

**Considerations from the IQ Induction Working Group in Response to Drug-  
Drug Interaction Guidances from Regulatory Agencies:**

**Focus on Down-regulation, CYP2C Induction and CYP2B6 Positive Control**

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**Supplemental Data**

**Supplementary Table 1:** Induction of CYP2C and CYP3A mRNA in Human Hepatocytes Following Treatment with Xenobiotics for 48 hrs

Company M	Mean (Fold of Induction)			
	n=3	n=10	n=3	n=10
<b>Carbamazepine (µM)</b>	<b>2C8</b>	<b>2C9</b>	<b>2C19</b>	<b>3A4</b>
1	1.0	1.1	0.83	1.5
3	0.78	1.2	0.84	2.8
10	1.1	1.2	0.92	4.2
30	1.2	1.4	0.71	7.2
100	2.8	1.9	1.4	32
300	3.1	2.1	2.9	37
500	1.9	1.9	2.2	18
	n=2	n=11	n=2	n=11
<b>Efavirenz (µM)</b>	<b>2C8</b>	<b>2C9</b>	<b>2C19</b>	<b>3A4</b>
0.1	1.0	1.0	0.81	1.2
0.3	1.3	1.1	1.0	1.5
1	1.5	1.3	0.87	1.7
2	2.2	1.4	1.2	3.1
3	2.2	1.5	1.3	12
10	2.4	1.6	1.6	20
	n=4	n=13	n=4	n=13
<b>Phenobarbital (µM)</b>	<b>2C8</b>	<b>2C9</b>	<b>2C19</b>	<b>3A4</b>
10	1.2	1.2	1.3	3.4
30	1.9	1.3	1.2	4.6
100	3.9	1.5	1.5	6.7
300	4.3	1.8	1.7	16
1000	7.1	2.0	3.2	46
2000	8.3	2.3	4.2	57
3000	7.3	2.0	3.7	54
	n=2	n=11	n=2	n=11
<b>Phenytoin (µM)</b>	<b>2C8</b>	<b>2C9</b>	<b>2C19</b>	<b>3A4</b>
1	0.84	0.88	0.94	1.4
3	1.3	1.1	1.0	2.3
10	1.4	1.1	1.0	3.7
30	2.1	1.2	1.5	7.2
100	2.8	1.3	1.6	23
300	3.1	1.4	2.3	30
1000	2.8	1.3	2.2	31
	n=5	n=14	n=5	n=14
<b>Rifampicin (µM)</b>	<b>2C8</b>	<b>2C9</b>	<b>2C19</b>	<b>3A4</b>
0.03	0.89	1.0	0.77	2.8
0.1	1.4	1.3	1.2	11

0.3	1.6	1.4	1.1	20
1	2.7	1.8	1.5	38
3	3.8	1.9	1.7	63
10	3.4	1.9	1.9	66
30	5.7	2.1	2.5	99
	n=2	n=11	n=2	n=11
<b>Ritonavir (µM)</b>	<b>2C8</b>	<b>2C9</b>	<b>2C19</b>	<b>3A4</b>
0.1	0.80	1.1	0.83	3.9
0.3	1.2	1.2	1.0	11
1	2.0	1.5	1.4	25
2	2.7	1.8	1.5	36
3	2.6	1.6	1.6	40
10	2.7	2.0	1.8	52
30	1.3	2.1	1.6	40
	<b>Mean (Fold of Induction)</b>			
<b>CRO 1</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>
<b>Carbamazepine (µM)</b>	<b>2C8</b>	<b>2C9</b>	<b>2C19</b>	<b>3A4</b>
0.23	0.5	0.9	1.0	1.7
0.69	0.9	0.9	1.1	1.1
2.1	1.1	1.0	1.0	2.5
6.2	1.5	1.1	1.0	4.4
19	1.7	1.4	1.1	7.2
56	2.5	1.5	1.1	6.9
167	3.0	1.7	1.2	6.6
500	2.3	1.7	1.2	2.1
<b>Dexamethasone (µM)</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>
0.11	1.2	1.3	1.0	1.5
0.34	0.9	1.0	0.8	0.8
1	1.0	1.1	0.8	1.1
3.1	0.9	1.1	0.7	1.0
9.3	1.3	1.3	0.7	1.9
28	1.7	1.2	0.7	3.7
83	4.3	2.0	1.1	6.5
250	3.4	2.0	1.1	12.1
<b>Nifedipine (µM)</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>
0.046	0.9	1.1	1.1	1.2
0.14	0.8	1.3	1.1	0.6
0.41	0.9	1.5	1.1	0.8
1.2	0.8	1.6	1.0	0.7
3.7	1.2	2.0	1.1	1.5
11	1.9	2.5	1.3	3.6
33	4.1	2.7	1.5	5.6
100	4.5	1.9	1.8	5.4
<b>Omeprazole (µM)</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>
0.1	0.8	0.9	1.0	0.7

0.4	0.7	1.0	1.0	1.0
1.2	0.7	1.0	0.9	1.2
3.7	0.9	1.0	0.9	1.4
11.0	0.8	1.1	0.8	1.8
33.0	0.8	1.1	0.8	2.2
100.0	0.7	0.8	0.6	1.8
<b>Phenytoin (µM)</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>
0.23	0.7	0.9	0.8	3.2
0.69	0.8	0.8	0.8	0.8
2.1	1.0	0.9	0.8	2.1
6.2	1.0	1.0	0.7	2.6
19	1.3	1.1	0.8	4.9
56	1.7	1.2	0.8	4.1
167	1.6	1.2	0.9	5.1
500	1.4	1.1	0.9	13.1
<b>Phenobarbital (µM)</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>
0.91	0.8	1.0	1.3	1.5
2.7	0.9	1.2	1.5	1.2
8.2	0.8	1.1	1.4	1.5
24	1.0	1.2	1.3	1.7
74	1.4	1.6	1.5	3.4
222	1.8	1.8	1.5	4.6
667	3.0	2.2	1.7	7.9
2000	2.9	2.1	1.8	5.6
<b>Pioglitazone (µM)</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>
0.046	1.1	1.2	1.0	1.1
0.14	1.0	1.2	1.0	0.7
0.41	1.5	1.6	1.1	1.0
1.2	1.5	1.4	1.0	1.0
3.7	2.4	2.0	1.2	1.9
11	2.8	1.9	1.0	2.8
33	3.0	1.7	1.0	2.8
100	3.0	1.7	1.4	3.8
<b>Rosiglitazone (µM)</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>
0.1	1.0	0.8	0.9	0.6
0.4	1.2	1.0	1.0	1.2
1.2	1.2	0.9	1.1	1.0
3.7	1.6	1.1	1.0	1.9
11.0	2.2	1.4	1.0	3.9
33.0	3.8	1.9	1.1	7.0
100.0	2.2	1.4	0.8	7.0
<b>Rifampicin (µM)</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>
0.1	1.0	1.1	0.9	2.8
0.2	1.5	1.2	0.9	5.7
0.6	1.7	1.3	1.0	6.8

1.8	2.0	1.6	1.0	8.0
5.5	2.0	1.6	0.9	11.5
17.0	1.7	1.7	0.8	12.2
<b>Sulfinpyrazone (<math>\mu\text{M}</math>)</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>
0.1	1.0	1.1	0.9	1.2
0.3	0.9	1.0	0.8	0.7
0.8	1.0	1.0	0.9	1.0
2.4	1.0	1.1	0.8	1.4
7.4	1.8	1.4	0.9	3.2
22.0	2.7	1.6	0.9	8.2
66.0	4.8	2.7	1.4	11.0
200.0	5.3	2.9	1.3	15.4
<b>Troglitazone (<math>\mu\text{M}</math>)</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>	<b>n=3</b>
0.1	1.0	0.9	1.1	0.7
0.2	1.0	0.9	0.9	0.9
0.7	1.3	1.1	1.0	1.5
2.2	1.3	1.3	0.9	2.8
6.6	2.5	1.8	1.3	4.4
20.0	3.7	2.2	1.7	6.2

n – number of replicates. Four different lots of human hepatocytes were used