Supplementary tables for Part II of Boyce *et al* "A biomedical evidence taxonomy oriented toward confidence assignment"

Table 1: The tables below show nine drug/drug or drug/drug-metabolite pairs that were excluded from our analysis of the DIKB's accuracy. Seven pairs were excluded because a validation set interaction or non-interaction involving the pair was supported by a single clinical trial that was also present in DIKB assertions that the system could use to infer the interaction or non-interaction. These clinical trials are referred to as "dual-use" evidence items. Two other pairs were accidentally excluded due to a transcription error.

Drug pairs excluded because of "dual-use" evidence items

drug/drug or drug/drug-metabolite pair	*source*	*confirms*	*also supports*
clarithromycin - beta-hydroxy-simvastatin	[12]	interaction	beta-hydroxy-simvastatin is a substrate of CYP3A4
clarithromycin - simvastatin	[12]	interaction	simvastatin is a substrate of CYP3A4
itraconazole - beta-hydroxy-simvastatin	[17]	interaction	beta-hydroxy-simvastatin's primary total clearance enzyme is CYP3A4, beta-hydroxy-simvastatin is a substrate-of CYP3A4
itraconazole - simvastatin	[17]	interaction	simvastatin's primary total clearance enzyme is CYP3A4, simvastatin is a substrate of CYP3A4
midazolam - atorvastatin	[16]	interaction	atorvastatin inhibits CYP3A4
midazolam - beta-hydroxy-simvastatin	[19]	non-interaction	beta-hydroxy-simvastatin does not inhibit CYP3A4
midazolam - simvastatin	[19]	non-interaction	simvastatin does not inhibit CYP3A4

Drug pairs excluded due to a transcription error

itraconazole - para-hydroxy-atorvastatin
midazolam - desacetyldiltiazem

Table 2: A small sample of the 65 statements the evidence board located in drug-product labeling that mentioned a pharmacokinetic interaction or non-interaction between one of the drug/drug and drug/drug-metabolite combinations shown in Appendix D (supplementary material). Three of these statements were not used in the validation set because they did not provide quantitative data. The arrows point to the drug or drug metabolite that, based on the statement, would be the object of a pharmacokinetic DDI involving the pair. Arrows with lines through them indicate the drug or drug metabolite that should not be affected by an metabolic inhibition interaction involving the other drug or drug metabolite in the pair.

Statement	*interaction/non-interaction*	*validation set*
"Human pharmacokinetic data suggest that SPORANOX [itraconazole] inhibits the metabolism of atorvastatin, cerivastatin, lovastatin, and simvastatin, which may increase the risk of skeletal muscle toxicity, including rhabdomyolysis." [13]	itraconazole - atorvastatin $\rightarrow$ itraconazole - lovastatin $\rightarrow$ itraconazole - simvastatin $\rightarrow$	no
"In a small pharmacokinetic study involving HIV infected patients, clarithromycin was shown to increase plasma concentrations of itraconazole." [13]	clarithromycin - itraconazole $\rightarrow$	no
"Similarly, following administration of 1 gram of erythromycin ethyl succinate and 200 mg itraconazole as single doses, the mean C_{max} and AUC $0-\infty$ of itraconazole increased by 44% (90% CI: 119-175%) and 36% (90% CI: 108-171%), respectively." [13]	itraconazole - erythromycin $\leftarrow$	yes
""When single 40 mg doses of simvastatin or atorvastatin, both substrates of CYP3A4, were given to healthy adult volunteers who had received nefazodone hydrochloride, 200 mg BID for 6 days, approximately 20 fold increases in plasma concentrations of simvastatin and simvastatin acid and 3 to 4 fold increases in plasma concentrations of atorvastatin and atorvastatin lactone were seen. These effects appear to be due to the inhibition of CYP3A4 by nefazodone because, in the same study, nefazodone had no significant effect on the plasma concentrations of pravastatin, which is not metabolized by CYP3A4 to a clinically significant extent." [23]	atorvastatin - nefazodone $\leftarrow$ nefazodone - simvastatin $\rightarrow$ nefazodone - beta-hydroxy-simvastatin $\rightarrow$ nefazodone - pravastatin $\not\rightarrow$	yes
"As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors (e.g., lovastatin and simvastatin). Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly." [1]	clarithromycin - HMG-CoA reductase inhibitors[a] $\rightarrow$	no

[a]The evidence board considered the following drugs and drug metabolites listed in the DIKB to be HMG-CoA reductase inhibitors:

- atorvastatin, ortho-hydroxy-atorvastatin, para-hydroxy-atorvastatin
- simvastatin, beta-OH-simvastatin (simvastatin acid), 6'-exomethylene-simvastatin, 6'-hydroxy-simvastatin, 6'-hydroxymethyl-simvastatin
- lovastatin, beta-OH-simvastatin (lovastatin acid), 6'beta-hydroxy-lovastatin
- fluvastatin, pravastatin, rosuvastatin

Table 3: The evidence-board accepted none of the 35 case reports it found that were relevant for use in the validation set. Most case reports did not provide adequate measurements of the purported victim drug's systemic concentration. The three reports cited here failed to meet inclusion criteria because they did not receive a rating of at least "probable" when co-investigator JH assessed the report using Drug Interaction Probability Scale [9]. Asterisks indicate the drug or drug metabolite considered to be the object of a metabolic inhibition interaction occurring between the pair.

Case Report	*Reported interaction*	*Reason for low DIPS score*
[3]	itraconazole - clarithromycin*	patients were taking concomitant medications that could have influenced clarithromycin levels
[21]	erythromycin - lovastatin*	The lovastatin level was drawn after the patient developed renal failure plus the patient was taking concomitant medications that could have influenced high lovastatin levels
[8]	midazolam* - erythromycin	The timing of the indicated effect of IV erythromycin on the first pass metabolism of oral midazolam is not consistent with a reasonable time-course for such an effect; the use of an unknown fruit juice in pre-op leaves open the possibility of a CYP3A4 inhibition by grapefruit juice

Table 9: The levels of evidence (LOEs) defined by the evidence-board. The LOEs use the *ranking categories* defined in Table 6 (manuscript) so that multiple evidence types can be represented by a single symbol. In this table, the symbol '::=' means the term to the left "is defined as" the term to the right, | means "or", and '+' means that "one or more occurrences of" of the symbol to the left are allowed. For example, LOE-1 of set `A` reads"LOE-1 is defined as one or more evidence types from the **pk-ct-pk** *ranking category* OR one or more evidence types from the **label-statement** *ranking category*."

ID	*LOEs*	*Applies to*
`A`	LOE-1 ::= **pk-ct-pk**+ | **label-statement**+	`bioavailability` `maximum-concentration`
`B`	LOE-1 ::= **pk-ct-pk**+ LOE-2 ::= **label-statement**+	`first-pass-effect` `fraction-absorbed`
`C`	LOE-1 ::= **pk-ct-pk**+ LOE-2 ::= **label-statement**+ LOE-3 ::= **na-primary-total-clearance-enz**+	`primary-total-clearance-mechanism`
`D`	LOE-1 ::= **pk-ct-pk-genotype**+ | **pk-ct-pk-phenotype**+ LOE-2 ::= **pk-ddi-rndm**+ | **pk-ddi-non-rndm**+ LOE-3 ::= **iv-met-enz-id-Cyp450-with-inh**+ LOE-4 ::= **label-statement**+ LOE-5 ::= **na-substrate-of**+	`controls-formation-of` `substrate-of` `is-not-substrate-of`
`E`	LOE-1 ::= **pk-ct-pk-phenotype**+ | **pk-ct-pk-genotype**+ LOE-2 ::= **pk-ddi-rndm**+ | **pk-ddi-non-rndm**+ LOE-3 ::= **label-statement**+	`primary-total-clearance-enzyme`

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ID	*LOEs*	*Applies to*
F	LOE-1 ::= **pk-ct-pk-phenotype+** | **pk-ct-pk-genotype+** LOE-2 ::= **pk-ddi-rndm+** | **pk-ddi-non-rndm+** LOE-3 ::= **label-statement+** LOE-4 ::= **na-primary-metabolic-clearance-enzyme+**	`primary-metabolic-clearance-enzyme`
G	LOE-1 ::= **pk-ct-pk+** LOE-2 ::= **iv-met-enz-id-Cyp450-with-inh+** LOE-3 ::= **label-statement+** LOE-4 ::= **na-substrate-of+**	`has-metabolite`
H	LOE-1 ::= **iv-met-inh-microsomal+** | **iv-met-inh-recombinant+** LOE-2 ::= **label-statement+**	`inhibition-constant`
I	LOE-1 ::= **pk-ddi-rndm+** | **pk-ddi-non-rndm+** LOE-2 ::= **iv-met-inh-microsomal+** | **iv-met-inh-recombinant+** | **label-statement+**	`inhibits`
J	LOE-1 ::= **pk-ddi-rndm+** | **pk-ddi-non-rndm+** | **iv-met-inh-microsomal+** | **iv-met-inh-recombinant+** LOE-2 ::= **label-statement+**	`does-not-inhibit`

K	LOE-1 ::= **iv-met-enz-id-Cyp450-microsomal+** | **iv-met-enz-id-Cyp450-recombinant+**
	LOE-2 ::= **label-statement+**
	LOE-3 ::= **nt-statement+**
		`does-not-permanently-deactivate-catalytic-function`
		`permanently-deactivates-catalytic-function`
		`in-vitro-probe-substrate-of-enzyme`

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ID	*LOEs*	*Applies to*
L	LOE-1 ::= **iv-met-inh-recombinant**+ LOE-2 ::= **iv-met-inh-microsomal**+ LOE-3 ::= **label-statement**+ LOE-4 ::= **nt-statement**+	in-vitro-selective-inhibitor-of-enzyme
M	LOE-1 ::= **pk-ddi-rndm**+ LOE-2 ::= **pk-ddi-non-rndm**+ LOE-3 ::= **label-statement**+ LOE-4 ::= **nt-statement**+	in-viVo-selective-inhibitor-of-enzyme sole-PK-effect-alter-metabolic-clearance
N	LOE-1 ::= **pk-ddi-rndm**+ | **pk-ddi-non-rndm**+ | **obs-eval**+ | **label-statement**+ LOE-2 ::= **nt-statement**+	pceut-entity-of-concern
O	LOE-1 ::= **pk-ct-pk-phenotype**+ | **pk-ct-pk-genotype**+ LOE-2 ::= **label-statement**+ LOE-3 ::= **nt-statement**+	polymorphic-enzyme

Table 16: 31 interaction and nine non-interaction predictions made by the DIKB that are unknown, but not refuted, in the validation set. We list next to each interaction its predicted magnitude and any relevant case report that we found along with our estimate (using the DIPS scale [9]) of the likelihood that the adverse event in the case report was caused by the interaction. For interactions, asterisks indicate the drug or drug-metabolite that the DIKB considers the object of a metabolic inhibition interaction involving the other drug or drug-metabolite in the pair. For non-interactions, they indicate the drug or drug-metabolite that should *not* be the object of such an interaction.

pair	*DIKB level*	*Case report/DIPS analysis*
alprazolam* - atorvastatin	PKI-1	none found
alprazolam* - clarithromycin	PKI-1	none found
alprazolam* - fluconazole	PKI-1	none found
atorvastatin - lovastatin*	PKI-3	none found
atorvastatin - beta-hydroxy-lovastatin*	PKI-3	none found
atorvastatin - simvastatin*	PKI-3	none found
atorvastatin - beta-hydroxy-simvastatin*	PKI-3	none found
atorvastatin* - fluconazole	PKI-3	[14]: *possible*; also on proton pump inhibitor
clarithromycin* - erythromycin	PKI-1	none found
clarithromycin - lovastatin*	PKI-3	[7]: *possible* for two cases; both patients also on another medication with interaction potential
clarithromycin - beta-hydroxy-lovastatin*	PKI-3	see clarithromycin - lovastatin
clarithromycin* - nefazodone	PKI-1	none found
diltiazem - alprazolam*	PKI-1	none found
diltiazem - atorvastatin*	PKI-3	[6]: *possible*, all patients on proton pump inhibitors that could interact and have been reported to cause rhabdomyolysis [15] : *possible*; Pt had CHF, valve disease and decr CO may cause decr renal function. CK elevation was mild and no myoglobin in urine.
diltiazem - beta-hydroxy-simvastatin*	PKI-3	[18]: *probable* [6]: *possible*; all patients on proton pump inhibitors that could interact and have been reported to cause rhabdomyolysis [10]: *possible*; patients on other medications with interaction potential
diltiazem - clarithromycin*	PKI-1	none found
erythromycin - lovastatin*	PKI-3	[21]: *probable* [24]: *probable* [4]: *probable*; note erythromycin + diltiazem combination
erythromycin - beta-hydroxy-lovastatin*	PKI-3	see erythromycin - lovastatin
fluconazole - lovastatin*	PKI-3	none found
fluconazole - beta-hydroxy-lovastatin*	PKI-3	none found
fluconazole - simvastatin*	PKI-3	[20]: *possible*
fluconazole - beta-hydroxy-simvastatin*	PKI-3	see fluconazole - simvastatin
itraconazole - clarithromycin*	PKI-1	[3]: *possible* for two cases; used historic controls for blood-level data when Pt not taking interacting drugs, clinical observational study
ketoconazole - atorvastatin*	PKI-3	none found
ketoconazole - clarithromycin*	PKI-1	none found
ketoconazole - lovastatin*	PKI-3	[22]: *probable*
ketoconazole - beta-hydroxy-lovastatin*	PKI-3	
ketoconazole - beta-hydroxy-simvastatin*	PKI-3	[5]: *probable* [2]: *probable* [11]: *probable*
nefazodone - lovastatin*	PKI-3	none found
nefazodone - beta-hydroxy-lovastatin*	PKI-3	none found
triazolam* - atorvastatin	PKI-3	none found
alprazolam* - beta-hydroxy-simvastatin	NO-PKI	n/a
alprazolam* - simvastatin	NO-PKI	n/a
lovastatin* - beta-hydroxy-simvastatin	NO-PKI	n/a
simvastatin - beta-hydroxy-lovastatin*	NO-PKI	n/a
simvastatin* - beta-hydroxy-simvastatin*	NO-PKI	n/a
simvastatin - lovastatin*	NO-PKI	n/a
triazolam* - beta-hydroxy-simvastatin	NO-PKI	n/a
triazolam* - simvastatin	NO-PKI	n/a
beta-hydroxy-simvastatin - beta-hydroxy-lovastatin*	NO-PKI	n/a

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