitant/palonosetron)*	Shionogi	Symproic *(naldemedine)*		
CARDIOVASCULAR	Actelion (J & J)	Opsumit *(macitentan)*	BMS	Camzyos *(mavacamten)*	Pfizer	Revatio *(sildenafil)*
	Bayer (and Merck)	Verquvo *(vericiguat)*	Johnson & Johnson	Xarelto *(rivaroxaban)*		
ENDOCRINE	AbbVie	Orilissa *(elagolix)*	Lilly	Olumiant *(baricitinib)*	Merck	Steglatro *(ertugliflozin)*
	Janssen	Invokana *(canagliflozin)*	Lilly	Mounjaro *(tirzepatide)*		
OTHER	Galderma	Aklief *(trifarotene)*	Takeda	Livtencity *(maribavir)*		

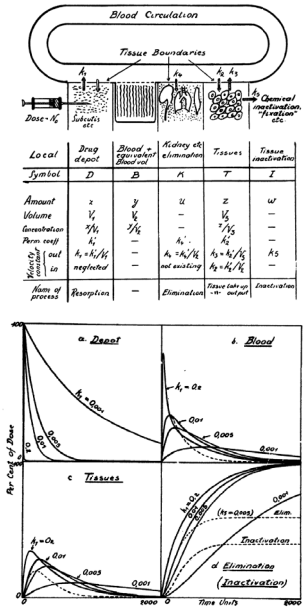
Updated July. 2023

- **Multiple Regulatory Authorities**
- **>100 new drugs, 325 label (simulation results in lieu of clinical studies)**

Courtesy, M Jamei

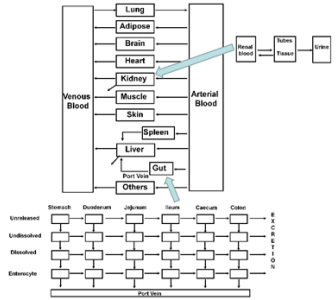
https://www.certara.com/app/uploads/2023/03/Certara_Brochure_Simcyp-PBPK-V22-2023-final-4.pdf

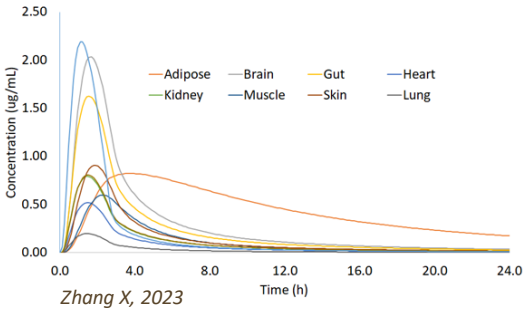
Shift in Mindset of Pharmacology Models



Teorell, Arch Intern Pharmacodyn, 1937

Tech Innovation





Zhang X, 2023

PBPK Industrialization

- Routine Applications
- Efficient Analysis
- Efficient Communications
- Powerful Knowledge Integration

"My Model? Your model? His model? Her model? Whose model???"

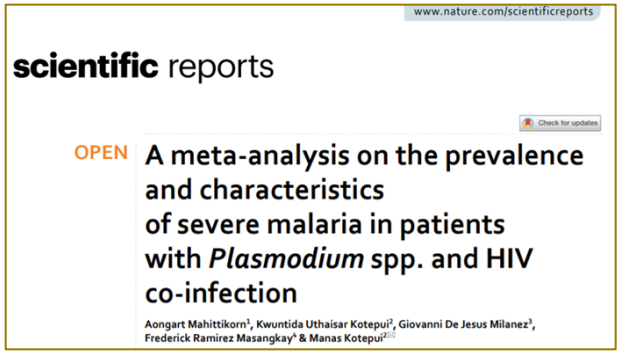
Rostami-Hodjegan, 2018

DDIs in Low Income Settings Are More Common

"It is estimated that one-third of the 40 million people living with HIV/AIDS worldwide are co-infected with TB. People with HIV are up to 50 times more likely to develop TB in a given year than HIV-negative people."

https://www.who.int/3by5/TBfactsheet.pdf

"The odds of SM (severe malaria) were significantly higher in co-infected patients than in Plasmodium mono-infected patients (OR 2.41; 95% CI 1.43–4.08; I 2 = 85%; P= 0.001)…."


www.nature.com/scientificreports

scientific reports

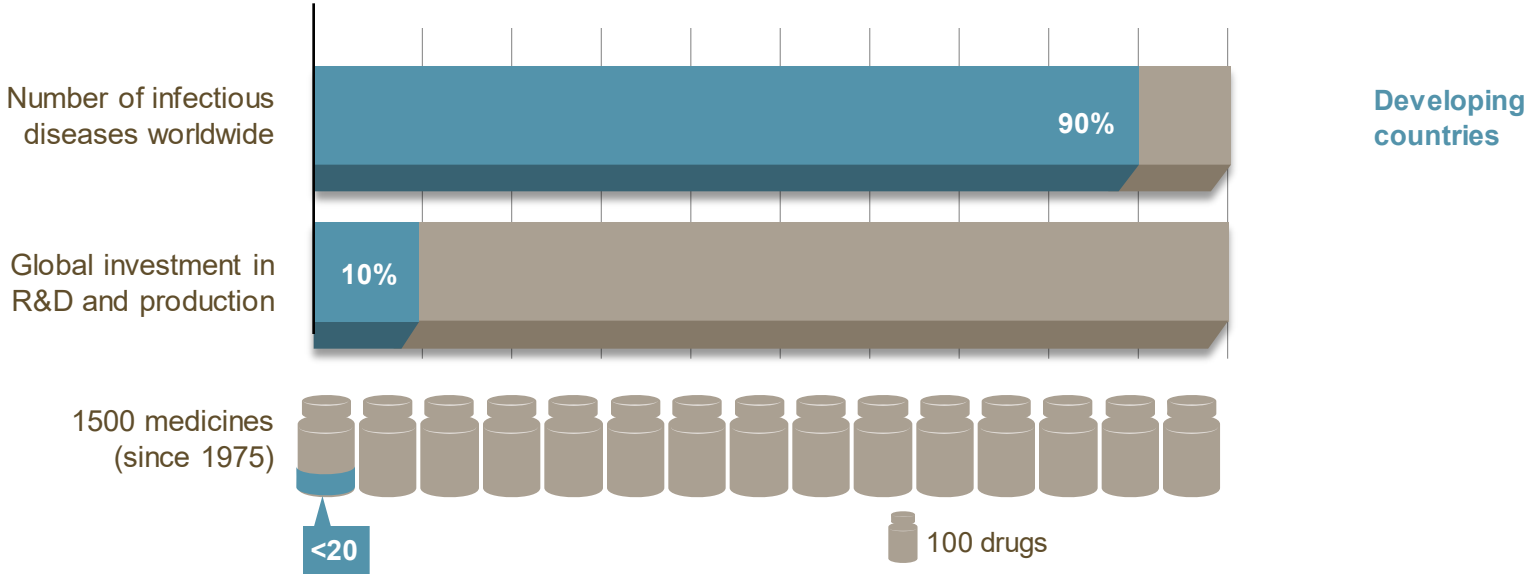
Check for updates

OPEN

A meta-analysis on the prevalence and characteristics of severe malaria in patients with *Plasmodium* spp. and HIV co-infection

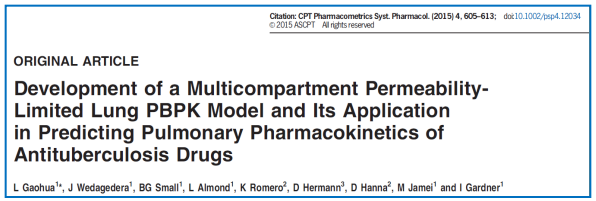
Aongart Mahittikorn[1], Kwuntida Uthaisar Kotepui[2], Giovanni De Jesus Milanez[3], Frederick Ramirez Masangkay[4] & Manas Kotepui[2,5]

Developing Countries Under-represented in Pharma R&D



Courtesy: Bill & Melinda Gates Foundation China Office

Collaborations to Manage Complex DDI and Comorbidity



Citation: CPT Pharmacometrics Syst. Pharmacol. (2015) 4, 605–613; doi:10.1002/psp4.12034
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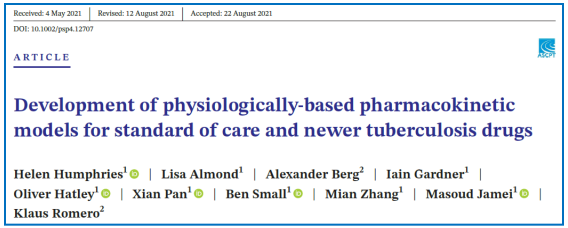
ORIGINAL ARTICLE

Development of a Multicompartment Permeability-Limited Lung PBPK Model and Its Application in Predicting Pulmonary Pharmacokinetics of Antituberculosis Drugs

L Gaohua[1]*, J Wedagedera[1], BG Small[1], L Almond[1], K Romero[2], D Hermann[3], D Hanna[2], M Jamei[1] and I Gardner[1]



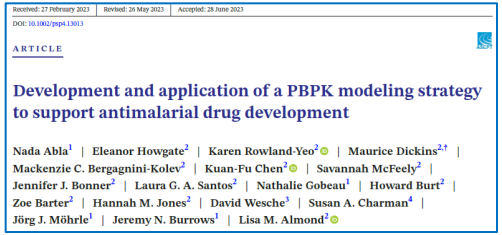
Received: 4 May 2021 | Revised: 12 August 2021 | Accepted: 22 August 2021

DOI: 10.1002/psp4.12707

ARTICLE

Development of physiologically-based pharmacokinetic models for standard of care and newer tuberculosis drugs

Helen Humphries[1] | Lisa Almond[1] | Alexander Berg[2] | Iain Gardner[1] | Oliver Hatley[1] | Xian Pan[1] | Ben Small[1] | Mian Zhang[1] | Masoud Jamei[1] | Klaus Romero[2]



Received: 27 February 2023 | Revised: 26 May 2023 | Accepted: 28 June 2023

DOI: 10.1002/psp4.13013

ARTICLE

Development and application of a PBPK modeling strategy to support antimalarial drug development

Nada Abla[1] | Eleanor Howgate[2] | Karen Rowland-Yeo[2] | Maurice Dickins[2,†] | Mackenzie C. Bergagnini-Kolev[2] | Kuan-Fu Chen[2] | Savannah McFeely[2] | Jennifer J. Bonner[2] | Laura G. A. Santos[2] | Nathalie Gobeau[1] | Howard Burt[2] | Zoe Barter[2] | Hannah M. Jones[2] | David Wesche[3] | Susan A. Charman[4] | Jörg J. Möhrle[1] | Jeremy N. Burrows[1] | Lisa M. Almond[2]

2015
Virtual lung

2021
11 TB drugs

2023
20 Antimalarials

2021
Levonorgestrel

Citation: CPT Pharmacometrics Syst. Pharmacol (2021) 10, 48–58; doi:

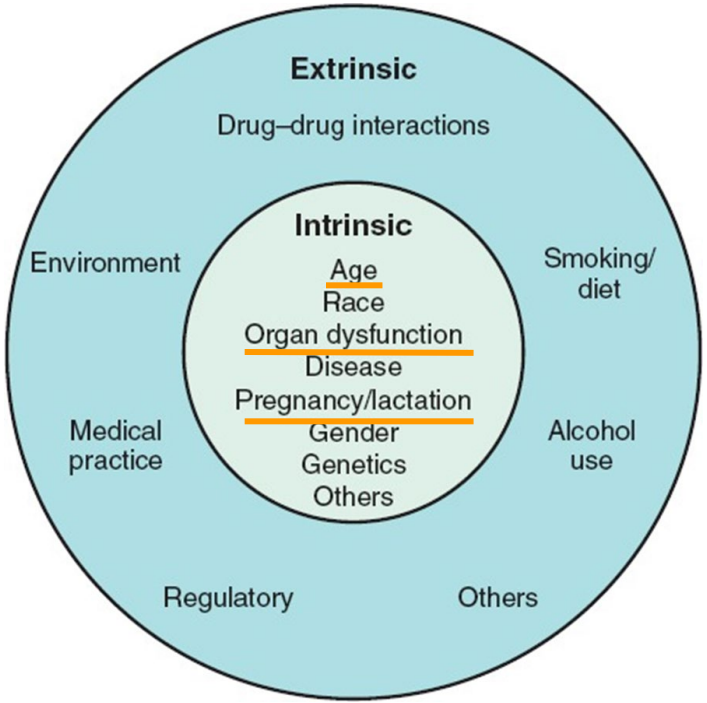
ARTICLE

Quantitative Assessment of Levonorgestrel Binding Partner Interplay and Drug-Drug Interactions Using Physiologically Based Pharmacokinetic Modeling

Brian Cicali[1], Karthik Lingineni[1], Rodrigo Cristofoletti[1], Thomas Wendt[2], Joachim Hoechel[2], Herbert Wiesinger[2], Ayyappa Chaturvedula[3], Valvanera Vozmediano[1] and Stephan Schmidt[1]*

Ongoing PBPK works
- *Lactation*
- *pregnancy*
- *Pediatrics*
- *Malnourishment*

Stagnation of PBPK Applications



Huang and Temple, Clin Pharmacol Ther, 2008

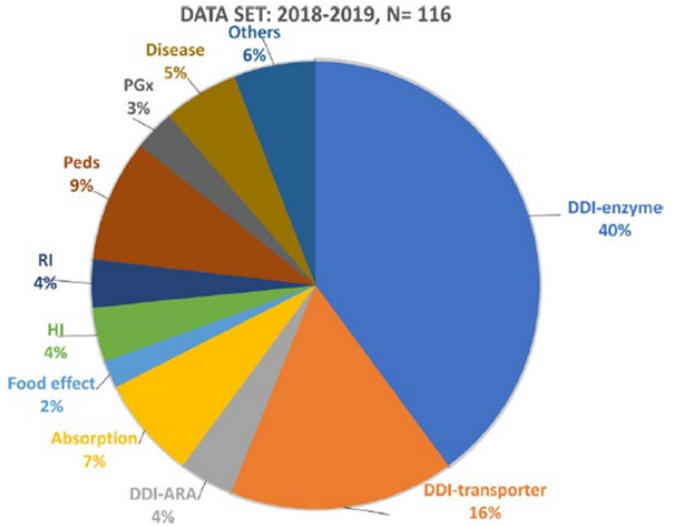


Figure 3. Distribution of physiologically based pharmacokinetic submissions by application areas (2018-2019). DDI-ARA, acid-reducing agent-mediated drug-drug interaction; DDI-enzyme, enzyme-mediated drug-drug interaction; DDI-transporter, transporter-mediated drug-drug interaction; HI, hepatic impairment; peds, pediatrics; PGx, pharmacogenomics; RI, renal impairment.

Zhang et al, J Clin Pharmacol, 2021

Bigger needs vs fewer or no applications!

Removing Barrier between Modelers and Non-modelers

Demystifying physiologically based pharmacokinetic modelling among non-modelers towards model-informed medicine use in under-served populations

Jolien Freriksen[1], Joyce van der Heijden[1], Marika de Hoop-Sommen[1], Trevor Johnson[2], Karen R Yeo[2], Essam Kerwash[3], Susan Cole[3], Janet Nooney[2], Rick Greupink[1], Ping Zhao [4], Saskia de Wildt[1,5]

[1] Radboud University, Nijmegen, Gelderland, The Netherlands
[2] Certara UK Limited, Sheffield, UK
[3] Medicines and Healthcare Products Regulatory Agency, London, UK
[4] Bill & Melinda Gates Foundation, Seattle, Washington, USA
[5] Erasmus MC-Sophia Children's Hospital, Rotterdam, The Netherlands

Workshop	Date, location and duration	Attendees	Populations discussed
Part of the Radboud Summer School "Introduction to Pharmacokinetic and Pharmacodynamic Analysis"	July 2021 Online Half day	26 delegates[a] (global) 5 tutors	Pediatric and pregnant population
Pre-congress course of the 19th European Society for Developmental Perinatal and Paediatric Pharmacology (ESDPPP) meeting	June 2022 In-person Liverpool (UK) One day	37 delegates (mostly European) 11 tutors	Pediatric and pregnant population
Part of the Radboud Summer School "Introduction to Pharmacokinetic and Pharmacodynamic Analysis"	July 2022 Online Half day	29 delegates[a] (global) 5 tutors	Pediatric and pregnant population
Satellite Session of the American Society for Clinical Pharmacology & Therapeutics (ASCPT) meeting	September 2022 Online One day	45 delegates (global) 14 tutors	Pediatric and pregnant population
Medicines and Healthcare products Regulatory Agency (MHRA) workshop	October 2022 In-person London (UK) One day + two online sessions	32 delegates[b] (mostly UK) 7 tutors	Pregnant population

Summary

- Technology innovation allows efficient and comprehensive evaluation of DDI scenarios
- Fit-for-purpose, practical analyses can support dosing decisions
- Knowledge-base continues to grow, enabling efficient learning across applications
- Technology innovation can further remove the barriers for many to understand and apply MIDD

Acknowledgements

Former colleagues at US FDA

Current collaborators in global health