Model-Based Approaches to DDI Risk Prediction: Navigating the Transition from In Vitro Data to In Silico Modeling

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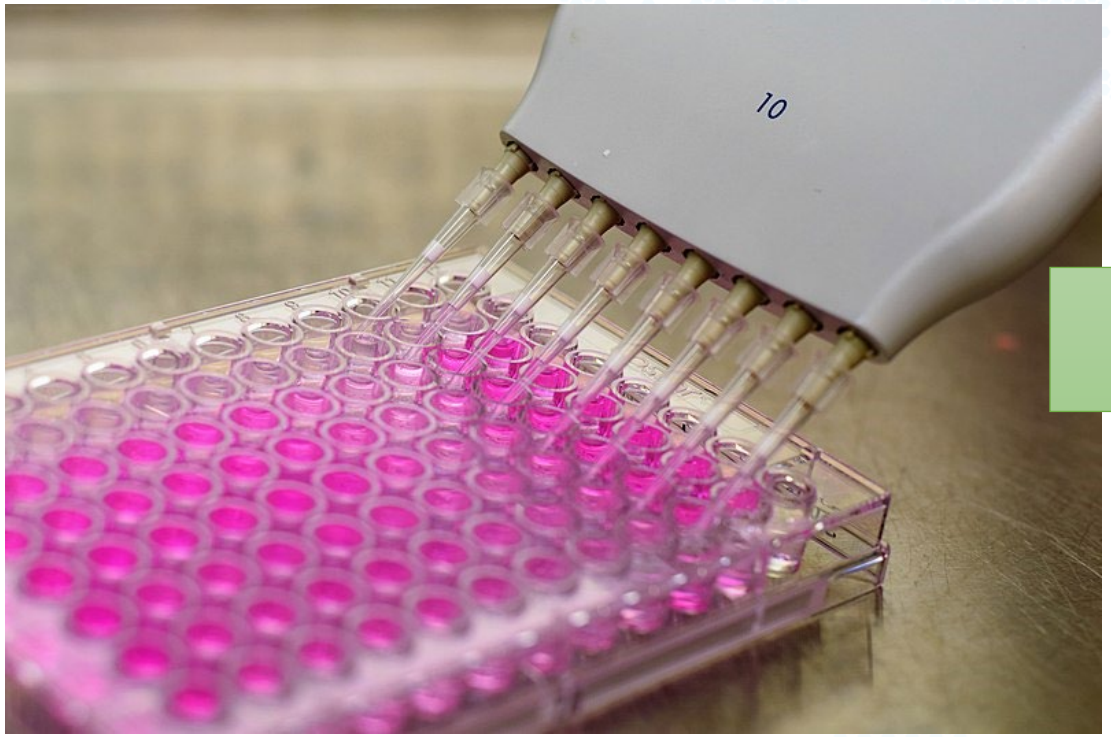
In Vitro to In Vivo Extrapolation



IVIVE

Not a stand alone study

A follow up analysis to routine in vitro ADME-DDI studies

FDA Guidance Verbiage - Background

"The evaluation of DDI potential often starts with in vitro experiments to identify potential factors influencing drug disposition to elucidate potential DDI mechanisms and to yield kinetic parameters for use in further studies. Results of in vitro experiments, along with clinical pharmacokinetic (PK) data, provide mechanistic information that can inform the need for and proper design of potential future clinical studies."

-- FDA 2020, ""Drug-Drug Interaction Assessment for Therapeutic Proteins Guidance for Industry"

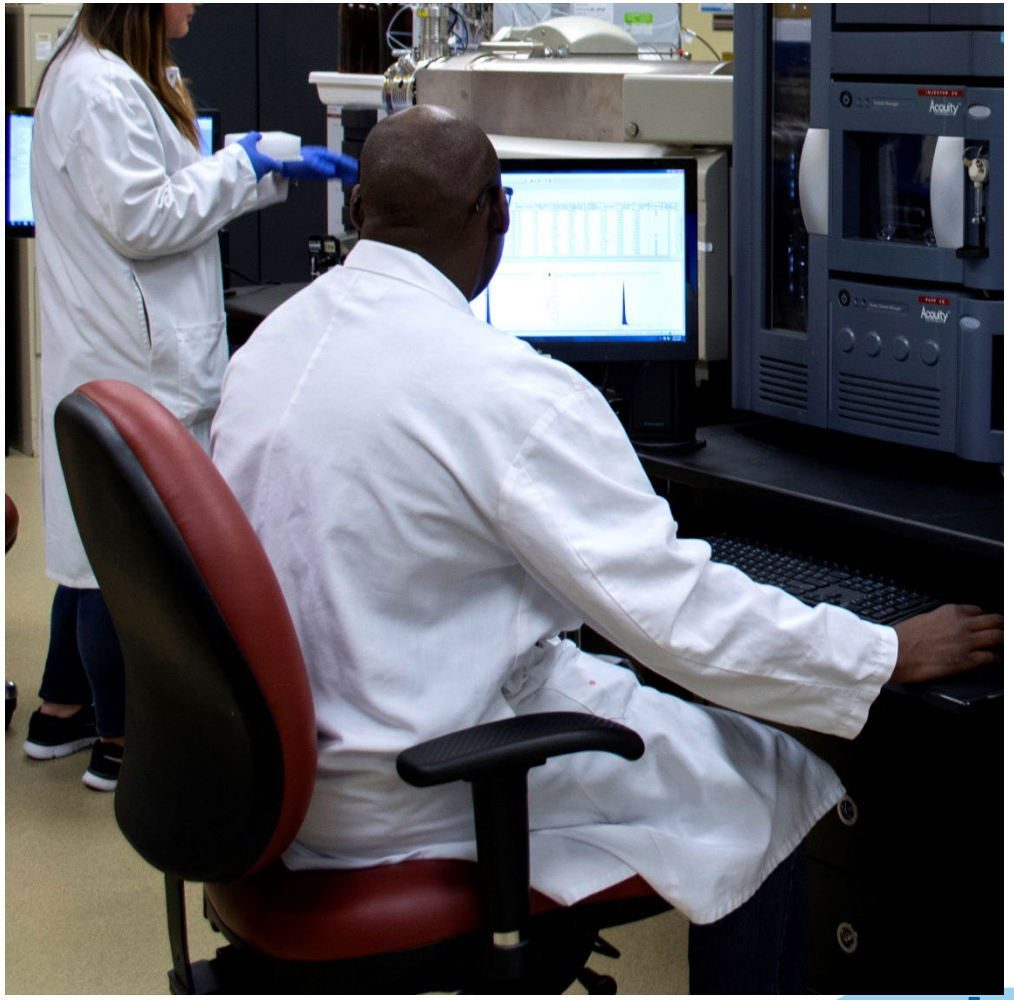
ADME & DDI study types for in vitro to in vivo prediction

Models focus on DDI via perpetrator potential of a drug

ADME component	Type of in vitro study to determine perpetrator potential
CYP450 Enzymes	1. CYP Inhibition – Identification of specific CYP enzymes inhibited by the drug 2. CYP induction – Induction potential for specific CYPs
Drug Transporters	1. Transporter inhibition – Profile specific inhibition of major Transporters

Models for DDI Prediction

- Basic static models
- Mechanistic static models
- Dynamic mechanistic models (PBPK)



What we can provide:

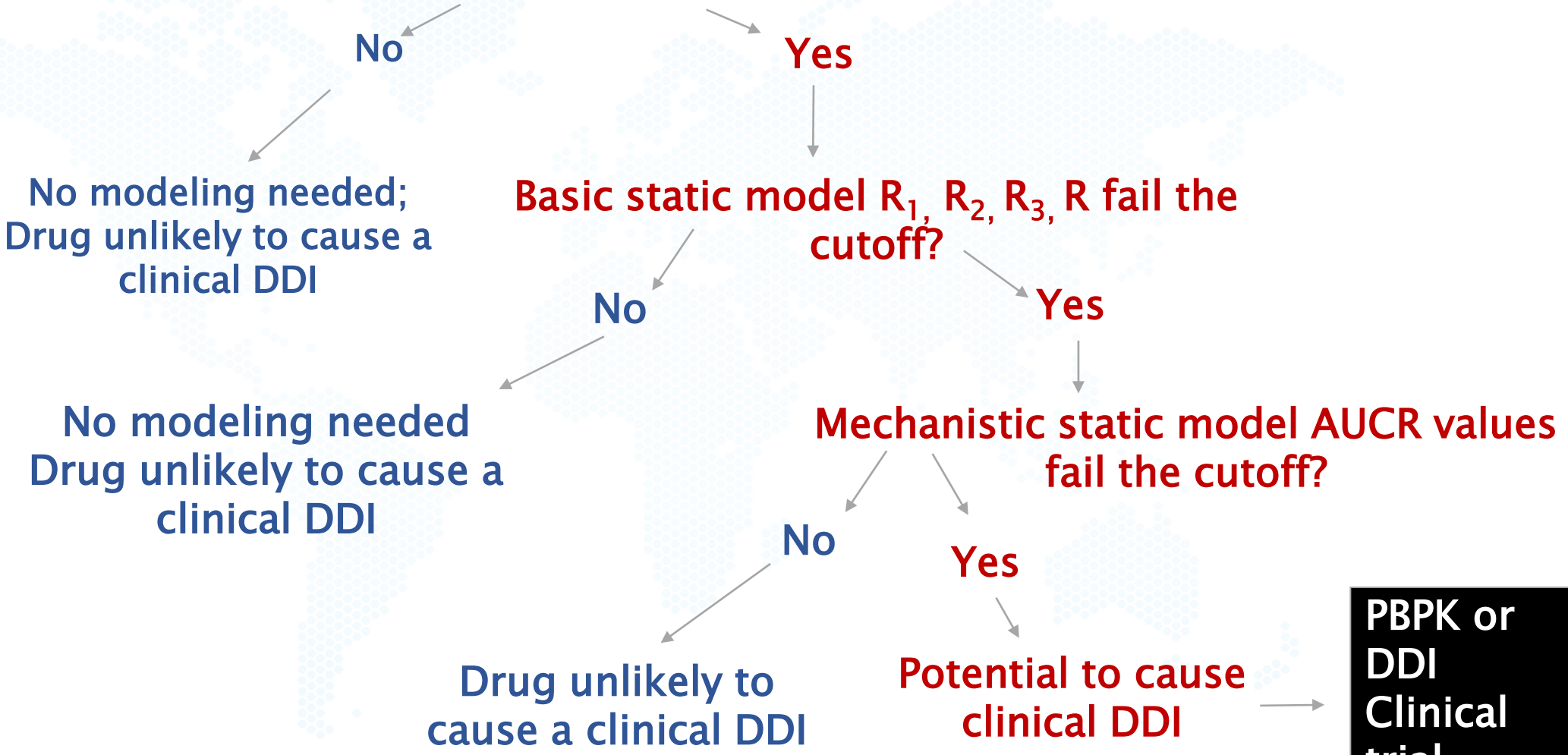
- Basic static models
- Mechanistic static models
- Dynamic mechanistic models (PBPK)

Predictive Models Based on Study Types

Study	Basic Static			Static Mechanistic
CYP inhibition	Hepatic:		Intestinal	AUCR
	Direct	TDI	Direct	
	R_1	R_2	$R_{1\ gut}$	
CYP induction	R_3, Relative Induction Score (RIS)			
Transporter inhibition	R			-

In vitro CYP Inhibition/Induction or Transporter Inhibition?

Decision Tree



Basic Static Models: CYP Inhibition and Induction

Type of Data	Equation	Cut Off Values
Hepatic CYP reversible inhibition	$R_1 = 1 + (I_{max,u} / K_{i,u})$	Potential to inhibit if $R1 \geq 1.02$
Intestinal CYP inhibition	$R_{1,gut} = 1 + (I_{gut} / K_i)$	Potential to inhibit if $R_{1,gut} \geq 11$
Hepatic CYP irreversible/TDI	$R_2 = (K_{obs} + k_{deg}) / k_{deg}$	Potential to inhibit if $R_2 \geq 1.25$
CYP induction	$R_3 = 1/[1 + d \times ((E_{max} \times 10 \times I_{max,u})/(EC_{50} + 10 \times I_{max,u}))]$ RIS = 1. $E_{max} \times I_{max,u} / EC_{50} + I_{max,u}$ 2. $I_{max,u} / EC_{50}$ values	Potential to induce if $R_3 \leq 0.8$ Potential to induce based on AUC decrease of victim drug depending on RIS

Basic Models: Transporter Inhibition

Transporter	Ratio	Potential to inhibit if
P-gp	I_{gut} / IC_{50}	Ratio ≥ 10
BCRP	I_{gut} / IC_{50}	Ratio ≥ 10
OATP1B1	$1 + (I_{in,max,u})$ / IC_{50}	Ratio ≥ 1.1
OATP1B3	$1 + (I_{in,max,u})$ / IC_{50}	Ratio ≥ 1.1
OAT1	$I_{max,u}$ / IC_{50}	Ratio ≥ 0.1
OAT3	$I_{max,u}$ / IC_{50}	Ratio ≥ 0.1
OCT2	$I_{max,u}$ / IC_{50}	Ratio ≥ 0.1
MATE1	$I_{max,u}$ / IC_{50}	Ratio ≥ 0.1
MATE2-K	$I_{max,u}$ / IC_{50}	Ratio ≥ 0.1

Predictive Models Based on Study Types

<table>
<tr><th>Study</th><th colspan="3">Basic Static</th><th>Static Mechanistic</th></tr>
<tr><td rowspan="3">CYP inhibition</td><td colspan="2">Hepatic:</td><td>Intestinal</td><td rowspan="4">AUCR</td></tr>
<tr><td>Direct</td><td>TDI</td><td>Direct</td></tr>
<tr><td>R_1</td><td>R_2</td><td>$R_{1\ gut}$</td></tr>
<tr><td>CYP induction</td><td colspan="3">R_3, Relative Induction Score (RIS)</td></tr>
<tr><td>Transporter inhibition</td><td colspan="3">R</td><td>-</td></tr>
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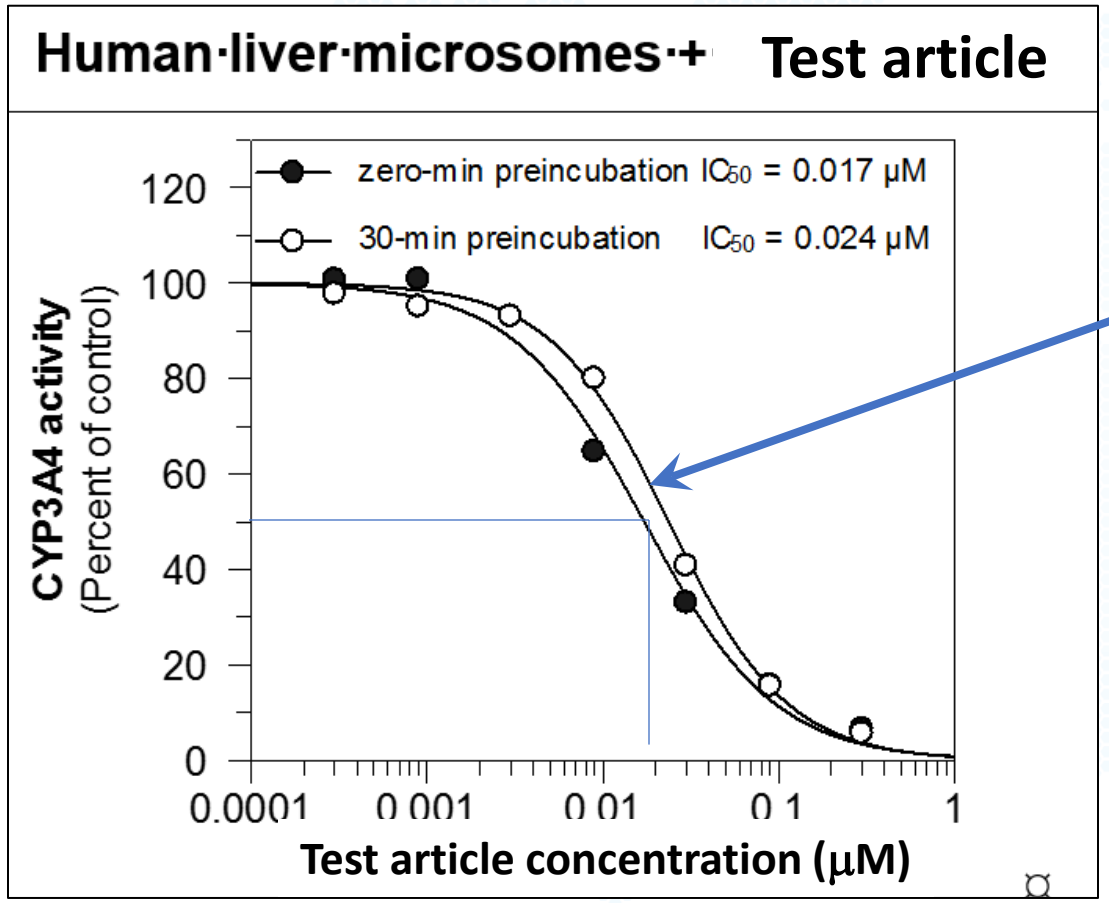
CYP Direct Inhibition – In Vitro Data



Superimposable curves indication direct or reversible inhibition

Kinetic Constants

IC_{50} (µM)	0.017
Ki (µM) = $IC_{50}/2$	0.0085

Study shows that the drug is a CYP3A4 direct inhibitor

Follow up Prediction Model: R_1 Value Determination

Hepatic CYP Direct inhibition

$$R_1 = 1 + (I_{max,u} / K_{i,u})$$

Potential to inhibit if $R_1 \geq 1.02$

Parameters required

- $I_{max,u}$ – Provided by sponsor ($I_{max,u}$ is unbound C_{max})
- $K_{i,u}$ – In vitro inhibition study data

R_1 Calculation for Hepatic Reversible Inhibition

Where $I_{max,u} = 0.025\ \mu M$

$K_{i,u} = 0.0084\ \mu M$

$$R_1 = 1 + (I_{max,u} / K_{i,u})$$

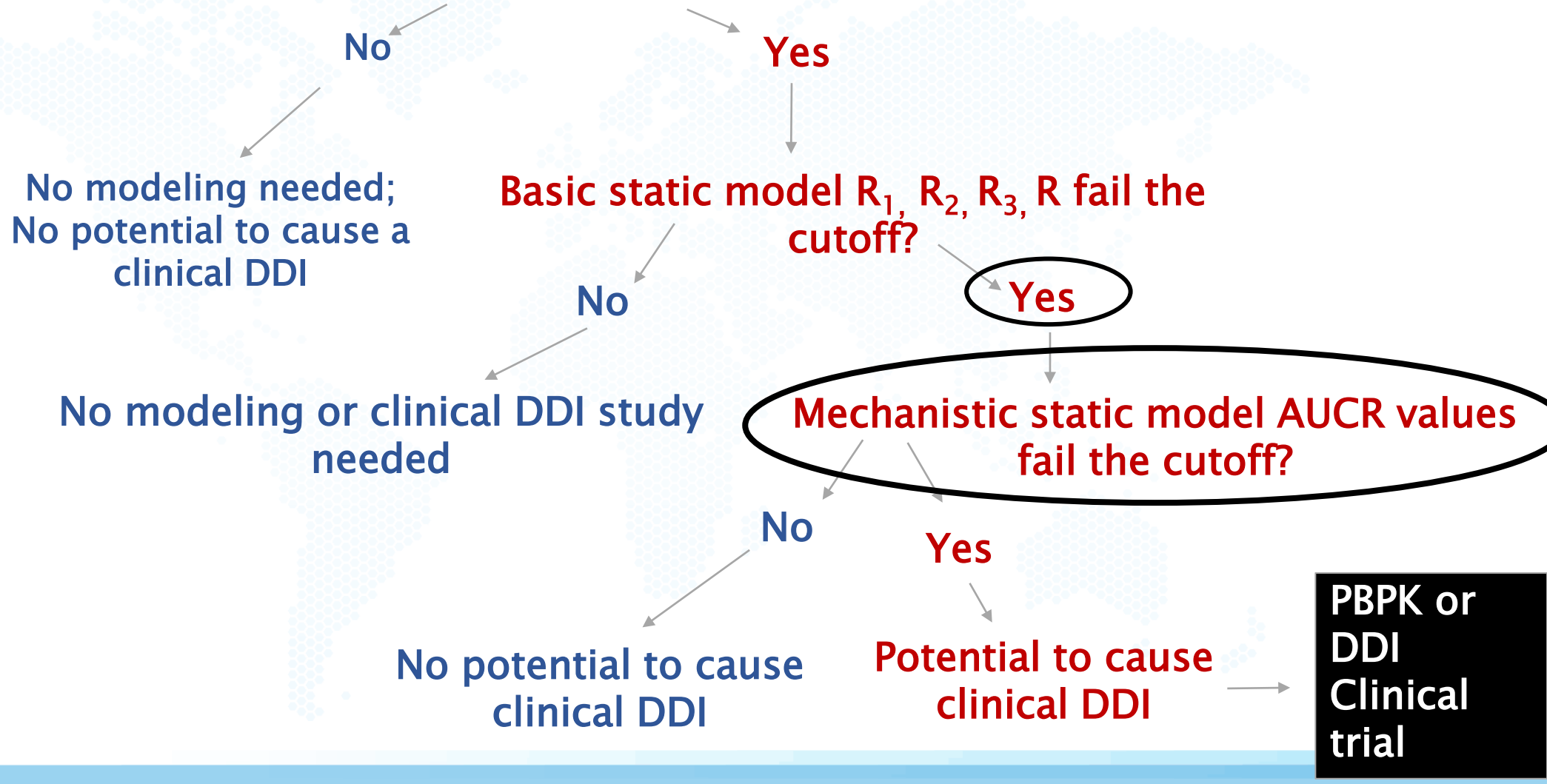
$$R_1 = 1 + (0.025 / 0.0084)$$

$$R_1 = 3.98$$

Potential to inhibit clinically if $R_1 \geq 1.02$

In vitro CYP Inhibition/Induction or Transporter Inhibition?

Decision Tree



Parameters Needed for Static Mechanistic Model

- Dose (μM)
- Maximal unbound total systemic ($I_{max,u}$)
- Fraction of metabolism of a victim drug (f_m)
- Hepatic blood flow (Q_h)
- Blood flow through enterocytes (Q_{en})
- Fraction of absorption (F_a)
- Intestinal availability (F_g)
- Hepatic inlet ($I_{in,max}$) and enterocytic (I_g) drug concentrations
- Extent of binding to plasma proteins ($f_{u,p}$)
- Blood–to–plasma concentration ratio (R_b)

Static Mechanistic Model

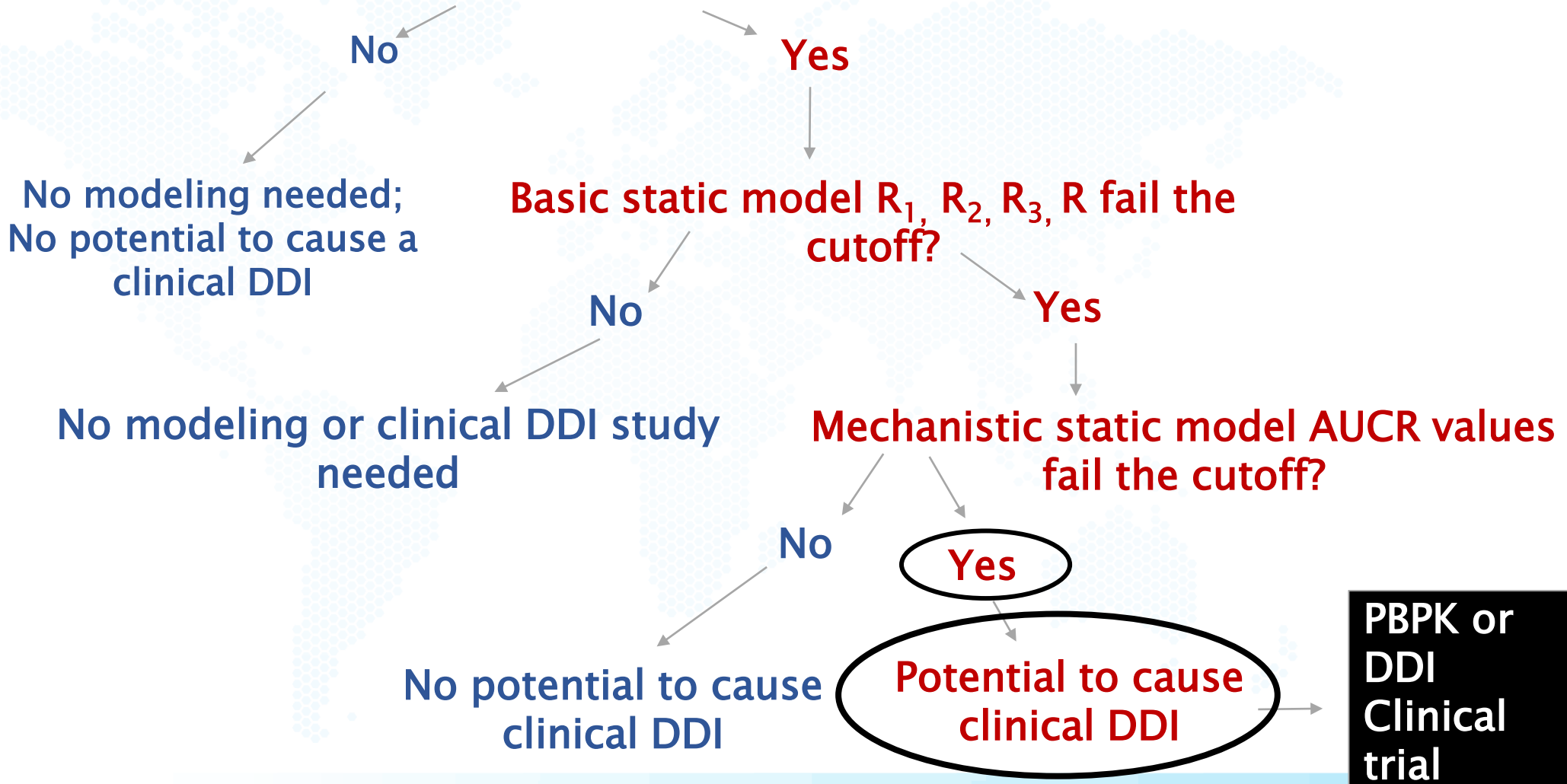
When the same CYP enzyme is inhibited and induced by the drug, a net effect is calculated.

$$AUCR = [\ 1 / ((A_g \times B_{g\,x}\, C_g) \times (1 - F_g) + F_g)\ ] \times [\ 1 / ((A_h \times B_{h\,x}\, C_h) \times f_m + (1 - f_m)\ ]$$

Potential to cause induction if AUCR ≤ 0.8
Potential to cause inhibition if AUCR ≥ 1.25

In vitro CYP Inhibition/Induction or Transporter Inhibition?

Decision Tree



Previous Consulting Project Example- Overall Modeling Strategy

Enzyme	Substrate (CYP inhibition)	R1 Value (Hepatic direct inhibition)	In vitro hepatocyte culture ID (CYP induction)	R3 Value (CYP induction)	MSM: AUCR Value
CYP2B6	Efavirenz	**2.51**	HC10-1	**0.726**	1.002
			HC5-30	**0.756**	1.002
			HC7-4	**0.637**	1.002
		≥1.02		≤0.8	≤0.8 ≥1.25

Conclusions:

- Based on the FDA guidance, CYP2B6 was not predicted to be affected by the drug to a clinically significant extent.
- C_{max} plasma concentrations would need to be >115-times greater than the observed C_{max} in patients before AUCR values will fall between the cutoff.

Summary

- Model-based approach to be offered as the follow up to the routine perpetrator potential studies i.e. CYP inhibition, CYP induction, and transporter inhibition
- Great value to the sponsors in assessing the clinical potential that may eliminate the need of conducting clinical studies
- Step-wise approach brings robustness to the prediction

Thank you for watching!

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