Getting the Best Dose

The Clinical Pharmacology Studies That Help Achieve This Goal

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Pivotal Steps and Avoiding Pitfalls for Startups – March 30-31, 2021

This will probably be your first response from Clinical Pharmacology at FDA

FDA has the following recommendations regarding the overall clinical pharmacology development program for *(insert drug name)*:

1. Optimize the dosing regimen prior to initiating trials intended to demonstrate safety and efficacy in support of a marketing application. Pool clinical pharmacokinetic, pharmacodynamic, activity and safety data, as well as nonclinical pharmacology data, to conduct integrated dose-response and exposure-response analyses for dose optimization.

2. Assess the following items to facilitate rational dose selection for efficacy and safety trials and dose adjustment for specific populations:

a. Optimal systemic exposure of the parent drug and any major active metabolites in the general patient population

b. Effect of intrinsic factors (e.g. renal or hepatic impairment, disease, age, sex, body weight) and extrinsic factors (e.g., food, concomitant drugs) on the systemic exposure of the parent drug and any major active metabolites

c. Effect of the parent drug and major metabolites on the systemic exposure of concomitant drugs

d. Effect of concomitant gastric acid-reducing agents on the pharmacokinetics of the drug, if the drug is less soluble at pH 6.0–6.5 (with a solubility < clinical dose/250 mL) than at pH 1–2 (Include if orally administered drug)

1. Request an EOP1 meeting following completion of the dose finding trial(s) to discuss dose selection for future clinical trials based on available pharmacokinetic, pharmacodynamic, safety, and activity data and to discuss the proposed clinical pharmacology development plan. Conduct the following evaluations before the EOP1 meeting to support the proposed dosing regimen(s) for further clinical development:

a. Identify any major metabolites and the activities of such metabolites

b. Identify the means by which parent drug and any major metabolites are eliminated and excreted

c. Determine the ability of parent drug and any major metabolites to act as substrates, inhibitors or inducers of drug metabolizing enzymes and transporters

d. Validate bioanalytical assays for quantification of the parent drug and any major active metabolites

e. Characterize single-dose/multiple-dose pharmacokinetics, dose proportionality and time-dependence of pharmacokinetics

f. Conduct preliminary evaluation of food effect on drug absorption (Include if orally administered drug)

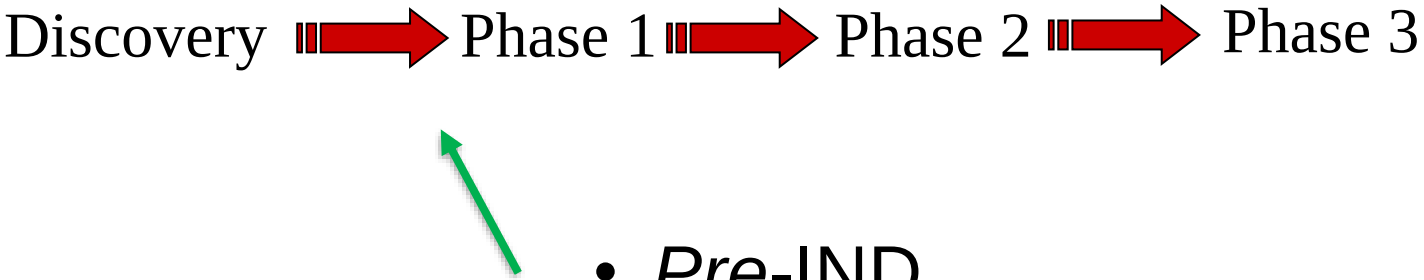
1. Collect pharmacokinetic samples in all patients enrolled in trials intended to demonstrate safety and efficacy to perform population pharmacokinetics and exploratory exposure-response analyses. Such trials generally have richer clinical outcomes data than other trials and therefore provide a greater opportunity for correlating drug exposure with clinical outcomes. Sparse pharmacokinetic sampling is often sufficient for this purpose.

2. Evaluate the potential for the drug to prolong the QT/QTc prolongation interval. Alternative proposals to 'thorough QT' study may be appropriate in oncology. Submit a QT/QTc evaluation plan to FDA QT-IRT team for review and comments.

Really, it’s not that bad
We are here to help you sort it out

Earliest Interactions with Clinical Pharmacology (CP) at FDA….

Drug Development Timeline



- *Pre*-IND
- IND-FIH
- Questions for FDA

Our Responses

- You will receive answers to your questions
- *And* some “standard comments”

CP-Standard Comments

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CP-Standard Comments...contd

1. Refer to the following FDA documents of "Guidance for Industry" for greater details regarding the above recommendations:

a. *Bioanalytical Method Validation*
b. *Exposure-Response Relationships – Study Design, Data Analysis, and Regulatory Applications*
c. *Population Pharmacokinetics*
d. *In Vitro Drug Interaction Studies – Cytochrome P450 Enzyme and Transporter- Mediated Drug-Drug Interactions*
e. *Clinical Drug Interaction Studies - Cytochrome P450 Enzyme and Transporter- Mediated Drug-Drug Interactions*
f. *Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*
g. *Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling*
h. *E14 Clinical Evaluation of QT/QTc*

If the study drug is for oral administration, add the following Guidances:

a. *Food-Effect Bioavailability and Fed Bioequivalence Studies*
b. *Assessing the Effects of Food on Drugs in INDs and NDAs – Clinical Pharmacology Considerations*
c. *Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs —General Considerations*

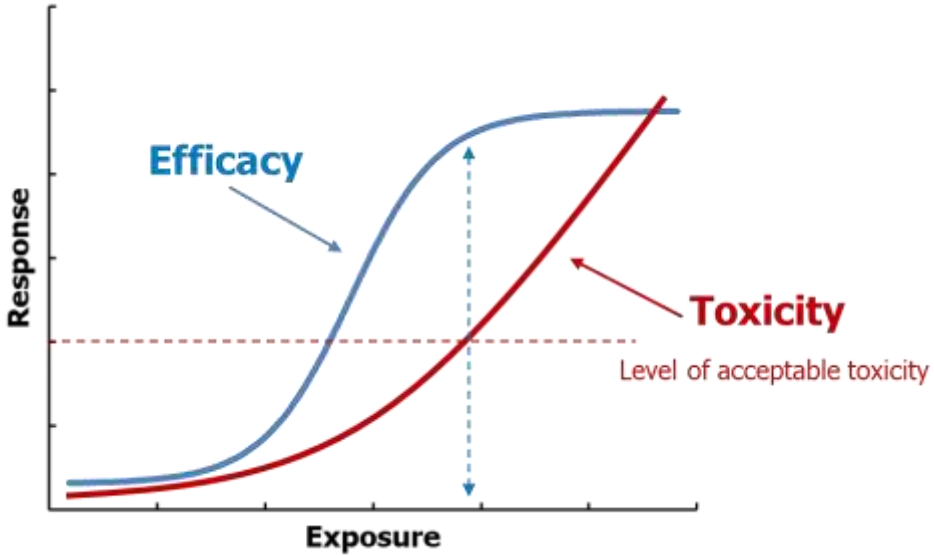
If the study drug is in a liposome formulation, add the following Guidance link:

- *Liposome Drug Products*

What Are We are Trying To Achieve?

1. Select the optimal dose for the patient population
   - *We need to do this early in development*
2. Adjust the dose for patients with specific considerations
   - DDI, renal/hepatic impairment

Selecting the Dose



- ”Safe and Effective”
- We are aiming for the optimal dose

Figure Courtesy of Dr. Lauren Price, DCP II/OCP/FDA

Selecting the Dose: The Need for Early Dose Optimization

e.g. BLENREP (Belantamab)

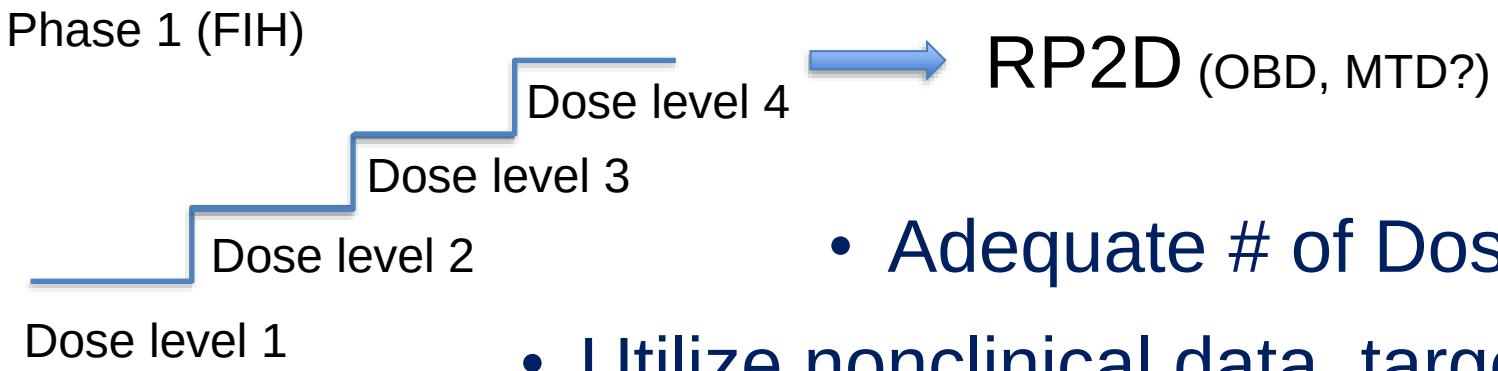
- Dose escalation 0.03 to 4.6 mg/kg
- Two Doses selected for Dose Expansion Trial!
  2.5 mg/kg and 3.4 mg/kg
- Ocular Toxicity---PMR safety and efficacy of lower dose (*1.92 mg/kg (n=4)*)

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/761158Orig1s000MultidisciplineR.pdf

Finding the Right Dose Later Can Be Quite Lengthy

Drug	Original dose	Revised Dose
Mylotarg	9 mg/m^2 d1,15 (2000)	3 mg/m^2 d1,4,7 (2017)
Marqibo	2 mg/m^2 (2005)	2.25 mg/m^2 (2012)
Jevtana	25 mg/m^2 (2010)	20 mg/m^2 (2017)

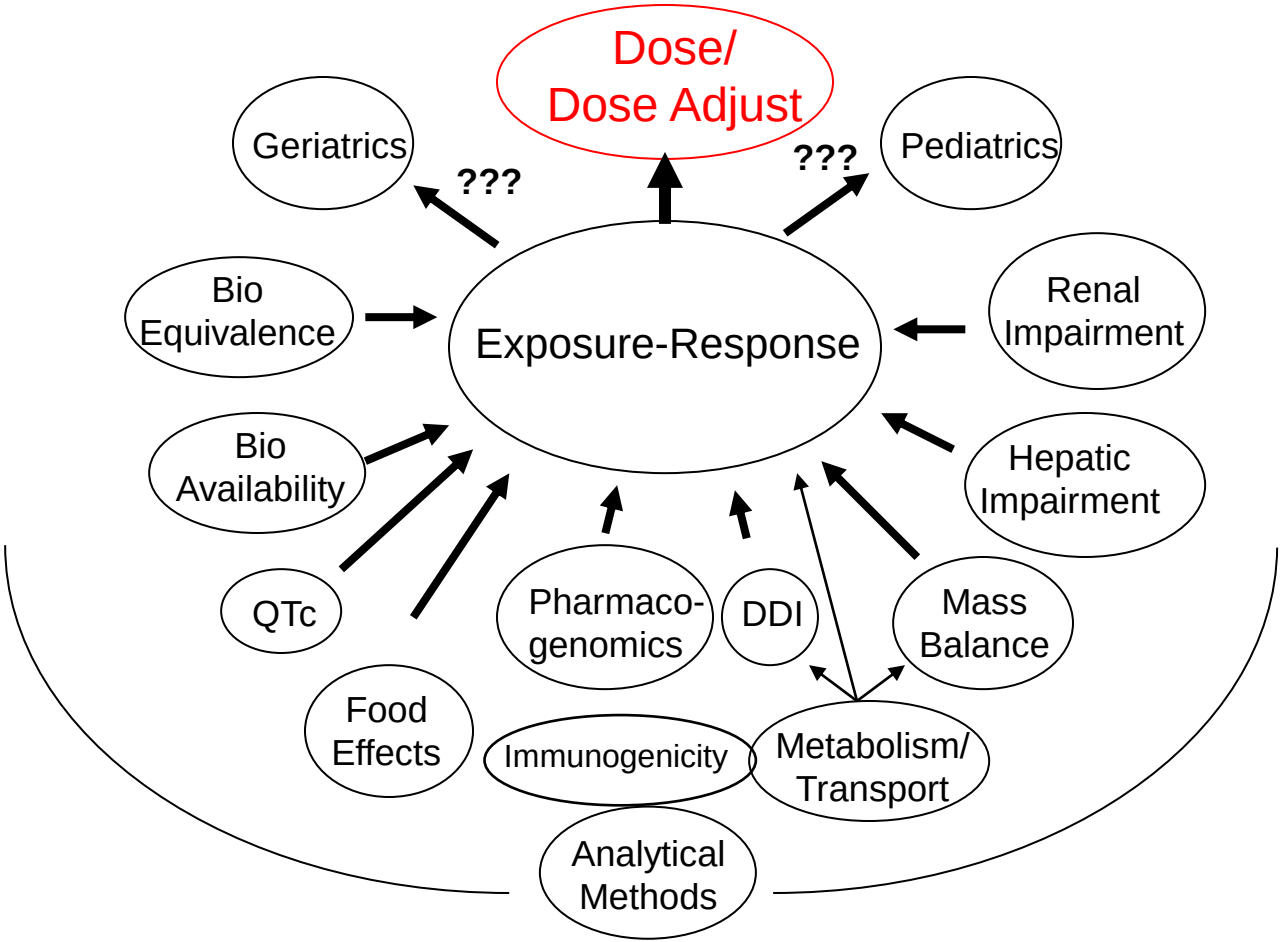
Selecting the Dose in Early Development



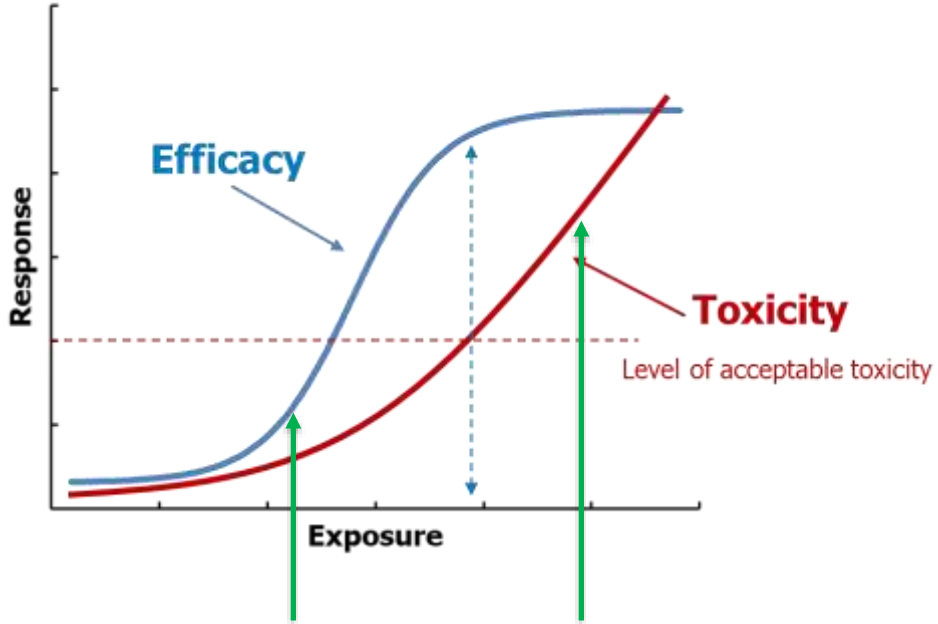
- Adequate # of Dose levels
- Utilize nonclinical data, target engagement
- Utilize clinical PK, PD, efficacy safety data
- Exposure –response analysis

Why do We Need All These CP Studies?

CP Issues Can Affect the E-R



Some or All CP Issues Can Affect Dosing



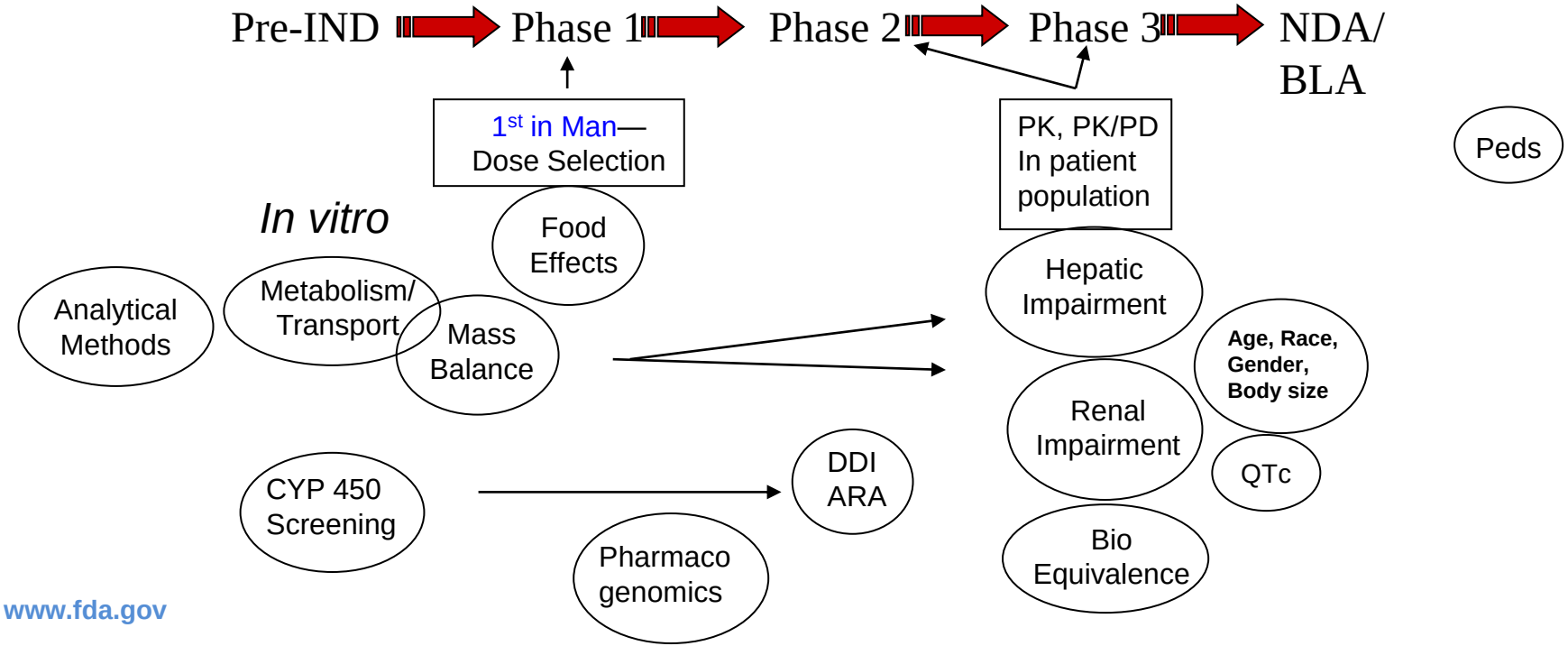
- Reduced efficacy
- Increased Toxicity

Which Studies Are Needed?

CP Study	Oral Drug	IV Drug	Biologic
Dose selection	✓	✓	✓
Assay	✓	✓	✓
Metabolism	✓	✓	✗
DDI (CYP450s & Transporters)	✓	✓	✗
ARA (PPIs)	✓	✗	✗
Food Effects	✓	✗	✗
QTc Prolongation	✓	✓	✗
Organ Dysfunction (RI, HI)	✓	✓	✗*
Age, Race, Gender, Body Size	✓	✓	✓
Immunogenicity/ADA	✗	✗	✓

When Do You Do These Studies?

One Possible Scenario



But Your Choices Have An Impact

Dosing and Administration (2014)

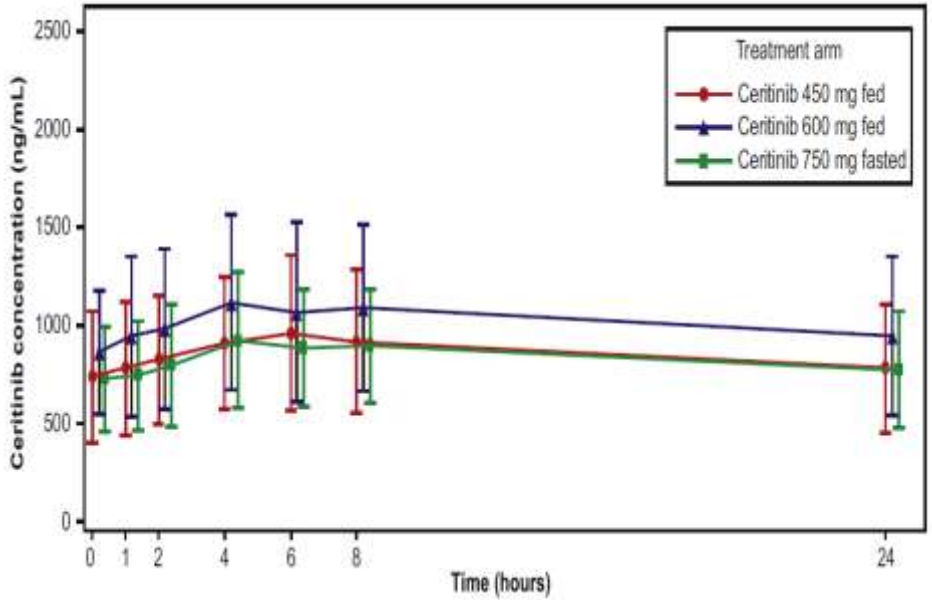
ZYKADIA is **750 mg** orally once daily ….on an empty stomach

	ZYKADIA N=255	
	All Grades	Grade 3–4
	%	%
Gastrointestinal disorders		
Diarrhea	86	6
Nausea	80	4
Vomiting	60	4
Abdominal pain[a]	54	2
Constipation	29	0
Esophageal disorder[b]	16	1

CP During Development

- FE: Increased AUC by 70-75%
- But can we capitalize on this?
- Post Marketing Study

Post Marketing Study



AE by Preferred Term, n (%)	Ceritinib, 450 mg, Fed (n = 44)		Ceritinib, 600 mg, Fed (n = 46)		Ceritinib, 750 mg, Fasted (n = 45)	
	All Grades, n (%)	Grade 3 or 4, n (%)	All Grades, n (%)	Grade 3 or 4, n (%)	All Grades, n (%)	Grade 3 or 4, n (%)
Diarrhea	21 (47.7)	0	28 (60.9)	0	29 (64.4)	0
Nausea	20 (45.5)	0	23 (50.0)	3 (6.5)	28 (62.2)	3 (6.7)
Vomiting	10 (22.7)	0	19 (41.3)	0	19 (42.2)	3 (6.7)
Abdominal pain	10 (22.7)	0	15 (32.6)	0	14 (31.1)	0

Cho BC, Kim DW, Bearz A, et al 2017 J Thoracic Oncol 12;1357-67

We Changed the Label

Recommended Dosage (2017)

… ZYKADIA is **450 mg** orally once daily **with food** until disease progression or unacceptable toxicity

- Would it have been better to do this upfront?

CP Studies in Early Development

How are you going to dose patients?

- Food Effect Studies
- ARA Studies
- DDI/Co-medications—

What About Rare Diseases?

Diseases with few patients?

- We still want to leverage the clinical pharmacology
- Use different approaches
  - Model-Informed Approaches (MIDD)
  - Conduct studies in alternative ways/populations

MIDD

e.g. IBRUVICA (ibrutinib)

- Strong CYP 3A4 inhibitors-24 fold increase in AUC
- Moderate Inhibitors? PBPK modelling & simulation
- Emerging applications of PBPK: FE, RI, HI
- E-R Modelling & Simulation: Dose optimization, trial design

Alternative Approaches

e.g. PEMAZYRE (pemigatinib)

- Renal Impairment Study?
- Broadened eligibility criteria: mild and moderate RI
- Assessed impact of RI on PK in efficacy study with population PK

Alternative Populations

e.g. VENCLEXTA (Venetoclax)

- Healthy Volunteers: Bioavailability/Food Effect Study, DDI study (inducer)
- Different Cancer Patient Populations

Can We Do These Studies as PMRs?

- FDA cannot agree to that request—
- But often DDI, severe RI/HI assessed post approval
- Patients who have these co-morbidities
  - dose adjustments

Take Away Messages

1. Dose selection is the primary goal.

2. Clinical pharmacology studies aim to support dose selection/adjustment

3. Multiple/alternative approaches to assessing CP

Closing Thought

Early interaction with FDA will aid you in your drug development program!

U.S. FOOD & DRUG ADMINISTRATION

Questions?

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Some Thank Yous

Dr. Jeff Summers
Dr. Atik Rahman
Dr. Lanre Okusanya
Dr. Stacy Shord
Dr. Lauren Price
Dr. George Shen


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