

# COCKTAIL DRUG-DRUG INTERACTION STUDIES

Drug-drug interaction (DDI) studies using validated **cocktail combinations of substrate drugs** enable simultaneous evaluation of a study drug's effects on multiple CYP450 enzymes and transporters.

## DESIGN EFFICIENCIES

- Limits number of clinical DDI studies
- Helps reduce timelines of clinical conduct
- Reduction in overall costs for DDI studies
- Fewer subjects exposed
- Potential for decrease in blood sample collection
- Convenience of established cocktails available



## VALIDATED COCKTAILS

A validated cocktail is a combination of substrate drugs that were shown not to interact from a pharmacokinetic (PK), pharmacodynamic (PD), and safety perspective, at doses that can be extrapolated to clinical dose levels.

**Table 1. Examples of Validated Cocktails**

	CYP / Transporter	Cooperstown 5+1 <sup>1</sup>	Geneva <sup>2</sup>	Basel <sup>3</sup>	Bristol-Myers Squibb <sup>4</sup>	Washington <sup>5</sup>	Oita <sup>6</sup>	Cologne <sup>7</sup>	Boehringer <sup>8</sup>	Gilead <sup>9</sup>
CYPs	CYP1A2	Caffeine 200 mg	Caffeine 50 mg	Caffeine 10 mg	Caffeine 200 mg					
	CYP2B6		Bupropion 25 mg	Efavirenz 50 mg						
	CYP2C8		Repaglinide 0.05 mg		Montelukast 10 mg					
	CYP2C9	S-Warfarin 100 mg + Vit K	Flurbiprofen 25 mg	Flurbiprofen 12.5 mg	Flurbiprofen 50 mg					
	CYP2C19	Omeprazole 40 mg	Omeprazole 10 mg	Omeprazole 10 mg	Omeprazole 40 mg					
	CYP2D6	Dextromethorphan 30 mg	Dextromethorphan 10 mg	Metoprolol 10 mg	Metoprolol 100 mg					
	CYP3A4	Midazolam (IV) 0.025 mg/kg	Midazolam 1 mg	Midazolam 2 mg	Midazolam 5 mg	Midazolam 5 mg				
Transporters	P-gp				Digoxin 0.25 mg	Digoxin** 0.25 mg	Digoxin 0.25 mg	Digoxin 0.5 mg	Digoxin 0.25 mg	Dabigatran Etexilate 75 mg
	BCRP						Rosuvastatin 5 mg		Rosuvastatin 10 mg	Rosuvastatin 10 mg
	OATP1B1/3				Pravastatin 40 mg			Pitavastatin 2 mg		Pravastatin 40 mg
	OAT1							Adefovir dipivoxil 10 mg		
	OAT3							Sitagliptin 100 mg	Furosemide 1 mg	
	OCT2/ MATE1/2-K							Metformin 500 mg	Metformin 10 mg	

\* Exploratory cocktails used in clinical trials, though not fully validated; \*\*Staggered by 1 hour

Although this is not a complete list of drug cocktails, we can discuss alternative designs and options if a certain CYP or transporter of interest is not in the above.

## BIOANALYTICAL CONSIDERATIONS

Celerion offers a wide range of validated, bioanalytical drug assays for DDI studies developed with the smallest sample collection volume in mind and low levels of detection.

**Table 2. Validated Bioanalytical Assays for Commonly Used Substrates**

CYP Substrates		Transporter Substrates
Bupropion & hydroxybupropion (CYP2B6)	Midazolam & hydroxymidazolam (CYP3A)	Atrovastatin & metabolites (OATP1B1; OATP1B3)
Caffeine & paraxantine (CYP1A)	Montelukast (CYP2C8)	Digoxin [plasma & urine] (P-gp)
Celecoxib (CYP2C9)	Omeprazole & 5-OH omeprazole (CYP2C19)	Dabigatran [free & total] (intestinal P-gp)
Dextromethorphan & dextrorphan (CYP2D6)	Repaglinide (CYP2C8)	Metformin [plasma & urine] (MATE-1, MATE-2K, OCT2)
Flurbiprofen & 4'-hydroxyflurbiprofen (CYP2C9)	Rosiglitazone (CYP2C8)	Pitavastatin & pitavastatin lactone (OATP1B1; OATP1B3)
Losartan & losartan acid metabolite (CYP2C8)	R-warfarin, S-warfarin (CYP2C9)	Pramipexole (OCT2)
Metoprolol (CYP2D6)	Tolbutamide & 4-OH-tolbutamide (CYP2C9)	Rosuvastatin (BCRP; OATP1B1; OATP1B3)
		Simvastatin & simvastatin hydroxy acid (OATP1B1; OATP1B3)

## CELERION DIFFERENTIATORS

- ✓ Extensive DDI experience: completed over 400 DDI trials since 2010
- ✓ Large bed-capacity at all our Clinical Units enables to accommodate large cohorts (up to ~50 participants)
- ✓ Our expert team of Protocol Writers can propose which validated cocktails would be best suited for your next DDI study
- ✓ Comprehensive list of validated bioanalytical drug assays for commonly used substrates

View our full list of [validated assays](#)

### References:

1. Chainuvati et al. (2003) CPT
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4. Tye et al. (2016) Int J Pharm
5. Kirby et al. (2006) JCP
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8. Wiebe et al. (2020) Clin PK
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