Clinical Pharmacology in Drug Development of Small Molecules: Methods and Applications

Hong Lu, PhD

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Biosketches

Hong Lu, PhD

Hong Lu has over 15 years of experience as a clinical pharmacologist and pharmacometrician in the pharmaceutical industry. She is a scientific director in Quantitative Clinical Pharmacology at Takeda. Prior to Takeda, she had various positions of increasing scope and job responsibility at Vertex, Merck and Alkermes. Hong led clinpharm and biopharm filings for the NDA of ELUMIDOR (buprenorphine and samidorphan) and contributed to the development of ARISTADA (Aripiprazol Lauroxil); and was a pharmacometric lead of ORKAMBI (ivacaftor and lumacoftor) and contributed to the development of KALYDECO (Ivacaftor) and INCIVEK (Telaprevir).

Hong serves on International Society of Pharmacometrics New England (ISoP NE) Committee and on Membership Committee of American College of Clinical Pharmacology (ACCP). She has a special interest in developing clinical pharmacology tools for informed decision-making in drug development and in pharmacy practice.

Hong graduated from Peking Union Medical College in China and obtained a MS in Pharmacology from Boston University School of Medicine and a PhD in Pharmaceutical Science from University of Rhode Island.

<u>Oral Presentations and Publications in 2020:</u>

- Lu H. Developmental Pharmacokinetics in Pediatric Populations: Translating the knowledge to model-informed dosing in Pediatrics. Presented at the Annual Rozman Symposium, June 16, 2020.
- Lu H. Applying Pharmacometric Modeling and Simulation to Dose Management in Antipsychotic Treatment: Depot Medications. Presented at the 2020 ACCP Annual Meeting. September 23, 2020.
- Lu H (Symposium Chair), Fang LY (Symposium Co-Chair), Zhao L, Gomeni R, Wang YN, Graff A. Symposium 14: Applying Pharmacometrics to Precision Dosing in the Lifecycle of Long-acting Injectable Products: Drug Development, Regulatory Approval & Clinical Practice. The 2020 ACCP Annual Meeting. September 23, 2020
- Lu H, Lu W and Rosenbaum S. Precision Dosing Management with Intelligent Computing in Digital Health. Advances in Intelligent Networking and Collaborative Systems. The 12th International Conference on Intelligent Networking and Collaborative Systems (INCoS-2020); DOI: 10.1007/978-3-030-57796-4_26

Disclaimer

- Examples presented in this talk are from publications and/or used for illustration purpose only.
- The views expressed in this talk represent my opinions and do not necessarily represent the views of Takeda.

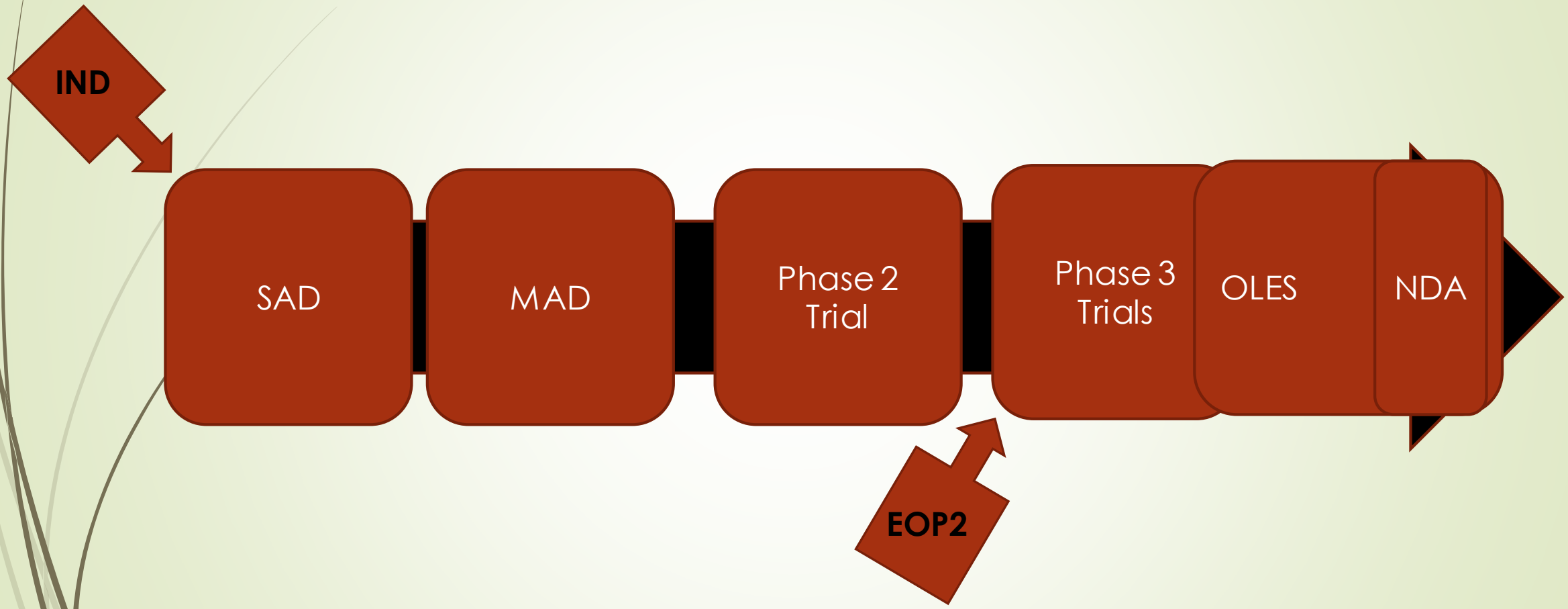
Learning Objectives

Following completion of this activity, participants will be able to:

- Describe the strategic roadmap in clinical drug development of small molecules
- Describe the need and approaches for generating clinical pharmacology data in submitting a US Marketing Application
- Understand the general principles of timing and designing clinical pharmacology studies and population PK analysis.

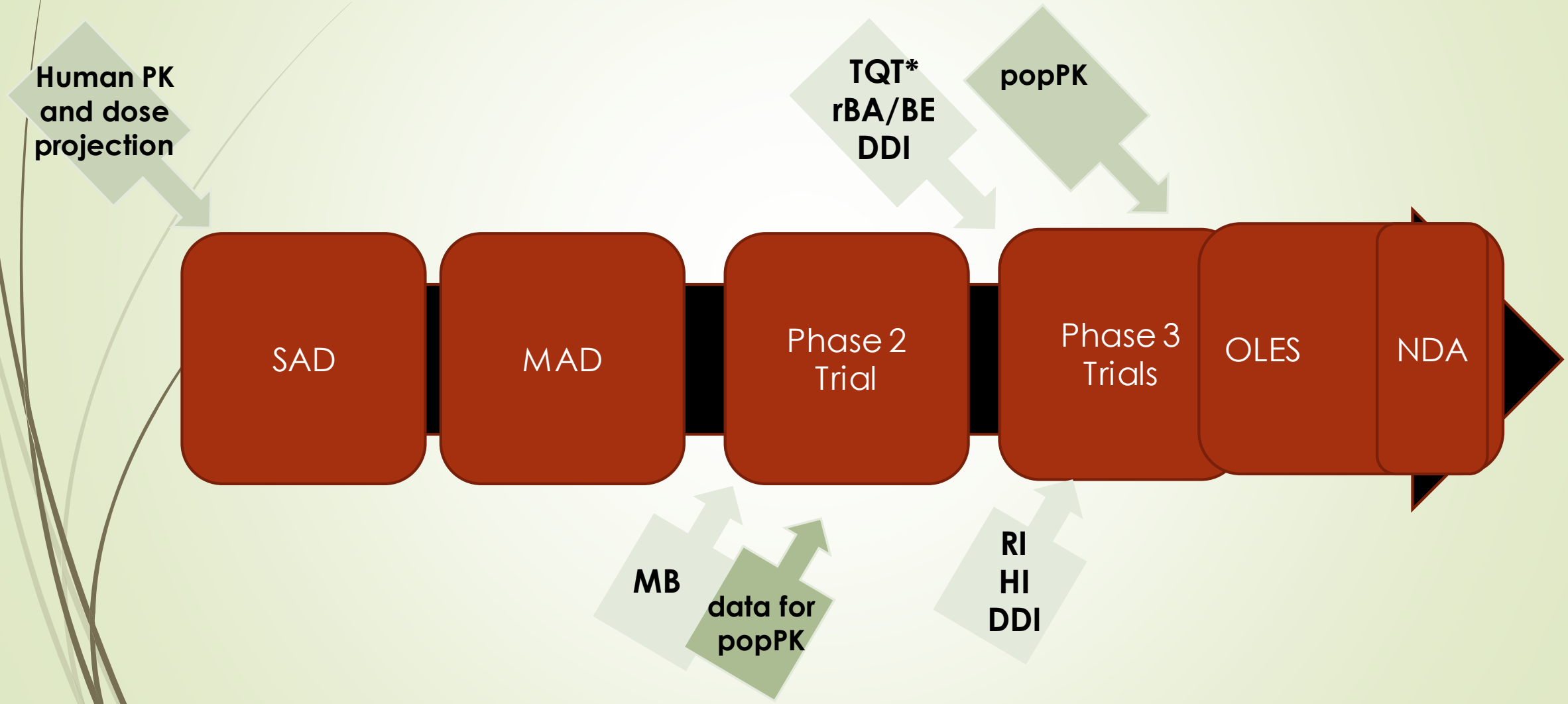
Roadmap of Pharmaceutical Development

Critical Path in Clinical Development



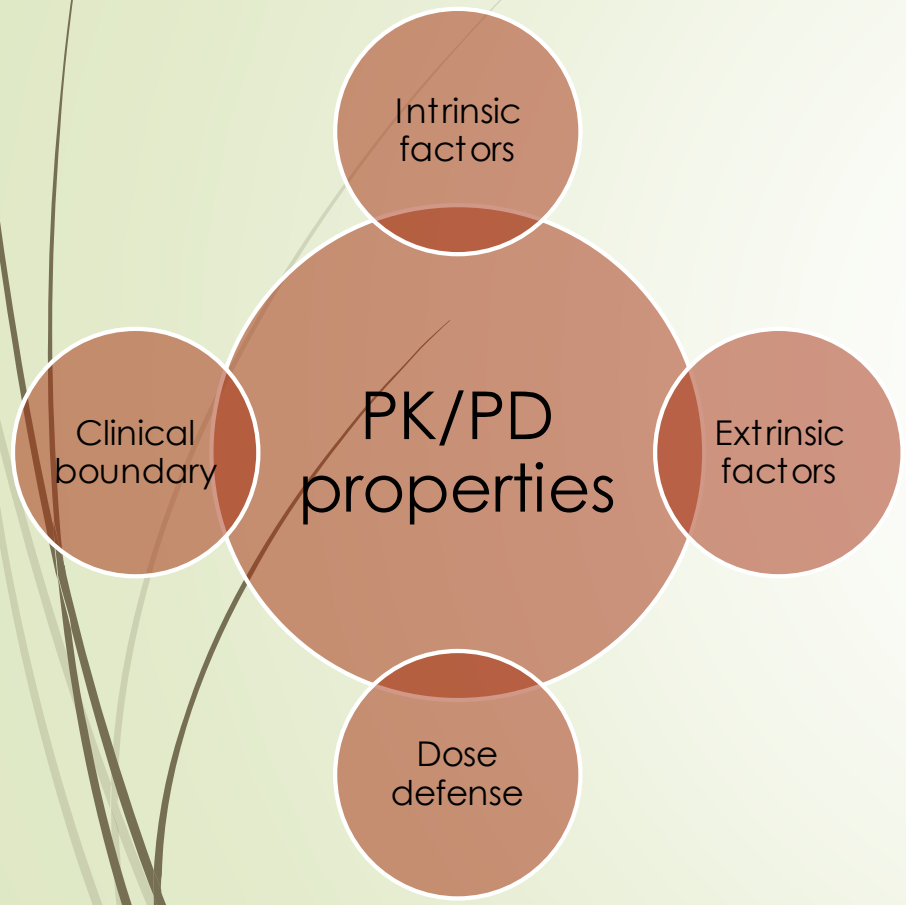
IND: investigational new drug; SAD: single ascending dose; MAD: multiple ascending dose; OLES: open label extension study; NDA: new drug application; EOP2: end-of-Phase 2

Clinical Pharmacology and Modeling Studies: Logical Flow



TQT: thorough QT; rBA : relative bioavailability; BE: bioequivalence; DDI: drug-drug interaction; popPK: population pharmacokinetics; MB: mass balance; RI: renal impairment; HI: hepatic impairment

Purposes of Clinical Pharmacology Work



- **Pharmacokinetics (PK) and Pharmacodynamics (PD)** in humans
  - Single- and multiple-doses PK characteristics
  - Dose proportionality
  - Absorption, Distribution, Metabolism and Excretion in human
- **Intrinsic and extrinsic factors** that influence the PK and PD profiles in humans
  - Physicochemical properties of the drug,
  - Product/formulation,
  - Administration route,
  - Patient's intrinsic and extrinsic factors (e.g., organ dysfunction, diseases, concomitant medications, food)
- **Dose and dose regimen defense** in target indication and target population
  - **Clinical exposure boundary** for safety and efficacy

The ultimate goal is

To determine the dose and dose regimen that achieve the target exposures in all the relevant target populations

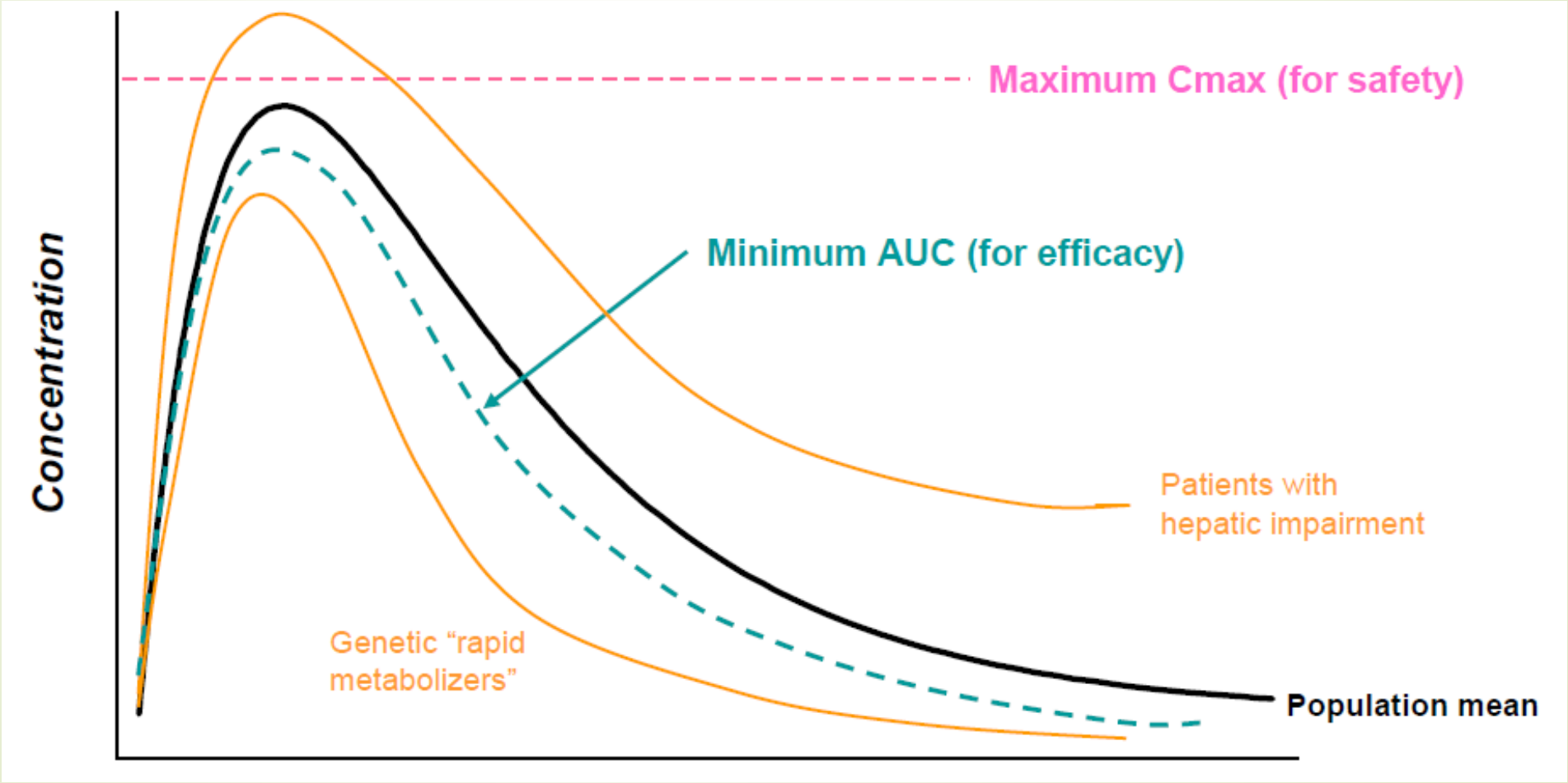


Figure for illustration purpose only

The ultimate goal is

to provide clinical pharmacology information (up to 50%) in a drug label

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
12.5 Pharmacogenomics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

How to Achieve the Goal

The Clinical Pharmacology and Biopharmaceutics (CPB) Review Template: The Question-Based Review (QBR)

Clinical Pharmacology Studies

- Single and multiple ascending dose PK
- Healthy vs. Patient PK
- Human ADME/Mass balance
- Drug interactions
- Pharmacogenomics
- Special population
  - Renal impairment
  - Hepatic impairment
  - Age, gender, ethnics
  - Pediatrics
- Special safety (e.g., QT prolongation; abuse liability)

- **Population PK modeling**
- **PBPK modeling**

Biopharmaceutical studies

- Bioavailability (BA) /Bioequivalence (BE)
- IVIVC
- Food effect

Exposure-Response (ER) analysis for efficacy and safety

- Dose selection and optimization
- Simulations for dosing regimen/dosing conditions

***In vitro* studies using human biomaterials**

- In vitro pharmacology
- Protein binding; Blood-plasma partition;
- *In vitro* drug metabolism, transporter and drug interactions

Bioanalytical Assays

- Assay validation and performance reports

Single and Multiple Ascending Dose Study

- Typically First-in-human study
- Randomized, placebo controlled, healthy subjects
- Starting dose determined by pre-clinical toxicology data
- Maximal dose capped by the NOAEL exposure
- Information gained:
  - Safety/tolerability; maximum tolerated dose (MTD)
  - PK parameters (e.g., Tmax, t1/2 and CL); PK variability, dose proportionality
  - Steady state PK parameters (accumulation ratio; time to steady state)
  - Preliminary exploration of elimination pathways; urine PK,
  - Exploratory metabolite profiling
  - Preliminary exploration of concentration-QT relationship

Typical SAD design

Alternating panel design, 4 periods, 8 dose levels, total N = 16

Protocol	PANEL	Number of Subjects	Period 1	Period 2	Period 3	Period 4
P001	A	N=2	Placebo	DOSE 3	DOSE 5	DOSE 7
		N=2	DOSE 1	Placebo	DOSE 5	DOSE 7
		N=2	DOSE 1	DOSE 3	Placebo	DOSE 7
		N=2	DOSE 1	DOSE 3	DOSE 5	Placebo
	B	N=2	Placebo	DOSE 4	DOSE 6	DOSE 8
		N=2	DOSE 2	Placebo	DOSE 6	DOSE 8
		N=2	DOSE 2	DOSE 4	Placebo	DOSE 8
		N=2	DOSE 2	DOSE 4	DOSE 6	Placebo

PK Pause PK Pause

Example

- *DOSE 1 =25 mg; DOSE 2 = 50 mg; DOSE 3 = 100 mg; DOSE 4 = 200 mg; DOSE 5 = 400 mg; DOSE 6 = 800 mg; DOSE 7 = 1600 mg; DOSE 8 = 200 mg (fed).*
- Each period, (PK, Holter ECG) data at fixed time points (e.g., predose, 0.5, 1, 2, 3, 4, 6, 12, 24 hrs)
- Urine PK at fixed time intervals up to 24 hrs postdose

Typical MAD design

Panels Run sequentially

Panel	Number of Subjects	Treatment Sequence		
A	8	DOSE1/placebo		
B	8		DOSE2/placebo	
C	8			DOSE3/placebo

PK Pause

Example

- *DOSE 1 =200 mg QD for 10 Days; DOSE 2 = 400 mg QD for 10 Days; DOSE 3 = 800 mg QD for 10 Days;*
- Each period, PK data at fixed time points (intense PK on Day 1 and 10; pre-dose on Days 3 to 9)
- Urine PK at fixed time intervals up to 24 hrs postdose

PK Parameters and Clinical Context (1)

Parent drug and Active Metabolites

- T_{max}
  - Represent the most appropriate time for safety assessment (e.g., ECG, PD)
- $T_{1/2}$
  - determining dosage interval
  - related to time to steady state after dose initiation or dose adjustment
  - influences the duration of monitoring after dosing and follow-up after withdrawal of therapy
  - determines adequate washout period between treatments (in crossover studies)
- C_{max}, C_{min}, AUC or MTD
  - Important for dose selection (viewed as relative to efficacy or safety via exposure-response analysis)
- Total Plasma CL and renal clearance (CL_R)
  - Inform the full or reduced design for renal/hepatic impairment study

PK Parameters and Clinical Context (2)

Parent drug and Active Metabolites

- PK variability
  - determines sample size for formal DDI, BA/BE, or food effect studies with pre-defined statistical criteria
- Dose proportionality
- Food effect results
  - Determines the dosing condition
  - enable definitive food effect study in late stage development
- Exploratory metabolite profiling
- PK-QTc analysis
  - Guide early drug development: go/no-go decision, dose selection.
  - enable a TQT waiver in late stage development

SAD/MAD PK readout and Interpretation

Example simulated and included for illustration purpose only

Single Dose PK (fasting)

- Rapid absorption (t_{max} of 0.5 hr)
- Short terminal half-life ~7 hr
- High oral clearance (close to HBF)
- Dose proportional PK over 25-1600 mg
- Low PK variability in exposure (<35% for both AUC and C_{max})

Urine PK

- Renal CL is 320 mL/min (greater than GFR);
- Urine excretion for parent drug is 21% of the dose; 39% for Metabolite

Food effect

- Minimal food effect

Multiple Daily Dose PK

- Steady-state reached after 3 to 4 days of treatment
- Little accumulation with once daily dosing
- Dose proportional PK over 200-800 mg

Metabolite Profiling

- No additional major metabolite identified in human

Clinical Conclusions

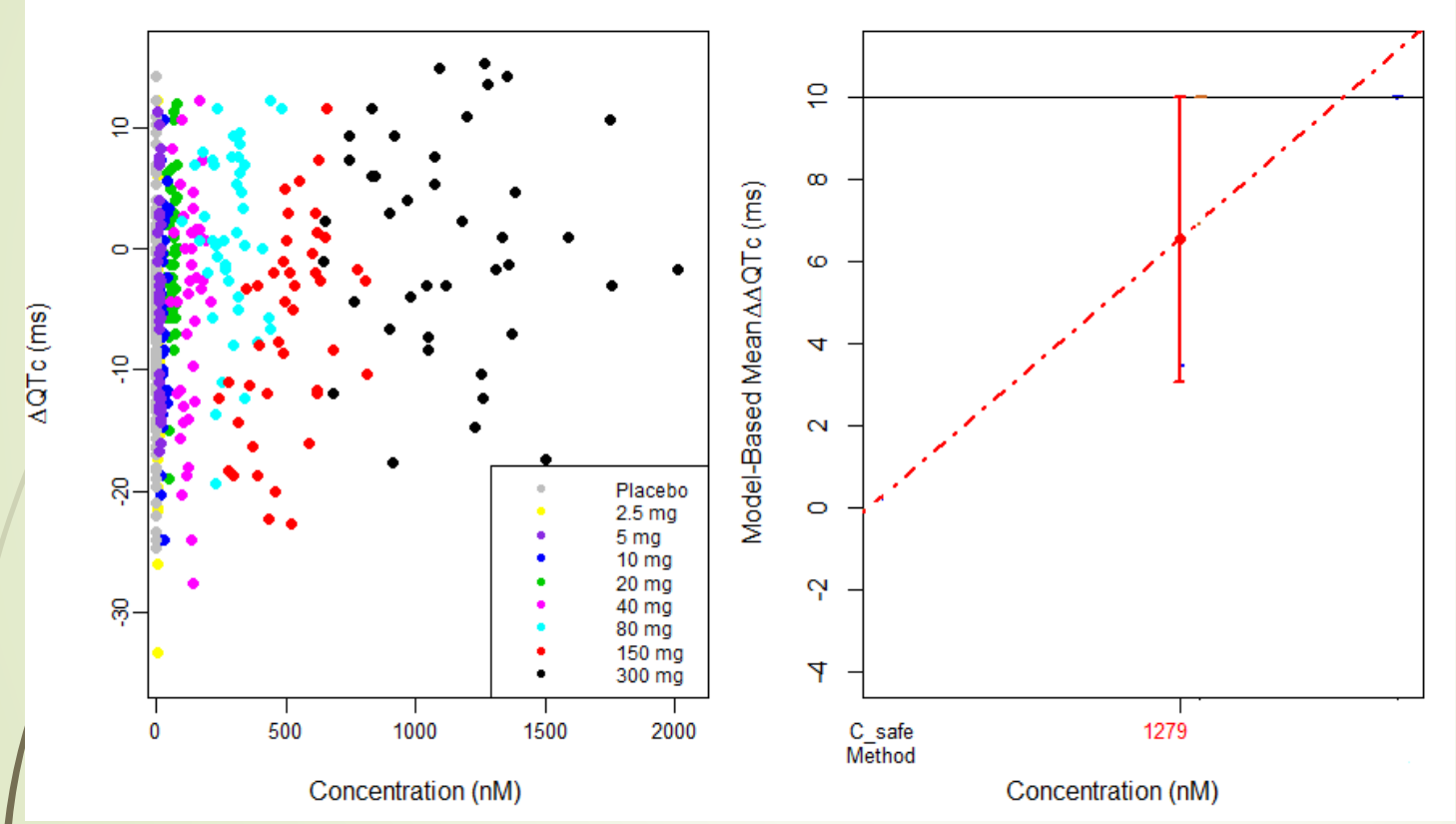
- Well tolerated up to 1600 mg single dose.
- Exposure at 800 mg once-daily in healthy volunteers are below the NOAEL exposure cap.
- Dosed with food in proof-of-concept study (PoC)
- Initiation of additional *in vitro* transporter studies with kidney transporters

PK/QTc Analysis from a SAD Trial

Example simulated and included for illustration purpose only

Holter-based ECG

Highest concentration (C_safe) at which 90% CI for true mean ΔΔQTc < 10 msec



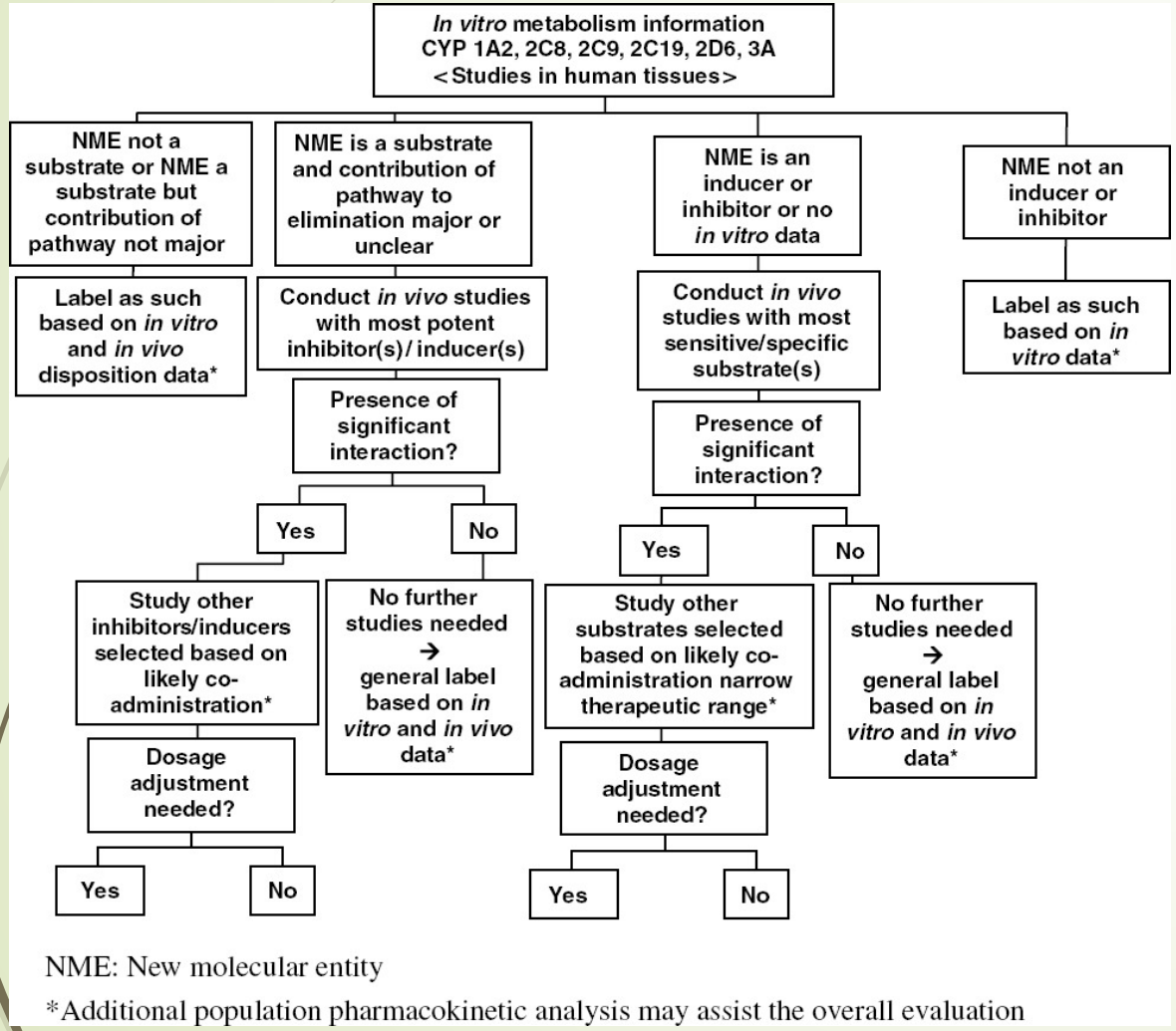
Dose (mg)	G. Mean Cmax
2.5	7
5	15
10	33
20	75
40	166
80	390
150	659
300	1511

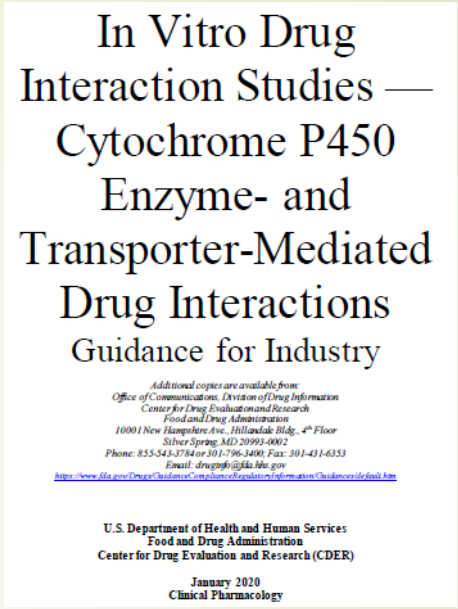
QTc signal between 150 mg and 300 mg

	Slope Estimate	(Std. Error)	C_safe
Base Model	0.005	(0.002)	1279

Assessment of the need for Clinical DDI Study

Decision Tree for Metabolism-Based Drug Interactions

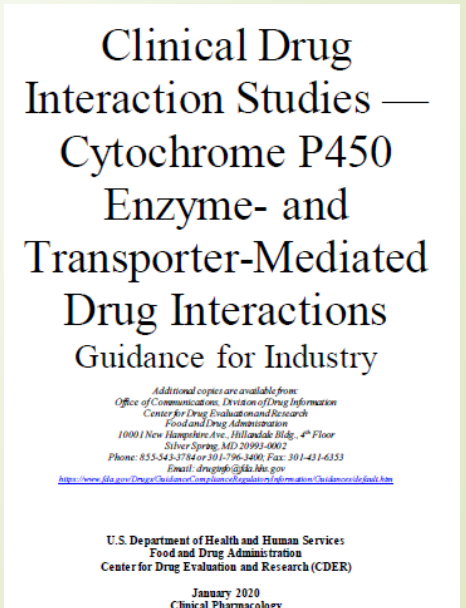



In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

January 2020
Clinical Pharmacology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Clinical Pharmacology

Clinical Pharmacology & Therapeutics, Volume: 81, Issue: 2, Pages: 298-304, First published: 27 December 2006, DOI: (10.1038/sj.clpt.6100054)

In Vitro Assessment of Drug Interaction Potential

- **Metabolism is the major clearance mechanism for A and B in humans.**
- **Both A and B are primarily metabolized via CYP3A4.**
- **No PK interaction between A and B.**
- **A is a weak inhibitor of CYP2D6 and 3A4; B is a weak inhibitor of CYP2C19.**
- **Major metabolites showed no inhibitory or induction on any of CYP enzymes.**
- **A and B are not P-gp substrates.**
- **A, B and metabolites showed no inhibition on any of major transporters.**

Investigational drug is a fixed dose combination of A and B

Enzyme	A	B
CYP3A4 substrate	YES	YES
CYP3A4 inducer	NO	NO
CYP3A4 inhibitor	Weak	NO
CYP3A4 TDI	NO	NO
CYP2B6, 1A2 inducer	NO	NO
CYP1A2 inhibitor	NO	NO
CYP2B6 inhibitor	NO	NO
CYP2D6 inhibitor	Weak	NO
CYP2C8 inhibitor	NO	NO
CYP2C9 inhibitor	NO	NO
CYP2C19 inhibitor	NO	Weak

Victim | Perpetrator | No interaction

Example included for illustration purpose only

Clinical Drug Interaction Assessment Strategy

Metabolism-based drug interactions

- PBPK to assess Victim potential of
  - Itraconazole (strong CYP3A4 inhibitor)
  - Fluconazole (moderate CYP3A4 inhibitor)
  - Rifampin (strong CYP3A4 inducer)
  - Efavirenz (moderate CYP3A4 inducer)
- Clinical DDI studies with Rifampin or Itraconazole
- PBPK to assess perpetrator potential of
  - Midazolam (a model CYP3A4 substrate)
  - Dextromethorphan (a model CYP2D6 substrate)
  - Omeprazole (a model CYP2C19 substrate)

Interactions with concurrent medications in target population

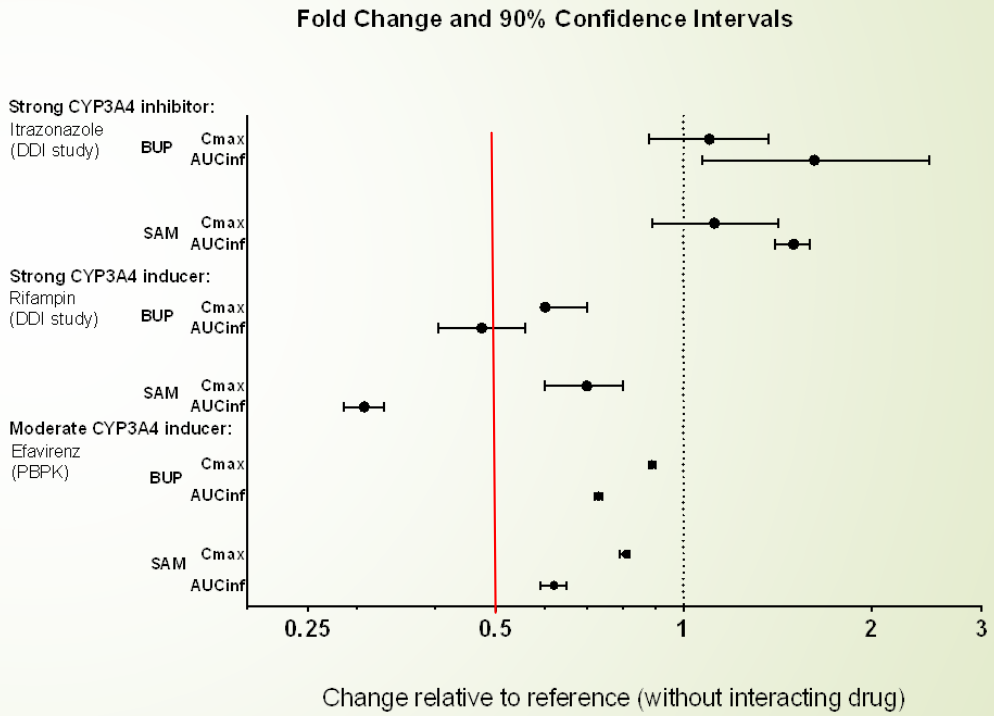
- Identify most commonly used concomitant medications in target population
- Are they CYP3A4 inducers or inhibitors?
  - Assessment via population PK modeling
- Are they substrates of CYP3A4, 2D6 and 2C19?
  - Extrapolated from PBPK modeling
- Assess the need of additional clinical DDI study with co-meds

General Design Principles for Clinical DDI Study

- Objective: To evaluate potential of investigational drug as "Perpetrator" (an inhibitor/inducer [I]) and "Victim" (substrate [S]) of certain metabolizing enzymes/transporters
- Preferably **crossover design** (parallel - if long t½ drug); healthy subjects (or patients for safety considerations or if desirable to evaluate PD endpoints)
- The choice of doses/dosing intervals/dosage forms of substrate and inhibitor/inducer, routes & timing of co- administration, number of doses should **maximize possibility of detecting an interaction**.
  - Evaluating an investigational drug as a potential substrate (Victim)
    - Need a dosage within the linear PK range (highest dosage in this range not required)
    - Potentially can utilize a single dose
    - Study a strong probe inhibitor/inducer first
  - Evaluating an investigational drug as a precipitant (Perpetrator)
    - Highest clinical dosage level
    - Dose to steady-state of parent
    - More extended dosing when:
      - Metabolites contribute to DDI
      - Precipitant demonstrates time-dependent
      - Investigating the potential for induction
  - Time co-administration to maximize the possibility of interaction

DDI Results Reporting and Interpretation

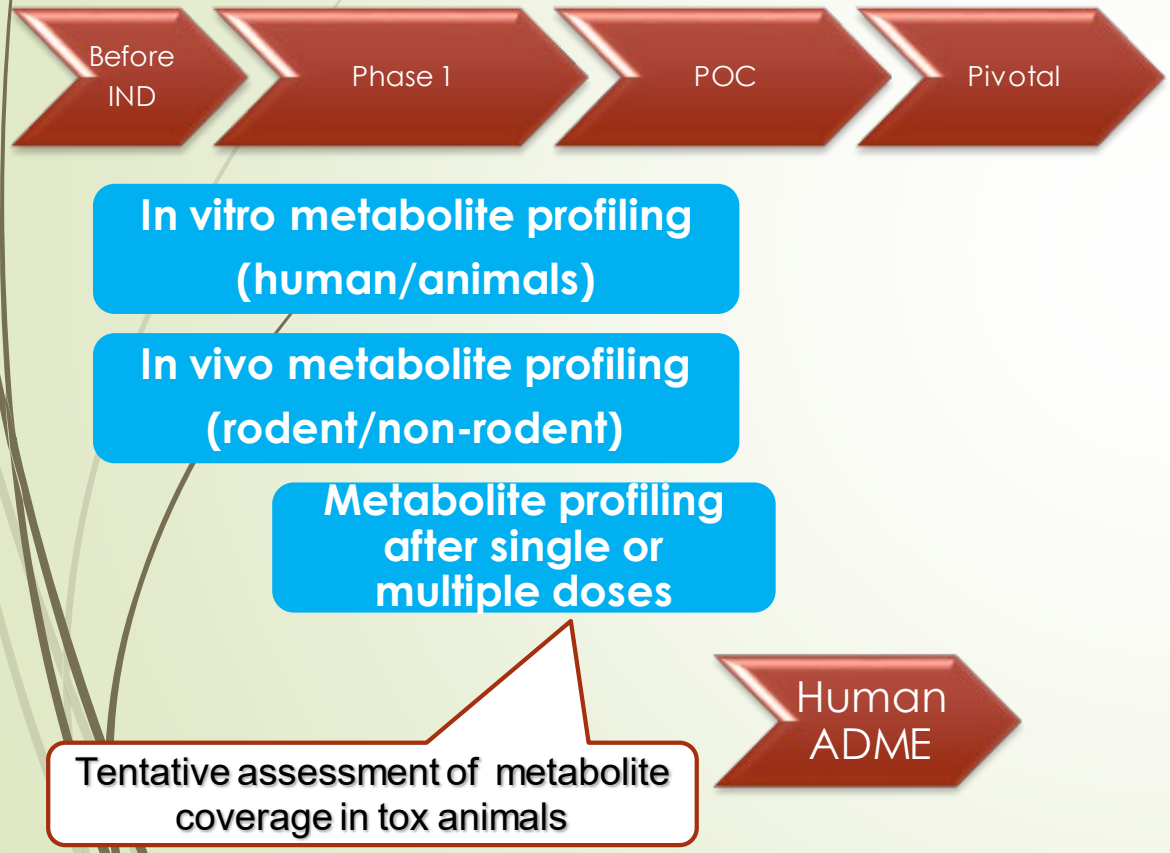
- Exposure-response information on the drug is important in assessing the clinical significance of the change in AUC of substrate by inhibitor/inducer.
- Itraconazole did not meaningfully altered exposure, indicating no dose adjustment with 3A4 inhibitors.
- Rifampin reduced exposure by >50%, indicating no strong 3A4 inducers allowed with co-administration.
- Clinically DDI study results agreed well with PBPK modeling.
- Efavirenz was predicted to decrease exposure <50%, indicating no dose adjustment with mild to moderate 3A4 inducers .



Lu H, Hard ML, von Moltke L. Effects of Itraconazole or Rifampin on the Pharmacokinetics of Buprenorphine and Samidorphan when Sublingually Administered in Combination as ALKS 5461 in Healthy Subjects. ACCP 2018.

Human ADME study: when, why and how

Human ADME study in parallel with Proof-of-concept study is an efficient and resource-conscious approach



Drug development objectives answered by human ADME

- Confirm (similarity of) metabolite profiles in humans vs. toxicology species
- Support choice of animal species for chronic toxicity studies
- Prediction of possible drug interactions; consequences of liver and renal failure; possibilities for improved formulations
- To assess potential retention of the investigational drug in the body

Study objectives of human ADME

- To assess the mass-balance: % recovery of 14C-labeled drug material from urine and feces
- To elucidate rates and routes of excretion
- To assess the absorption, bioavailability, and blood/plasma ratio
- To assess the metabolite profile and metabolite structures

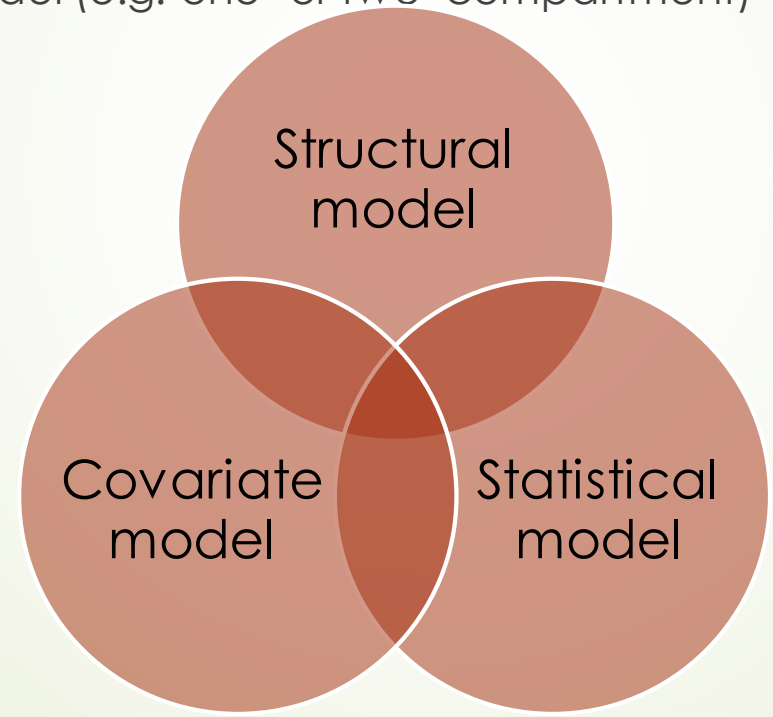
General Considerations for Human ADME Study

- Nonclinical dosimetry study
  - Rat Quantitative Whole-Body Autoradiography (QWBA) to determine radioactive dose in human
- Radiosynthesis
  - Choice of radioisotopes position in the drug molecule and type
  - Non-GMP batches and GMP batches preparation
- Availability of formulation and route of administration
- Study dose selection
  - Pharmacological active dose or a dosage within the linear PK range
- Tissue sampling
  - Plasma, whole blood, urine, feces
- Bioanalysis
  - AMS, LC-MS/MS, Liquid scintillation counting (LSC)
- Study conduct
  - Subject retention and discharge procedures
- Study results reporting and interpretation
  - Metabolite ID report and clinical study report

Population PK Modeling

- Functions describe typical time concentration time course
- Often represented as differential functions
  - Absorption model (e.g., first order, transit-compartment)
  - Elimination model (e.g. one- or two- compartment)

- Explains variability by subject characteristics (covariates)
- E.g., weight, age, genotype, special population



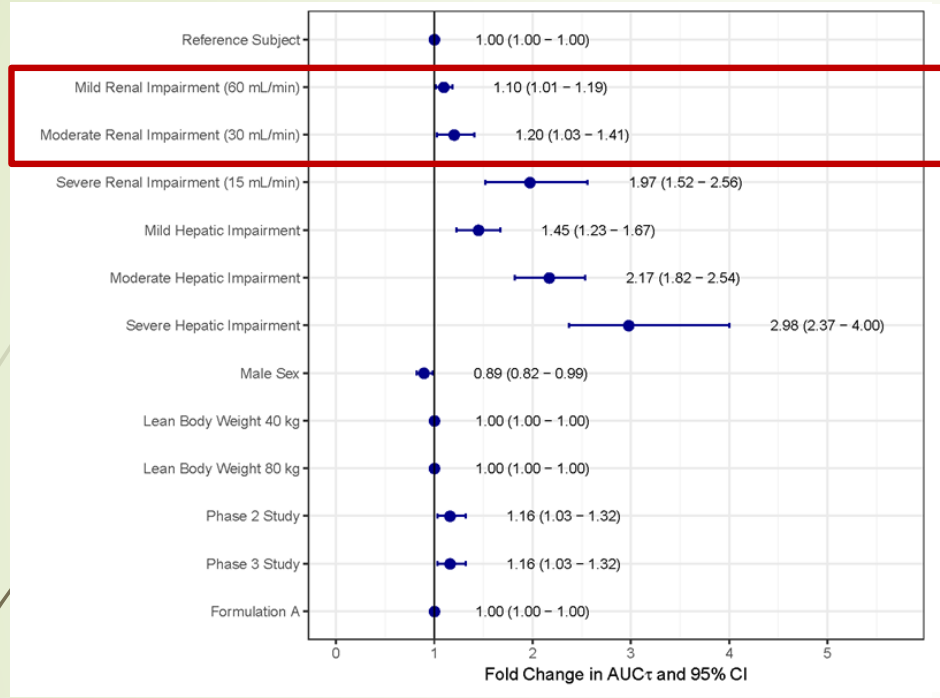
- Variability around structural model
- E.g., Between-subject, between-occasion, residual

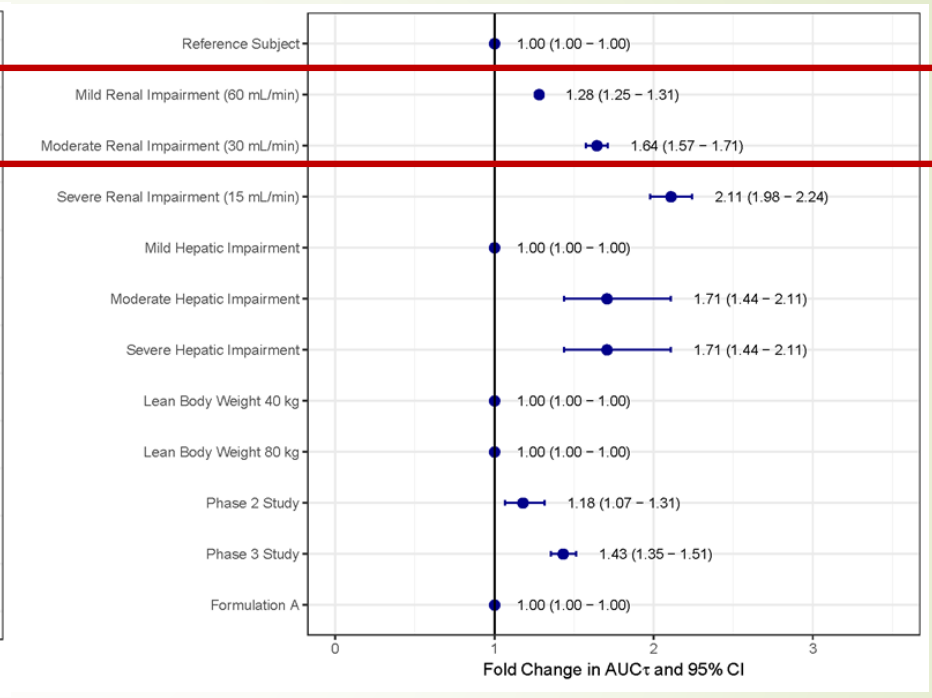
Balance Individual and Population Information

- Studies provide rich and sparse PK sampling schedules
- Studies include both healthy volunteers and patient population
- Studies provide PK data over a wide range of dose levels
- Studies provide large population information with subject characteristics
  - Special populations if possible (e.g., creatinine clearance)
  - Concurrent medications
  - Demographic data (e.g., age, gender, ethnics)
  - Formulations

#data per subject \ #subjects available	Many	Few
Many	Both individual and population model are robust	Individual information is most robust
Few	Population information is most robust	Neither individual nor population information is robust

Population PK Results Reporting and Interpretation





- **Age, gender, body weight, race, patient disease** had no effect on the PK of the fixed dose combination.
- **Formulation** resulted in no clinically significant impact on exposure.
- Increased exposures in subjects with **severe renal impairment and hepatic impairment** were accounted by the covariate model.
  - Increase predicted in subjects with **mild and moderate renal impairment**.

McDougall D, Stringer F, Lu H, Hard M, von Moltke L. A Population Pharmacokinetic Model of Buprenorphine Following Sublingual Administration of ALKS 5461 in Patients With Major Depressive Disorder. ACoP 9 (2018)

McDougall D, Stringer F, Lu H, Hard M, von Moltke L. A Population Pharmacokinetic Model of Samidorphan Following Sublingual Administration of ALKS 5461 in Patients With Major Depressive Disorder. ACoP 9 (2018)

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Backups

Clinical Pharmacology Applications by Drug Development Stage: Not a Cookbook

Inform Internal Decision Making — **Support Regulatory Submission**

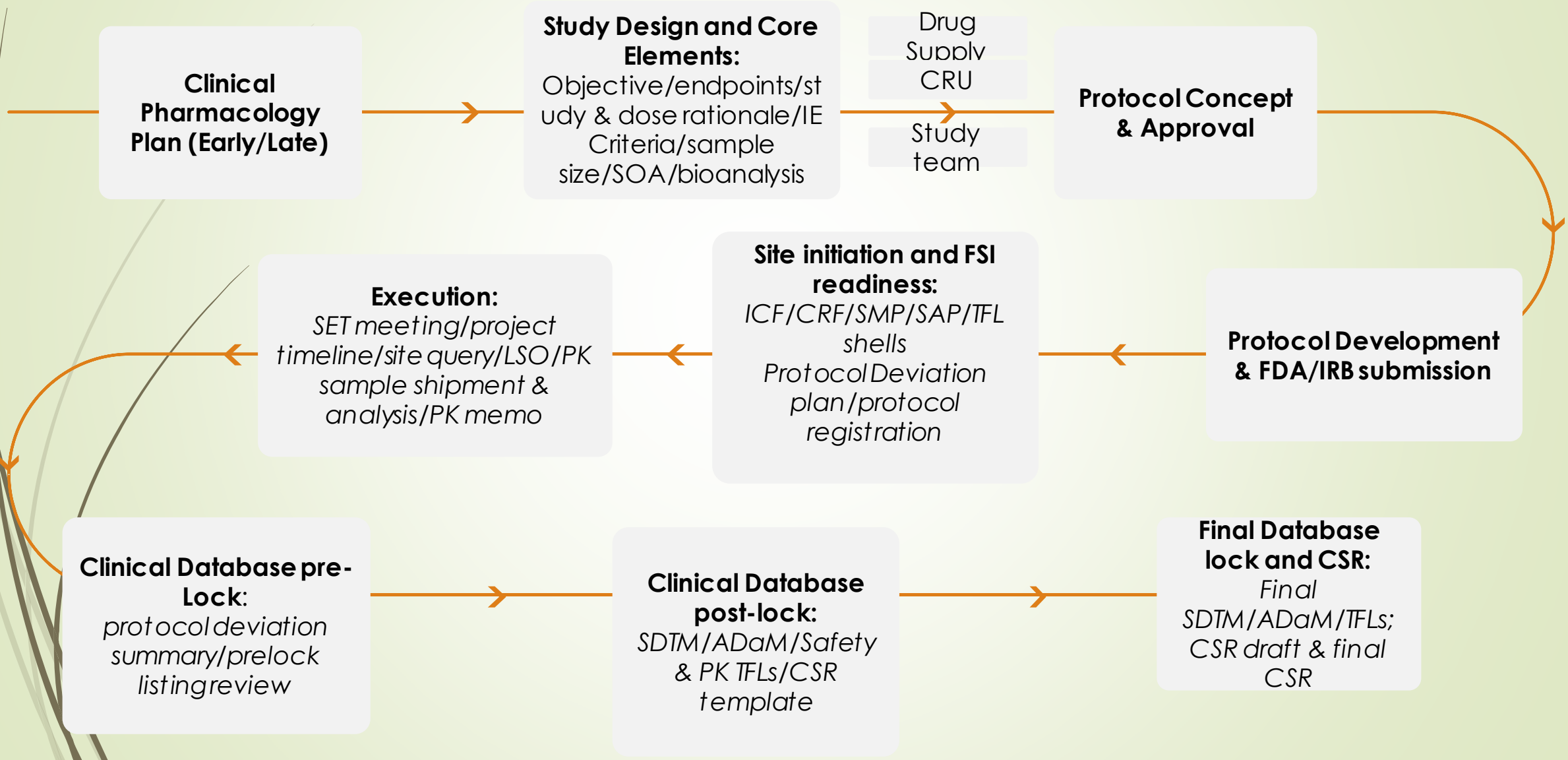
Preclinical to IND	Early Phase (Phase 1 to PoC)	Late Phase (Phase 2/3)
Key (Clinical) Studies		

• Biomarker/PD
• Toxicology/TK
• Nonclinical PK/PD
• Nonclinical ADME
• In vitro metabolism, CYP/Transporter assay
• Physicochemical Property/BCS
	• SAD/MAD
	  • Metabolite profiling
	  • Preliminary food effect
	• PK in Healthy vs. Patients
	• Evaluate needs for DDI
	• BA/BE studies (formulation switch)
	• Enable Proof of Concept (PoC)
	• Mass balance
		• Definitive DDI
		• Renal/Hepatic
		• Definitive food effect
		• BE for to-be-marketed formulation
		• Thorough QT study/ECG evaluation
		• PK and PD sampling scheme
		• Pediatric plan

Key Modeling Activities		

• PK predictions from animal to human
• Human efficacious dose projections
  • PK target
  • PD target
	• Dose range selection for Phase 2
	• SAD/MAD for popPK base model
	• IVIVC consideration
	• Concentration-QT consideration
		• Dose optimization for Phase 3
		• Exposure-response analysis to build clinical boundary
		• PopPK Model refinement (covariates)

Clinical Pharmacology Studies: Designing, Conducting and Reporting



Application of PKPD modeling in Drug Development of Large Molecules

Rong Deng, PhD

December 10, 2020

Nanjing International DMPK Symposium

Biosketches

Rong Deng, PhD

- Dr. Rong Deng is currently an independent consultant on preclinical Pharmacokinetics/Pharmacodynamics (PK/PD), translational PK/PD, clinical pharmacology and pharmacometrics. Before she worked as an independent consultant, she was a Principal Scientist in the Department of Clinical Pharamcolgy at Genentech. Dr. Deng is a subject matter expert on biologics PK and M&S. She has presented at multiple international and regulatory meetings (AAPS, AAPSNBC, PAGE, ASCPT, cFDA, FDA, EMA and etc), organized workshops and symposium on biologics PK and PK/PD modeling topics. Dr. Deng is the co-author of over 50 peer-reviewed publications/book chapters with a Ph.D. in Pharmaceutical Sciences from the University of Buffalo in 2005.
- Recent Oral Presentations and Publications (partial list)
  - **Deng R,** She G, Maia M, Lim JJ, Peck MC, McBride JM, Kulkarni P, Horn P, Castro A, Newton E, Tavel JA, Hanley WD. Pharmacokinetics of the Monoclonal Antibody MHAA4549A Administered in Combination With Oseltamivir in Patients Hospitalized With Severe Influenza A Infection. J Clin Pharmacol. 2020 Nov;60(11):1509-1518
  - **Deng R,** Gibiansky L, Lu T, Li X, Lu D, Li C, Girish S, Wang J, Boyer M, Shankar N, Humphrey K, Freise K, Salem AH, Seymour JF, Kater A, Miles D. Exposure–response analysis of venetoclax in combination with rituximab in patients with relapsed or refractory chronic lymphocytic leukemia: pooled results from a phase 1b study and the phase 3 MURANO study. Leuk Lymphoma. 2020 Jan;61(1):56-6
  - Organizer and Moderator. Will antibody-based anti-infective therapies save conventional treatment failures? ---Opportunities and challenges of development of antibody-based anti-infective therapies 2019 ASCPT annual meeting, Washington, DC, March 16, 2019
  - **Deng R,** Boswell CA, Putnam WS, Tang MT, Garg A, Li C, Chung S, Girish S. Chapter 15: Monoclonal antibodies: From structure to therapeutic application in Pharmaceutical Biotechnology Fundamentals and Applications, fifth edition, Edited by Crommelin DA, Sindelar RD and Meibohm B, Informa Healthcare, New York. March 2019
  - **Deng R**, Gibiansky L, Lu T, Agarwal P, Ding H, Li X, Kshirsagar S, Lu D, Li C, Girish S, Wang J, Boyer M, Humphrey K, Freise KJ, Salem AH, Seymour JF, Kater AP, Miles D. Bayesian Population Model of the Pharmacokinetics of Venetoclax in Combination with Rituximab in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia: Results from the Phase III MURANO Study. *Clin Pharmacokinet. 2019 Jun 18*
  - **Deng R**, Zhou C, Li D, Cai H, Sukumaran S, Carrasco-Triguero M, Saad O, Nazzal D, Lowe C, Ramanujan S, Kamath AV. Preclinical and translational pharmacokinetics of a novel THIOMAB™ antibody-antibiotic conjugate against Staphylococcus aureus. MAbs. *2019 Jun 20:1-13*

Disclaimer

- All examples presented in this talk are from publications and used for illustration purpose only.
- The views expressed in this talk represent my opinions.

Objectives

Following completion of this activity, participants will be able to:

- Understand the PK difference between small molecules and large molecules
- Describe the strategic roadmap in clinical drug development of large molecules
- Understand the role of clinical pharmacology in clinical drug development of large molecules

Antibodies Are the Largest and Most Rapidly Expanding Class of Biopharmaceutical

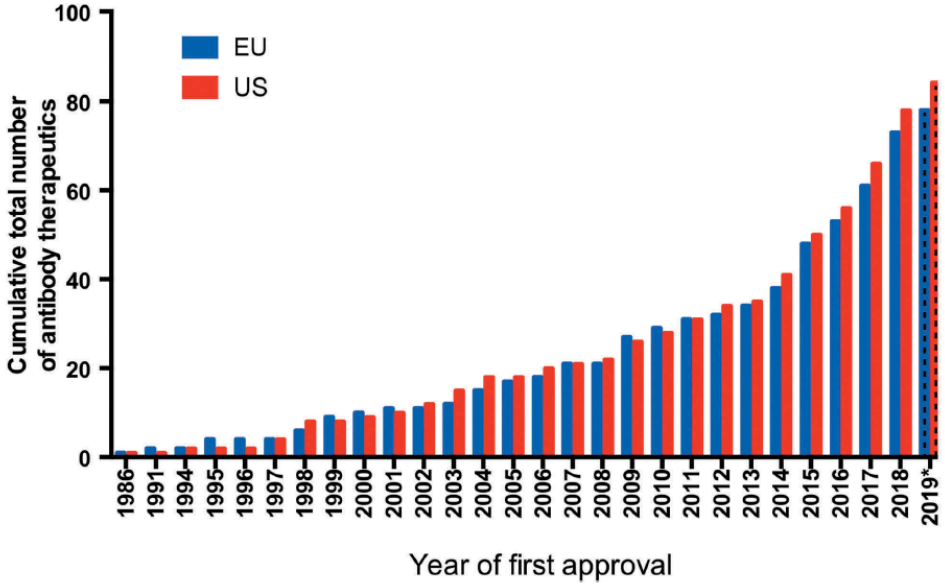
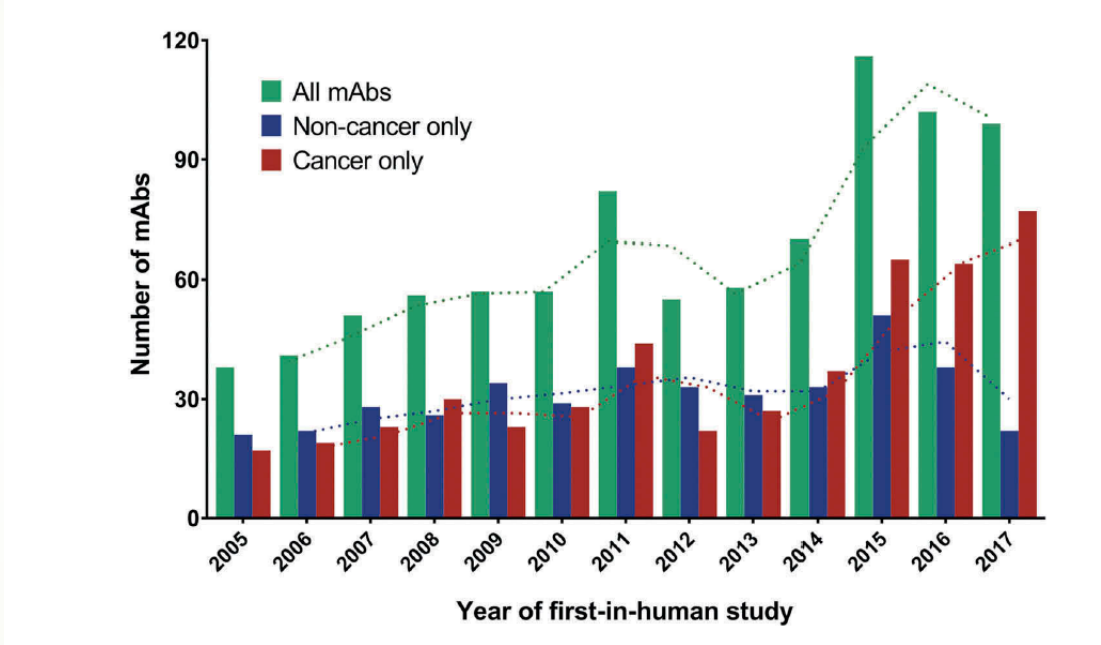


Figure 1. Cumulative number of antibody therapeutics first approved in the US or EU, 1986–2019.

*Data available as of November 28, 2019. Biosimilar antibody and Fc fusion protein products were excluded. A table of US- and EU-approved antibody therapeutics is available at https://www.antibodysociety.org/resources/approved-antibodies/.



As of October 14, **9** antibody therapeutics had been granted first approvals in the US in 2020, and an additional 17 are in regulatory review. *

Kaplon H, Muralidharan M, Schneider Z, Reichert JM. Antibodies to watch in 2020. MAbs. 2020;12(1):1703531. doi:10.1080/19420862.2019.1703531

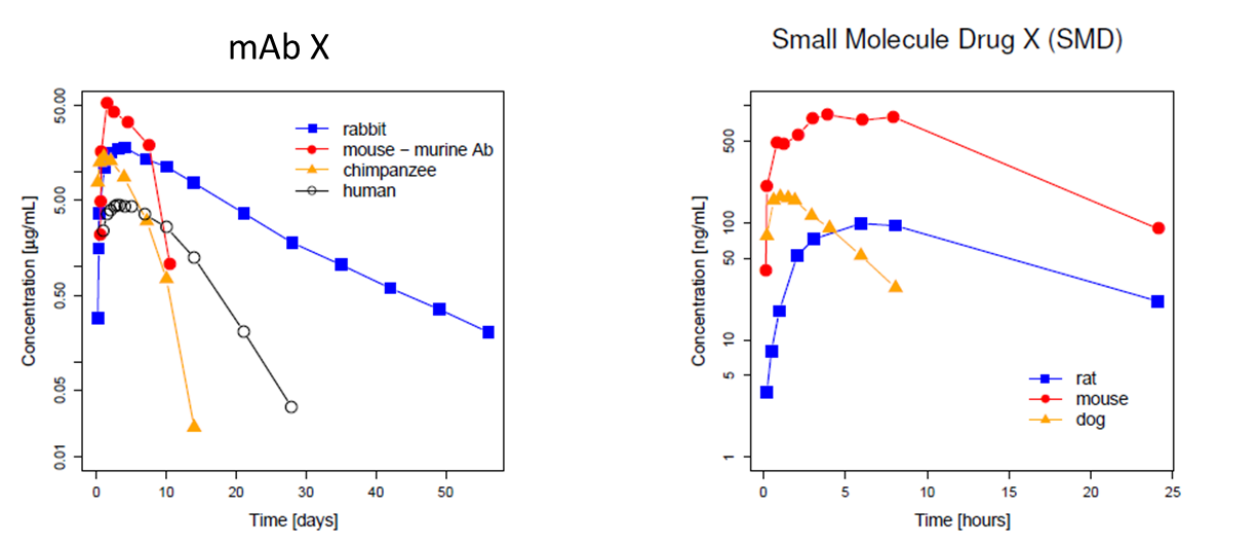
*https://www.antibodysociety.org/resources/approved-antibodies/

How Does PK Differ?

Small Molecule Drugs	Monoclonal Antibodies	Antibody Drug Conjugates
High potency and low specificity	Low potency and high specificity	High potency and high specificity
PK usually independent of PD	PK usually dependent of PD	Same as MAB
Binding generally nonspecific (can affect multiple enzymes)	Binding very specific for target protein or antigen	Same as MAB
Linear PK at low doses (usually therapeutic doses); nonlinear PK at high doses (after saturation of metabolic enzymes)	Nonlinear PK at low doses; linear PK at high doses after saturation of target	Same as MAB
Relatively short $t_{1/2}$ (hours)	Long $t_{1/2}$ (days or weeks)	Long $t_{1/2}$ of antibody; sustained delivery of small molecule (formation rate limited)
Oral delivery often possible	Need parenteral dosing. Subcutaeneous (SC) or intramusclular (IM) is possible	Need parenteral dosing. SC or IM has not been tested
Metabolism by cytochrome P450 or other phase I/ phase II enzymes	Catabolism by proteolytic degradation	Catabolism by proteolytic degradation; small molecule component can undergo excretion unchanged or metabolism by cytochrome P450 enzymes or other phase I/ phase II enzymes
Renal clearance often important	No renal clearance of intact antibody. May be eliminated by damaged kidneys. Antibody fragment might be eliminated by renal clearance.	Combination of mAb and small molecule; Released small molecule can be cleared renally and/or hepatically
High volume of distribution due to binding to tissues	Distribution usually limited to blood and extra-cellular space	Same as MAB
No immunogenicity	Immunogenicity may be seen	Same as MAB
Narrow therapeutic window	Large therapeutic window	Depends on potency of payload

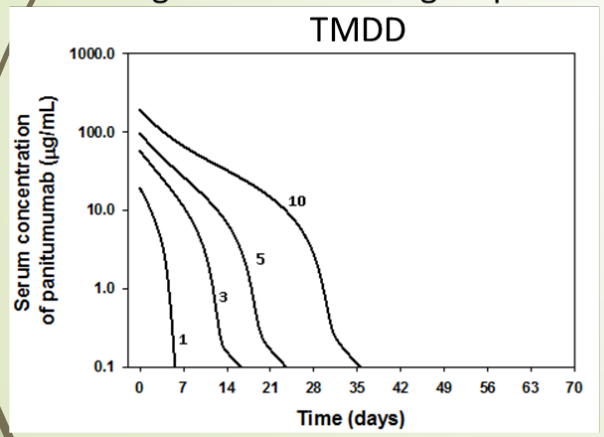
Deng R et al . Chapter 15: Monoclonal antibodies: From structure to therapeutic application in Pharmaceutical Biotechnology Fundamentals and Applications, fifth edition, Edited by Crommelin DA, Sindelar RD and Meibohm B, Informa Healthcare, New York. March 2019

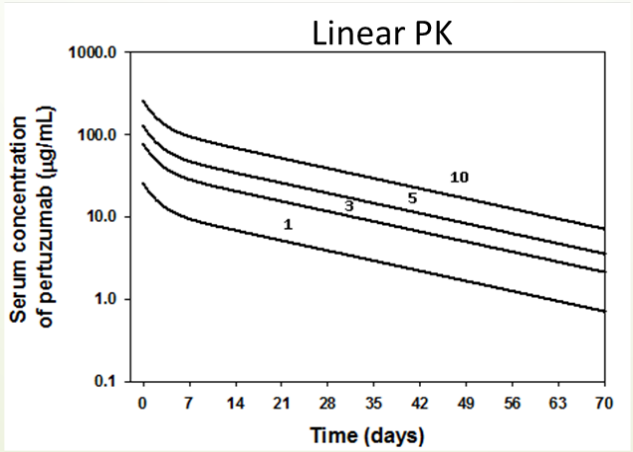
PK Example: mAb vs SMD



MAbs

Target-mediated Drug Disposition

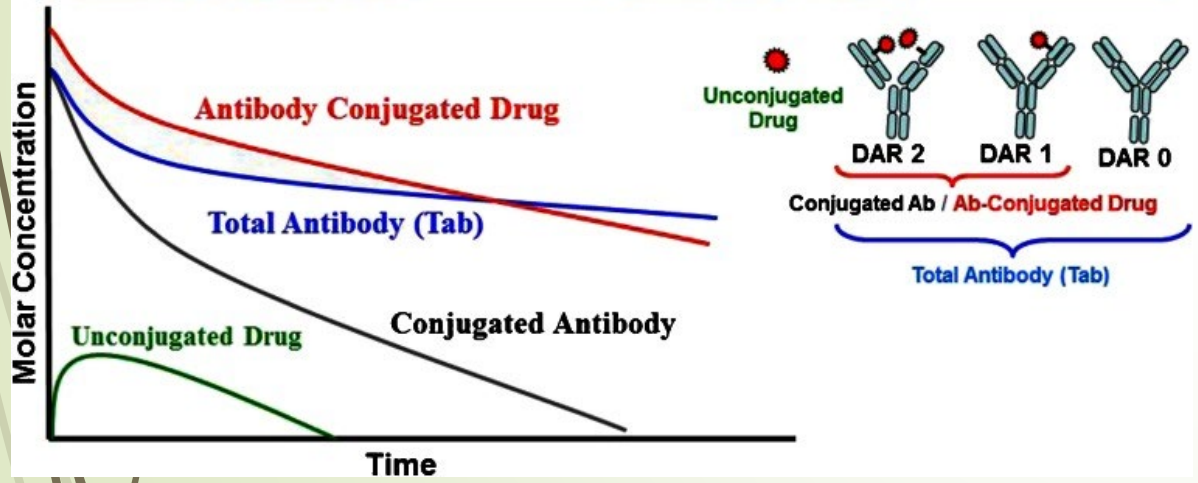


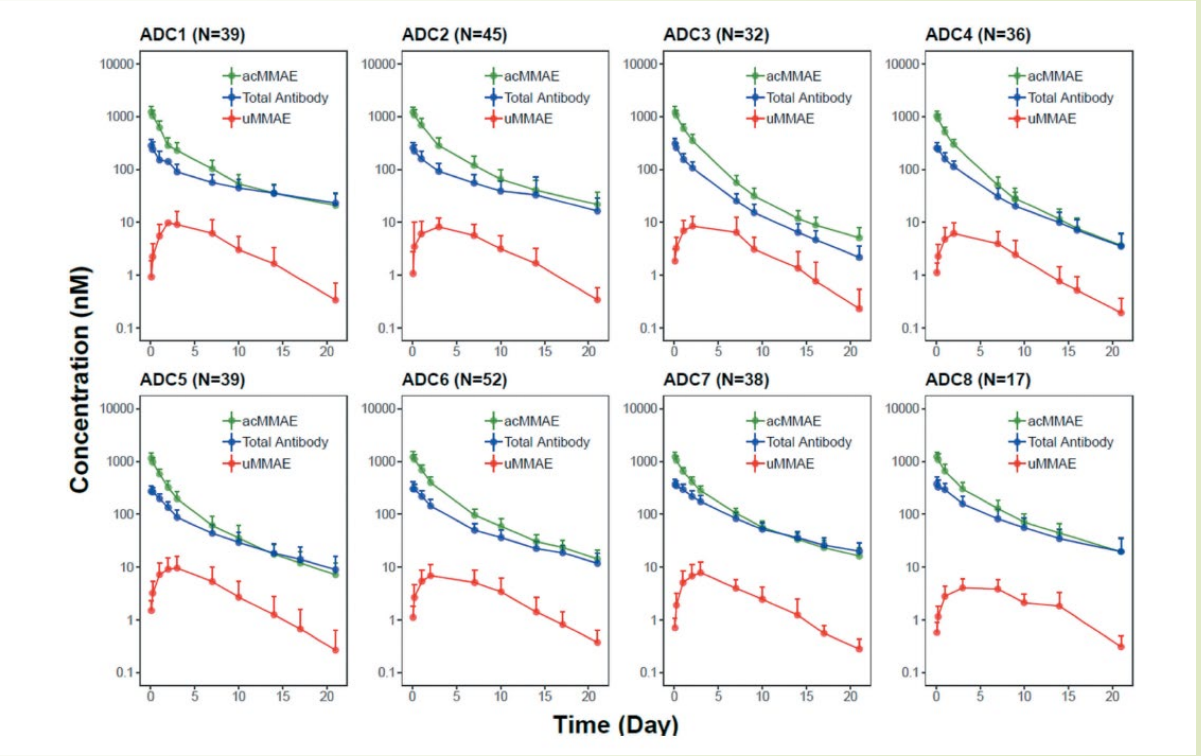


- mAbs show slow clearance (mAb time units in days, SMD time units in hours
- mAbs show often nonlinear PK in binding species
- Both mAb and SMD can exhibit species differences
  - (SMD: e.g. CYP450 metabolism, mAbs: e.g., target expression, affinity)

PK examples: ADC

Antibody Related PK Assays	Small Molecule Related PK Assays
Total Antibody (Tab) - Measures both conjugated & unconjugated antibody	**Antibody Conjugated Drug** - Measures drug associated with antibody
Conjugate Antibody - Measures only conjugated antibody	**Unconjugated Drug** - Measures unconjugated drug

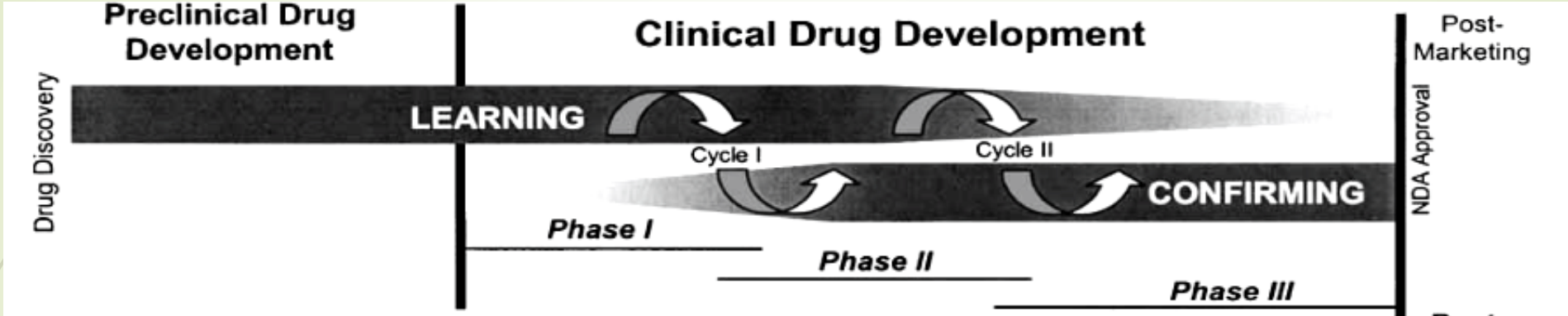




Kamath AV, Iyer S. Preclinical Pharmacokinetic Considerations for the Development of Antibody Drug Conjugates. Pharm Res. 2015;32(11):3470-3479. doi:10.1007/s11095-014-1584-z

Li C, Zhang C, Li Z, et al. Clinical pharmacology of vc-MMAE antibody-drug conjugates in cancer patients: learning from eight first-in-human Phase 1 studies. *MAbs*. 2020;12(1):1699768. doi:10.1080/19420862.2019.1699768

Applications of PK/PD Concepts during Preclinical and Clinical Drug Product Development



Preclinical PK/PD

- Development of mechanism-based models
- Evaluation of *In vivo* potency and intrinsic activity
- Evaluation of *In vivo* drug interactions
- Identification of bio-/ surrogate markers and animal models for efficacy/toxicity
- Dosage form and dosage regimen optimization
- Integrated information supporting 'go/no go' decision

Transitional PK/PD

- Extrapolation of preclinical data to humans
- Allometric scaling
- Dose selection/ escalation

Clinical PK/PD

Analytical PK/PD

- Characterization of dose-concentration-effect relationship
- Evaluation of dosage forms and administration pathways
- Therapeutic index
- Food effects
- Gender effects
- Special populations (children, elderly)
- *In vivo* evaluation of active metabolites
- Drug/Drug interactions
- Drug/Disease interactions
- Tolerance development
- Evaluation of drug analogues
- Population PK/PD
- Bridging studies

Predictive PK/PD

- Simulations
- Trial forecasting

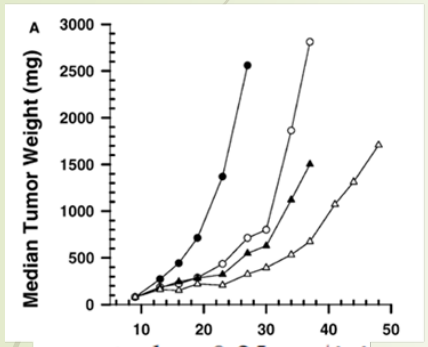
Post-Marketing PK/PD

- Post-marketing surveillance

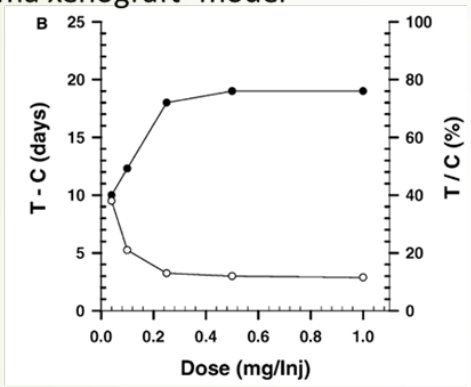
Meibohm B, Derendorf H. Pharmacokinetic/pharmacodynamic studies in drug product development. J Pharm Sci. 2002 Jan;91(1):18-31. doi: 10.1002/jps.1167.

Cetuximab Preclinical PK/PD Study to Help Defining the Optimal Clinical Exposure

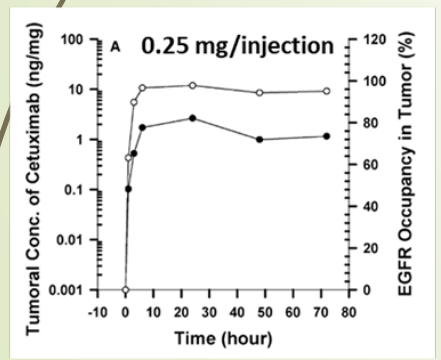
GEO human colon carcinoma xenograft model

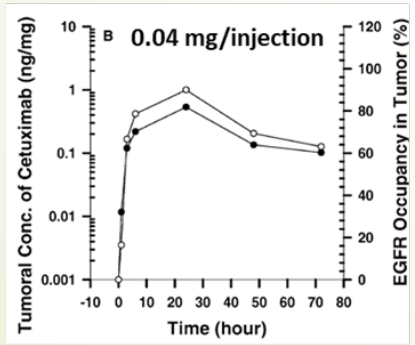


● control, △ 0.25 mg/ inj
▲ 0.1 mg/inj, ○ 0.04 mg/inj



● T - C at tumor size of 1 g
○ T / C % at the end of treatment





● tumoral concentration of cetuximab, ○ % EGFR occupancy

Luo FR et al., Cancer Chemother Pharmacol. 2005 Nov;56(5):455-64.

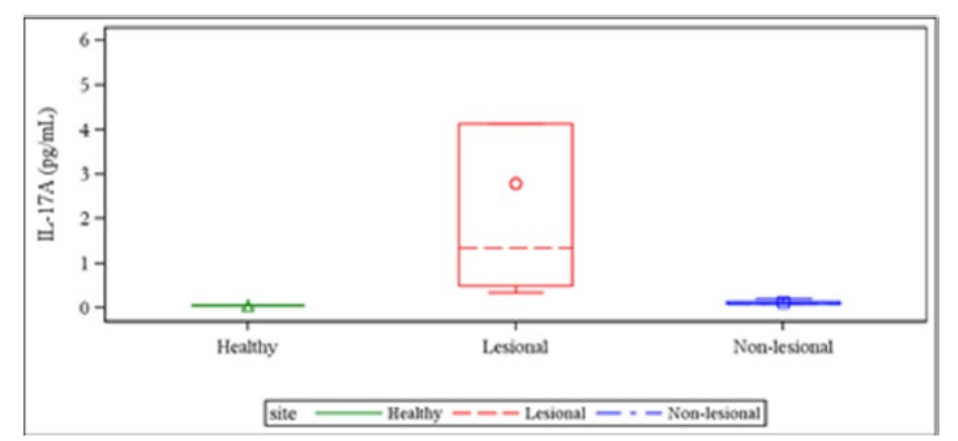
- The estimated $C_{ss,\,avg}$ is 73.1 µg/mL for Cetuximab in GEO human colon carcinoma xenograft model at the optimal dose of 0.25 mg/inj q3dx5
  - Reach 100% EGFR occupancy in tumor
- The estimated $C_{ss,avg}$ of Cetuximab in cancer patients is within the range of 50-100 µg/mL at current clinical dose

PK/PD studies in the preclinical stages including the receptor occupancy in the tumors lay a solid foundation for defining the optimal clinical drug exposure

Secukinumab PK/PD in Skin Provides Importantly Supportive Evidence of MOA

PKPD study to understand MOA

- High baseline free IL-17A levels in diluted dermal ISF from lesional psoriasis patients
- Significant secukinumab exposure in the target tissue skin (dermal interstitial fluid, blister fluid and skin biopsy samples)
  - Skin to serum ratio: **23%** in healthy volunteers versus **28-39%** in psoriasis patients
    - Different from reported skin partition coefficient value (~15%)*
- Significant decrease of β-defensin-2, a relevant IL-17A pathway marker after secukinumab treatment
  - Confirm the role of IL-17A homo- and heterodimers in psoriasis



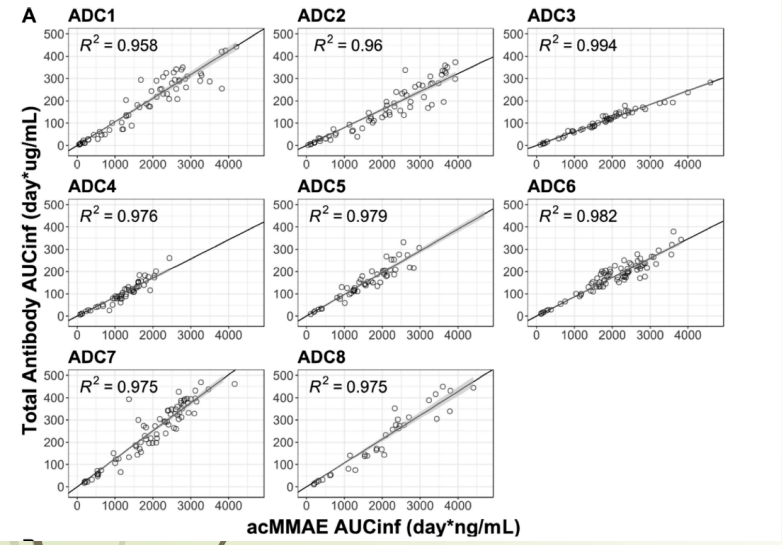
- **First time to use open flow microperfusion (OFM) for PK/PD assessment of a therapeutic antibody and relevant biomarkers**
- **Disease status has impact on target expression level and mAb skin penetration**

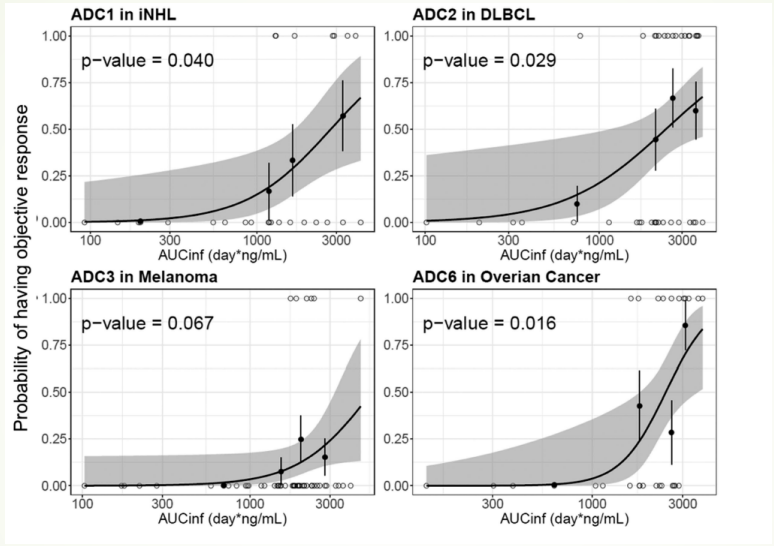
**Shah D et al MAbs. 2013 Mar-Apr;5(2):297-305*

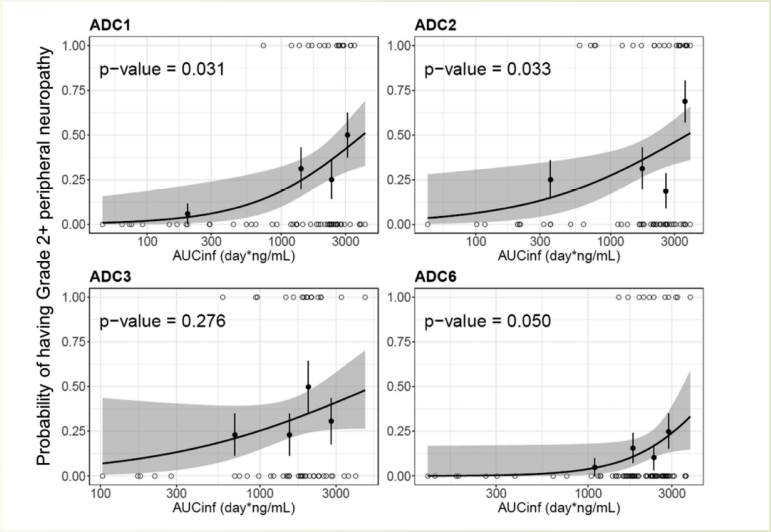
http://abstracts.aaps.org/Verify/aaps2013/postersubmissions/T2335.pdf
http://abstracts.aaps.org/Verify/NBC14/Invited/Submission/out/NBC14-000056.pdf
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM419023.pdf

Platform analysis to reduce PK sampling

Integrated Platform Analysis for ADC







Strong correlation between total Ab and acMME

Key efficacy and safety endpoints tested correlate well with acMMAE exposure not with unconjugated MMAE

Platform analysis (PK and exposure-response analysis) suggested that acMMAE analyte alone might be adequate for vc-MMAE ADCs to support the clinical pharmacology strategy used during late-stage clinical development.

Li C, Zhang C, Li Z, et al. Clinical pharmacology of vc-MMAE antibody-drug conjugates in cancer patients: learning from eight first-in-human Phase 1 studies. *MAbs*. 2020;12(1):1699768. doi:10.1080/19420862.2019.1699768

Labeling update
Intrinsic factor: body weight

Labeling update: Fixed Dosing vs Body Weight-based Dosing

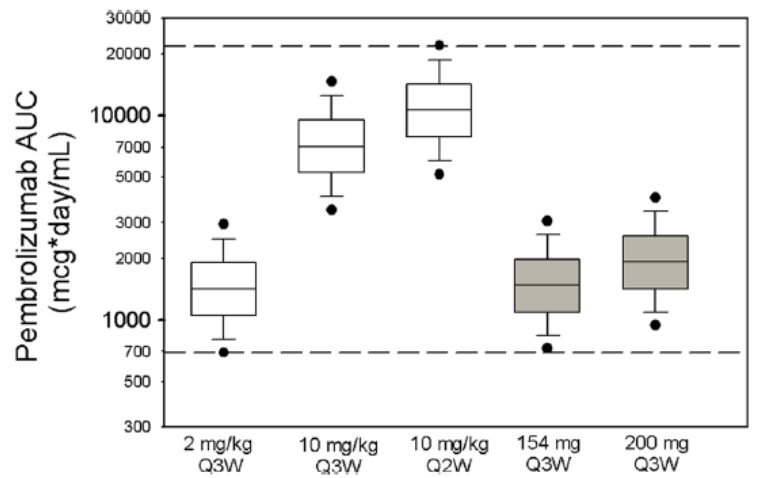


Fig. 1 Simulated distribution of steady-state AUC exposures (2800 replicate simulations) for the weight-based regimens of 2 mg/kg Q3W, 10 mg/kg Q3W, and 10 mg/kg Q2W compared with the simulated distribution of exposures for two potential fixed-dose regimens (log scale): *Box*: *straight middle line* = median; *edges* = 25th and 75th percentiles; *whiskers* = 10th and 90th percentiles; *dots* = 5th and 95th percentiles. *Horizontal dashed lines* represent the range of exposures (5th percentile of 2 mg/kg Q3W and 95th percentile of 10 mg/kg Q2W) from dose regimens demonstrated to have comparable efficacy and tolerability in melanoma and NSCLC trials

- A previously established population PK (popPK) model as well as exposure-response results from patients with advanced melanoma or non–small cell lung cancer (NSCLC) were used to evaluate the potential application of a fixed dosing regimen with the aim of maintaining pembrolizumab exposures within the range demonstrated to provide near maximal efficacy and acceptable safety.

$$CL = CL_{TV} \cdot \left(\frac{WT}{Median(WT)}\right)^{\alpha - CL} \cdot e^{\eta_1} \quad (1)$$

$$Vc = Vc_{TV} \cdot \left(\frac{WT}{Median(WT)}\right)^{\alpha - Vc} \cdot e^{\eta_2} \quad (2)$$

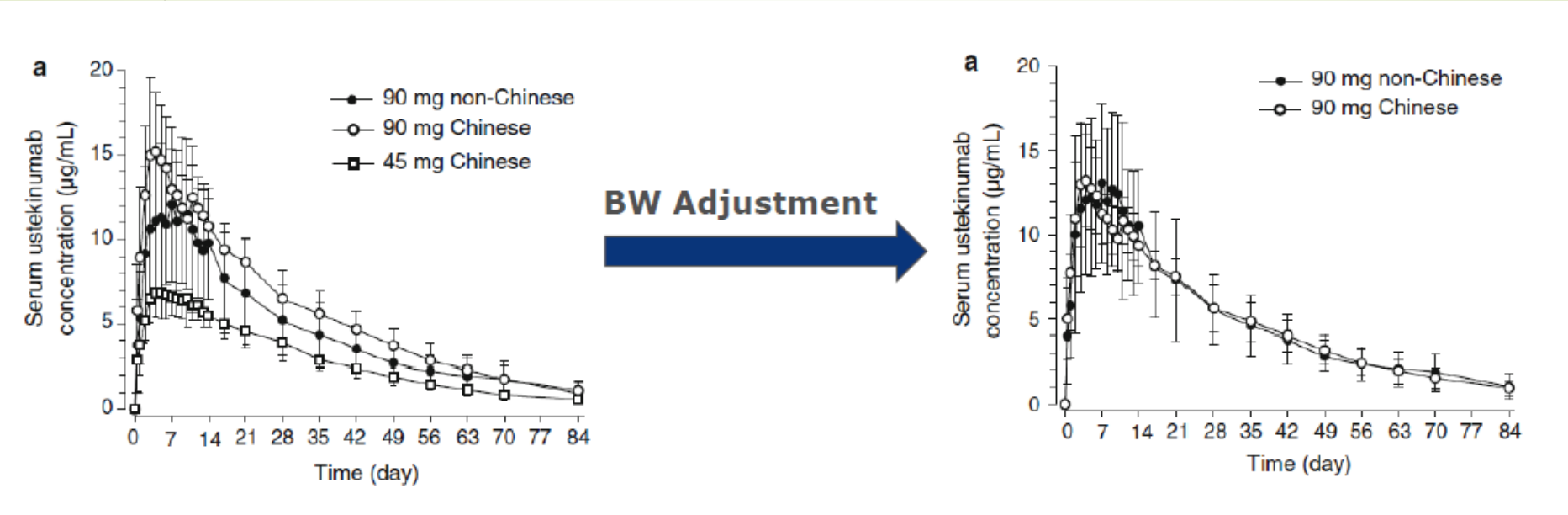
- Doses of 200 mg and 2 mg/kg provide similar exposure distributions with no advantage to either dosing approach with respect to controlling PK variability. These findings suggest that weight-based and fixed-dose regimens are appropriate for pembrolizumab.

- **Simulations based on population PK to support the flat dosing**

Freshwater T, Kondic A, Ahamadi M, et al. Evaluation of dosing strategy for pembrolizumab for oncology indications. J Immunother Cancer. 2017;5:43. Published 2017 May 16. doi:10.1186/s40425-017-0242-5

Intrinsic factor: body weight

Body Weight Effects on mAb PK

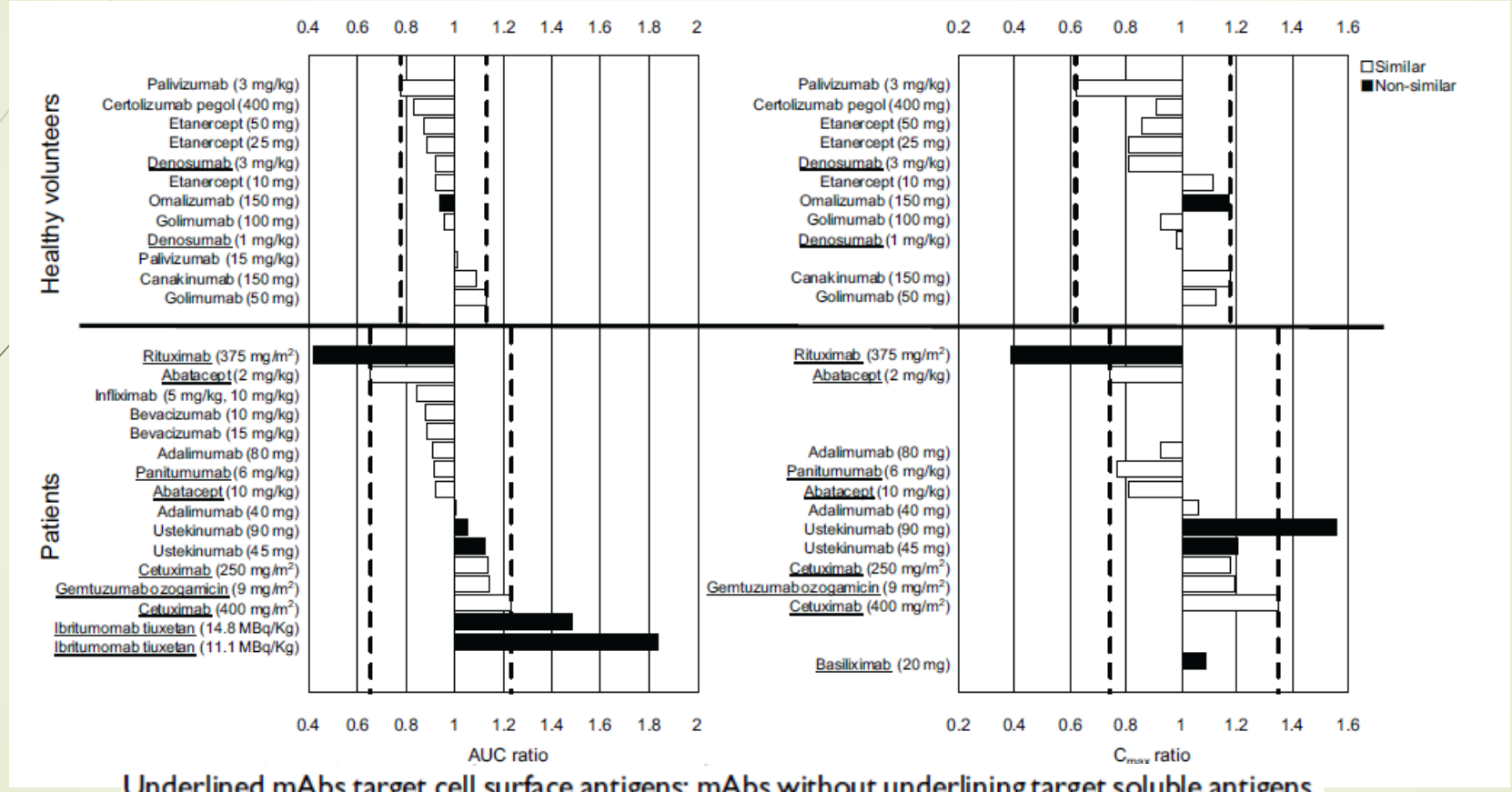


- The pharmacokinetics of ustekinumab were comparable between Chinese and non-Chinese healthy male subjects when exposure parameters were adjusted by subject body weight. [1]
  - No need to have dose adjustment
- Population PK analysis: most mAbs have BW or BSA as the covariate on CL (17 out of 18 mAbs) [2]
- Given the many practical advantages and potentially larger therapeutic window of most mAb, fixed dosing is recommended with mAbs, due to their smaller PK variability relative to PD, safety and efficacy [3,4]

[1] Zhu Y et al Clin Drug investigation 2013; [2] Dirks N et al Clin Pharmacokinetcet 2010 49 (10):633; [3] Bai S et al Clin Pharmacokinet. 2012 Feb 1;51(2):119-35; [4] Wang DD et al J Clin Pharmacol. 2009 Sep;49(9):1012-24

Lack of Ethnic Effect on mAb PK

Japanese v. Non-Japanese subjects



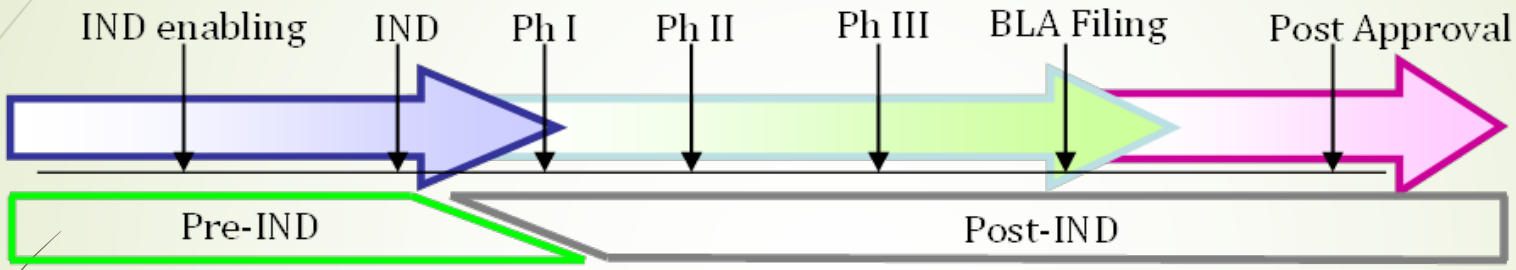
Underlined mAbs target cell surface antigens; mAbs without underlining target soluble antigens.

PK differences were observed for some mAbs

1. **Body weight and target expression level**
2. **No need for dose adjustment**

Chiba K, Yoshitsugu H, Kyosaka Y, Iida S, Yoneyama K, Tanigawa T, Fukushima T, Hiraoka M. A comprehensive review of the pharmacokinetics of approved therapeutic monoclonal antibodies in Japan: Are Japanese phase I studies still needed? J Clin Pharmacol. 2014 May;54(5):483-94. doi: 10.1002/jcph.231.

High Level PKPD/Toxicity Study for Large Molecules in Drug Development



Preclinical

- Mechanism of action
- In vitro and in vivo efficacy
- Safety pharmacology
- Toxicology / Toxicokinetics (acute/repeat dose in relevant species)
- Tissue cross-reactivity
- Local tolerance
- PK Support for molecule selection
- Assay Support for PK/PD
- PK/PD Support for Dose/Route/Regimen
- Assay development

Nonclinical

- General Toxicity / Toxicokinetics
- Reproductive Toxicity / Toxicokinetics
- Immunotoxicity

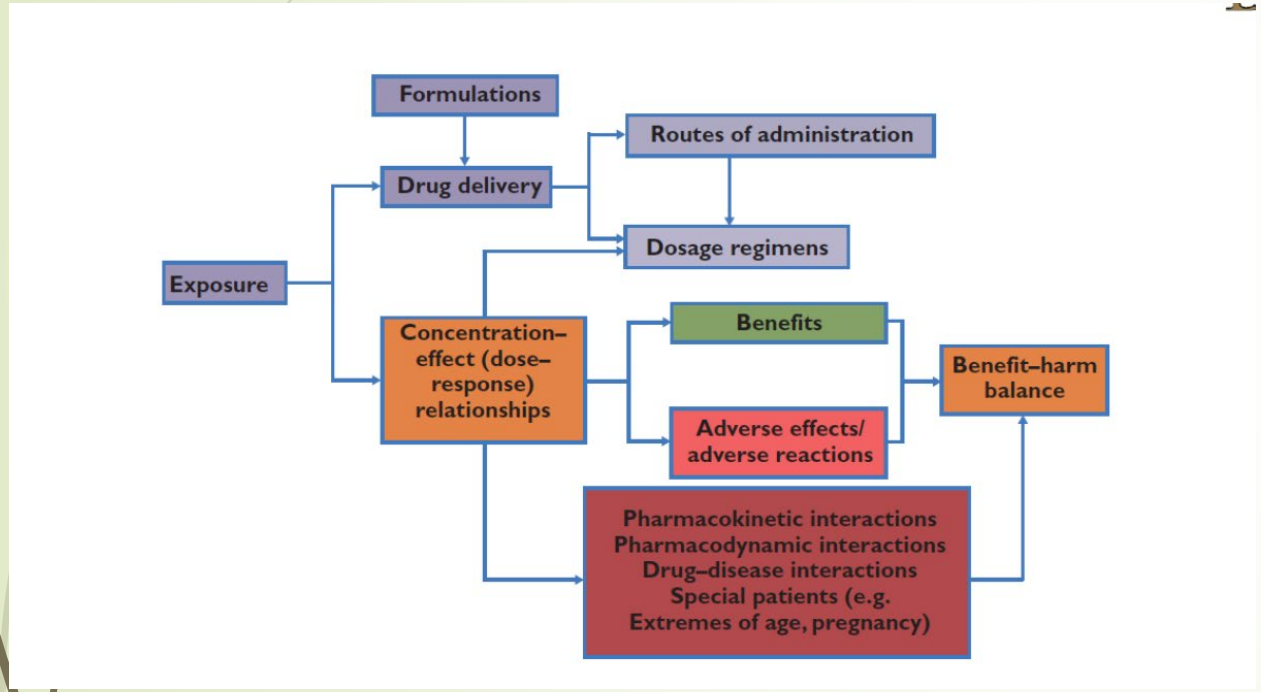
Clinical

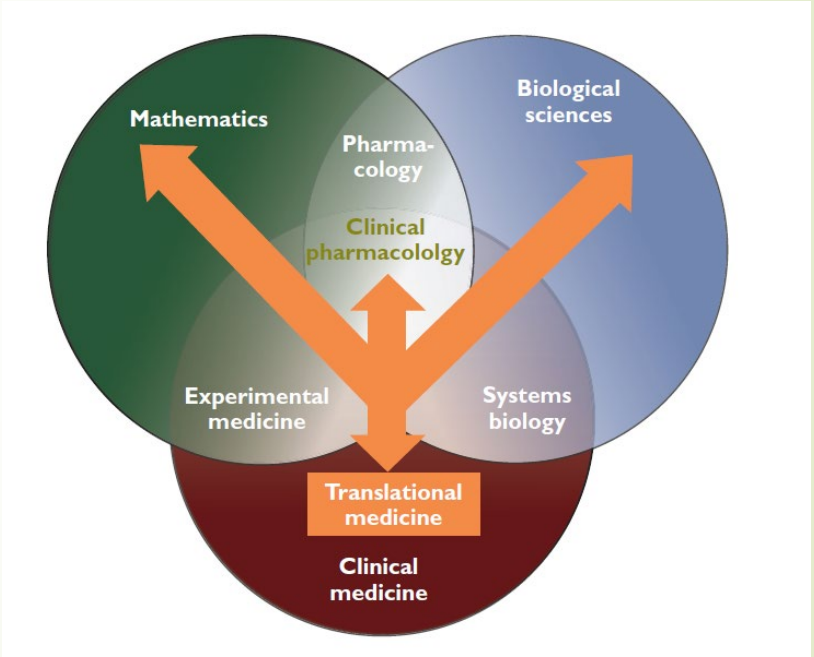
- Safety and efficacy
- Characterization of dose-concentration-effect relationship
- Material comparability studies
- Mechanistic Modeling approach
- Immunogenicity-anti-drug antibodies and neutralizing antibodies
- Mechanism of action
- Proof of concept
- Population Pharmacokinetics/Predictions

- Post-marketing commitments
- Drug-drug interaction studies
- Dose optimization
- Pharmacovigilance

Deng R et al . Chapter 15: Monoclonal antibodies: From structure to therapeutic application in Pharmaceutical Biotechnology Fundamentals and Applications, fifth edition, Edited by Crommelin DA, Sindelar RD and Meibohm B, Informa Healthcare, New York. March 2019

The Roles of Clinical Pharmacology in Drug Development





Understanding the relation between exposure to a drug and its clinical effects to enable right dose to right patient

Richards D. Developing and delivering clinical pharmacology in pharmaceutical companies. Br J Clin Pharmacol. 2012 Jun;73(6):870-3. doi: 10.1111/j.1365-2125.2012.04227.x

Conclusions

- Clinical pharmacology play a crucial role in drug development for both small molecules and large molecules with some differences
- Clinical pharmacology studies including modeling and simulation can contribute to
  - Translation from preclinical to clinical
    - Candidate comparison, selection, human PK and dose prediction
  - Better understanding of MOA
  - Dose and schedule selection and adjustment for label recommendations
    - DDI
    - Special population
    - Ethnicity
  - Study design optimization
  - Predicting and characterizing ADME
  - And more ……
    - Risk/benefit characterization, outcome predictions from early clinical response
    - Comparator/standard-of-care differentiation and commercialization strategy
    - Precision dosing in clinical care

Acknowledgements

Dr. Lin Xu

Dr. Zheming Gu

Ms. Jingliang Zhao

2020 Nanjing Internal DMPK Symposium Preparatory Committee

References (1)

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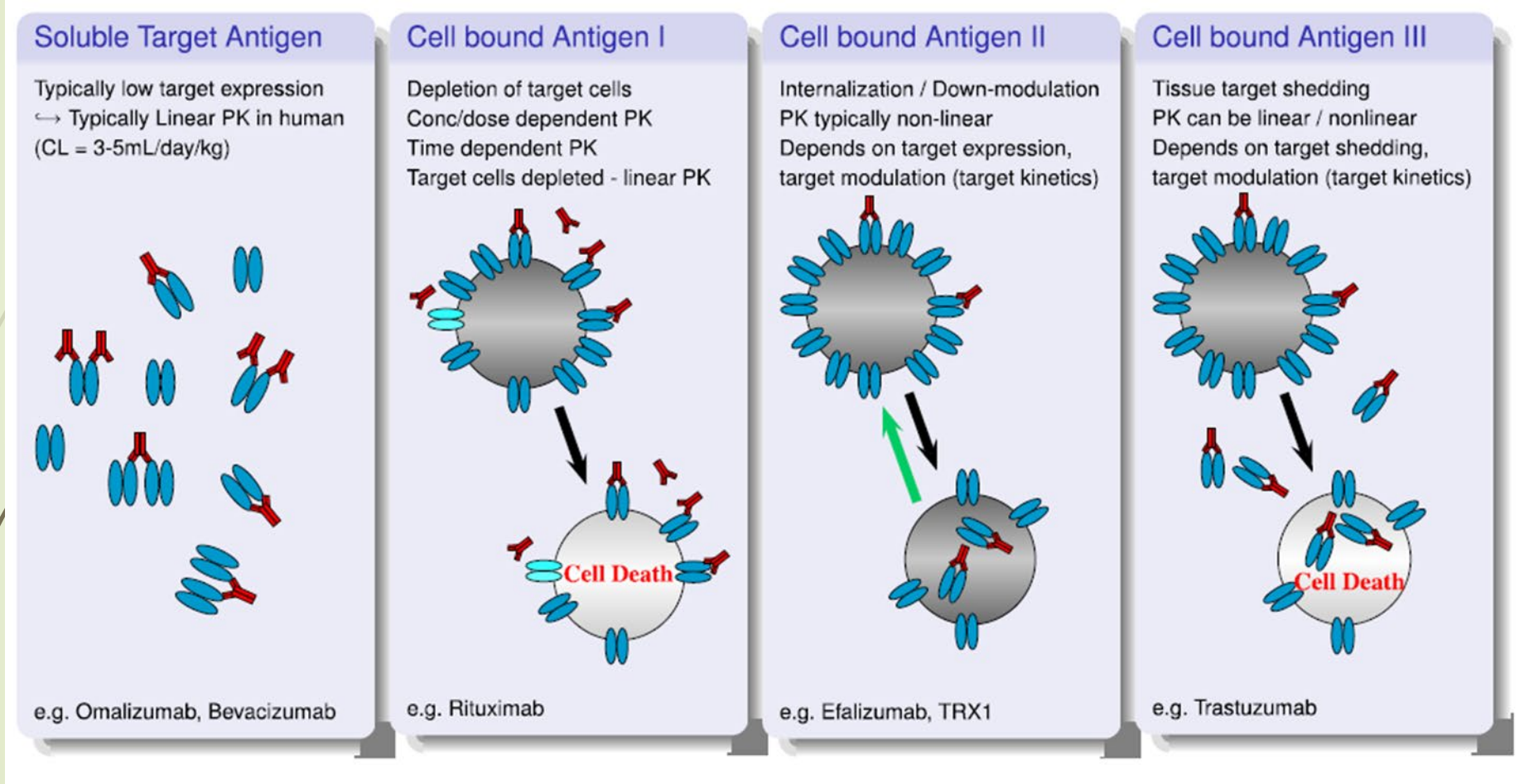
Backups

mAbs: Target Antigen Biology Drives PK/PD



PD measures can be direct or indirect depending on MOA of drug, target biology and location of targets

Deng R et al., Exp Opin Drug Metab Tox, 2012