

Evolution of Qualification DDI Matrix

April 9, 2025

Key dates

- **March 15, 2023: Briefing document with original qualification matrix**
- Feedback/Discussed in June, 2023

- **December 21, 2023: Updated qualification matrix**
- Discussed on March 6, 2024: SAWP meeting
- Discussed on July 10, 2024: SAWP meeting (2nd list of issues)

- **December 16, 2024: Updated qualification matrix**
- Discussed on January 15, 2025: SAWP meeting

March 15, 2023: Briefing document with original qualification matrix

Enzyme	Competitive Inhibition	MBI	ALL
CYP1A2	20	0	20
CYP2C8	3	13	16
CYP2C9	17	4	21
CYP2C19	6	5	11
CYP2D6	17	9	26
CYP3A4/5	59	52	111
	122	83	205

December 21, 2023: Updated qualification matrix

Enzyme	Competitive Inhibition	MBI	ALL
CYP1A2	42	0	42
CYP2C8	7	10	17
CYP2C9	25	3	28
CYP2C19	15	13	28
CYP2D6	32	14	46
CYP3A4/5	66	28	94
	187	68	255

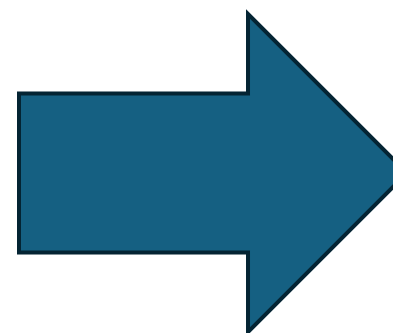
December 16, 2024, Updated qualification matrix

Enzyme	Competitive Inhibition	MBI	ALL
CYP1A2	42	0	42
CYP2C8	7	10	17
CYP2C9	19	3	22
CYP2C19	15	13	28
CYP2D6	34	10	44
CYP3A4/5	64	29	93
	181	65	246

December 16, 2024, Updated qualification matrix & derivation of Database

FINAL DDI QUALIFICATION MATRIX – DECEMBER 16, 2024

Enzyme	Competitive Inhibition	MBI	ALL
CYP1A2	42	0	42
CYP2C8	7	10	17
CYP2C9	19	3	22
CYP2C19	15	13	28
CYP2D6	34	10	44
CYP3A4/5	64	29	93
	181	65	246



DATABASE

Enzyme	Models A and B
CYP1A2	39
CYP2C8	17
CYP2C9	19
CYP2C19	23
CYP2D6	40
CYP3A4	82
	220

After preprocessing of the DDI data (n=246), 220 studies remained for which both GMR and the geometric SD of individual ratios were available in clinical studies.

Evolution of Substrate & Inhibitor Files in Qualification DDI Matrix

April 9, 2025

2023 06

Certara Drug Interaction Solution database
(UoW-DIDB)
Search for DDIs with : CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A



Substrates (34*)	3	2	5	3	6	16
Inhibitors (CI) (12**)	2	1	3	1	5	5 (+1)
Inhibitors (MBI) (12***)	0	1	1 (+1)	1 (+1)	1	9 (+3)

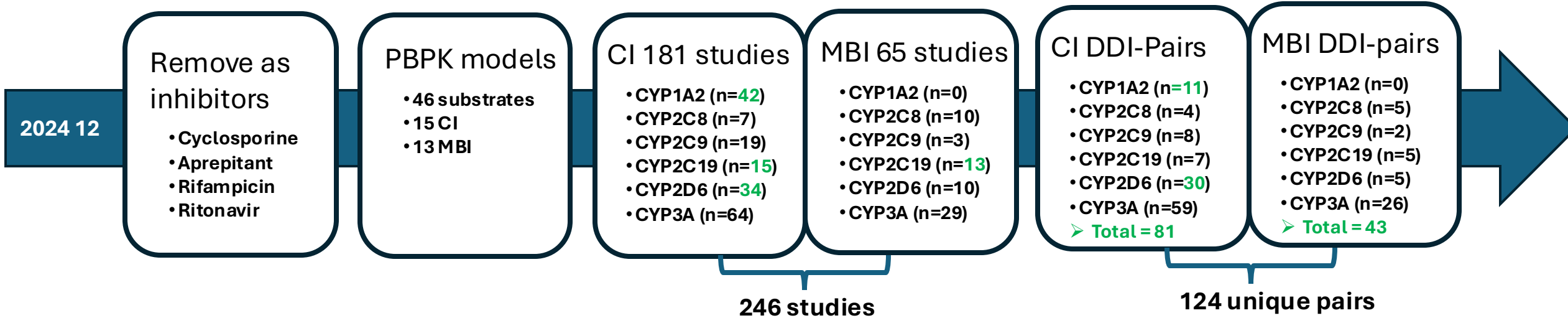
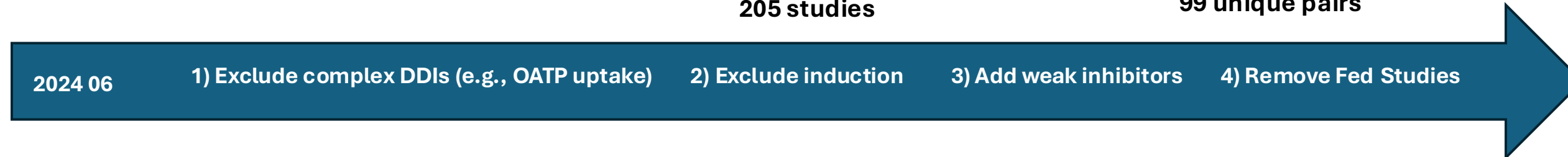
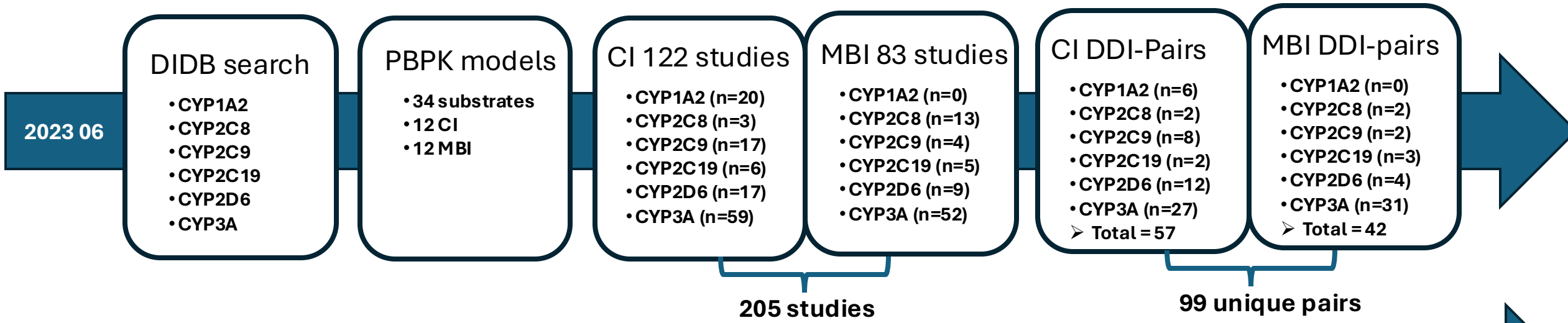
CI (n=122 studies)	20	3	17	6	17	59
MBI (n=83 studies)	0	13	4	5	9	52
Total studies	20	16	21	11	26	111

205 DDIs

*Repaglinide as CYP2C8 and CYP3A substrate

**Fluconazole as CYP2C9 and CYP3A inhibitor; Fluvoxamine as CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 inhibitor

***Amiodarone as CYP2C9 and CYP3A inhibitor



2023 06

Substrates

- CYP1A2 (n=3)
- CYP2C8 (n=2)
- CYP2C9 (n=5)
- CYP2C19 (n=3)
- CYP2D6 (n=6)
- CYP3A (n=16)

➤ Total = 34

Added as substrates

Duloxetine (CYP1A2)

Olanzapine (CYP1A2)

Lansoprazole (CYP2C19)

Voriconazole (CYP2C19)

Montelukast (CYP2C8)

Pioglitazone (CYP2C8)

Tucatinib (CYP2C8)

Paroxetine (CYP2D6)

Propranolol (CYP2D6)

Carbamazepine (CYP3A4)

Mirabegron (CYP3A4)

Verapamil (CYP3A4)

Substrates

- CYP1A2 (n=5)
- CYP2C8 (n=5)
- CYP2C9 (n=5)
- CYP2C19 (n=5)
- CYP2D6 (n=8)
- CYP3A (n=19)

➤ Total = 46

2024 12

2023 06

Inhibitors

- CYP1A2 (n=2)
- CYP2C8 (n=3)
- CYP2C9 (n=5)
- CYP2C19 (n=5)
- CYP2D6 (n=9)
- CYP3A (n=20)

➤ Total = 25
➤ Pathways = 44

10 inhibitor (pathways) added

Cimetidine (CYP1A2)

Propranolol (CYP1A2)

Cimetidine (CYP2C19)

Omeprazole (CYP2C19)

Voriconazole (CYP2C19)

Clopidogrel (+ glucuronide) (CYP2C8)

Tucatinib (CYP2C8)

Cimetidine (CYP2D6)

Duloxetine (CYP2D6)

Mirabegron (CYP2D6)

4 CYP3A4 perpetrators removed

Cyclosporine (complex)

Aprepitant (inducer)

Rifampicin (inducer)

Ritonavir (inducer)

Inhibitors

- CYP1A2 (n=4)
- CYP2C8 (n=6)
- CYP2C9 (n=5)
- CYP2C19 (n=8)
- CYP2D6 (n=11)
- CYP3A (n=16)

➤ Total = 28
➤ Pathways = 50

2024 12

Substrates	Enzyme	13-Mar-23	16-Dec-24	13-Mar-23	16-Dec-24
Caffeine	CYP1A2	YES	YES	1	1
Duloxetine	CYP1A2	NO	YES		2
Olanzapine	CYP1A2	NO	YES		3
Theophylline	CYP1A2	YES	YES	2	4
Tizanidine	CYP1A2	YES	YES	3	5
Imipramine	CYP2C19	YES	YES	4	6
Lansoprazole	CYP2C19	NO	YES		7
Omeprazole	CYP2C19	YES	YES	5	8
S-Mephenytoin	CYP2C19	YES	YES	6	9
Voriconazole	CYP2C19	NO	YES		10
Montelukast	CYP2C8	NO	YES		11
Pioglitazone	CYP2C8	NO	YES		12
Repaglinide	CYP2C8	YES	YES	7	13
Rosiglitazone	CYP2C8	YES	YES	8	14
Tucatinib	CYP2C8	NO	YES		15
Celecoxib	CYP2C9	YES	YES	9	16
Flurbiprofen	CYP2C9	YES	YES	10	17
Phenytoin	CYP2C9	YES	YES	11	18
S-Warfarin	CYP2C9	YES	YES	12	19
Tolbutamide	CYP2C9	YES	YES	13	20
Atomoxetine	CYP2D6	YES	YES	14	21
Desipramine	CYP2D6	YES	YES	15	22
Dextromethorphan	CYP2D6	YES	YES	16	23
Metoprolol	CYP2D6	YES	YES	17	24
Nebivolol	CYP2D6	YES	YES	18	25
Paroxetine	CYP2D6	NO	YES		26
Propranolol	CYP2D6	NO	YES		27
Tolterodine	CYP2D6	YES	YES	19	28
Alfentanil	CYP3A4	YES	YES	20	29
Alprazolam	CYP3A4	YES	YES	21	30
Aprepitant	CYP3A4	YES	YES	22	31
Atazanavir	CYP3A4	YES	YES	23	32
Carbamazepine	CYP3A4	NO	YES		33
Clarithromycin	CYP3A4	YES	YES	24	34
Dexamethasone	CYP3A4	YES	YES	25	35
Ibrutinib	CYP3A4	YES	YES	26	36
Midazolam	CYP3A4	YES	YES	27	37
Mirabegron	CYP3A4	NO	YES		38
Nifedipine	CYP3A4	YES	YES	28	39
Quinidine	CYP3A4	YES	YES	29	40
Repaglinide	CYP3A4	YES	YES	7	13
Rifabutin	CYP3A4	YES	YES	30	41
Sildenafil	CYP3A4	YES	YES	31	42
Simvastatin	CYP3A4	YES	YES	32	43
Triazolam	CYP3A4	YES	YES	33	44
Verapamil	CYP3A4	NO	YES		45
Zolpidem	CYP3A4	YES	YES	34	46

34 46

Perpetrator	Enzyme	13-Mar-23	16-Dec-24	13-Mar-23	16-Dec-24
Cimetidine	CYP1A2	NO	YES		4
Ciprofloxacin	CYP1A2	YES	YES	6	6
Fluvoxamine	CYP1A2	YES	YES	13	14
Propranolol	CYP1A2	NO	YES		22
Cimetidine	CYP2C19	NO	YES		4
Fluconazole	CYP2C19	YES	YES	11	12
Fluoxetine	CYP2C19	YES	YES	12	13
Fluvoxamine	CYP2C19	YES	YES	13	14
Nor-fluoxetine	CYP2C19	YES	YES	12	13
Omeprazole	CYP2C19	NO	YES		20
Ticlopidine	CYP2C19	YES	YES	23	25
Voriconazole	CYP2C19	NO	YES		28
Clopidogrel	CYP2C8	NO	YES		8
Clopidogrel acyl glucuronide	CYP2C8	NO	YES		8
Gemfibrozil	CYP2C8	YES	YES	14	15
Gemfibrozilglucuronide	CYP2C8	YES	YES	14	15
Trimethoprim	CYP2C8	YES	YES	24	26
Tucatinib	CYP2C8	NO	YES		27
Amiodarone	CYP2C9	YES	YES	1	1
Fluconazole	CYP2C9	YES	YES	11	12
Fluvoxamine	CYP2C9	YES	YES	13	14
Mono DesethylAmiodarone	CYP2C9	YES	YES	1	1
Sulphaphenazole	CYP2C9	YES	YES	22	24
Bupropion	CYP2D6	YES	YES	3	3
Cimetidine	CYP2D6	NO	YES	4	4
Cinacalcet	CYP2D6	YES	YES	5	5
Duloxetine	CYP2D6	NO	YES		10
Fluoxetine	CYP2D6	YES	YES	12	13
Fluvoxamine	CYP2D6	YES	YES	13	14
Hydroxy-bupropion	CYP2D6	YES	YES	3	3
Mirabegron	CYP2D6	NO	YES		18
Nor-fluoxetine	CYP2D6	YES	YES	12	13
Paroxetine	CYP2D6	YES	YES	18	21
Quinidine	CYP2D6	YES	YES	19	23
Amiodarone	CYP3A4	YES	YES	1	1
Atazanavir	CYP3A4	YES	YES	2	2
Cimetidine	CYP3A4	YES	YES	4	4
Clarithromycin	CYP3A4	YES	YES	7	7
Cyclosporine	CYP3A4	YES	NO	8	
Desmethyl-diltiazem	CYP3A4	YES	YES	9	9
Diltiazem	CYP3A4	YES	YES	9	9
Erythromycin	CYP3A4	YES	YES	10	11
Fluconazole	CYP3A4	YES	YES	11	12
Fluoxetine	CYP3A4	YES	YES	12	13
Fluvoxamine	CYP3A4	YES	YES	13	14
Hydroxy-itraconazole	CYP3A4	YES	YES	15	16
Itraconazole	CYP3A4	YES	YES	15	16
Ketoconazole	CYP3A4	YES	YES	16	17
Nor-fluoxetine	CYP3A4	YES	YES	12	13
Nor-verapamil	CYP3A4	YES	YES	17	19
Rifampicin	CYP3A4	YES	NO	20	
Ritonavir	CYP3A4	YES	NO	21	
Verapamil	CYP3A4	YES	YES	17	19
Aprepitant	CYP3A4	YES	NO	25	

Classified as internal staff & contractors by the European Medicines Agency

25 28