Appendices to parts I and II of Boyce *et al* "A biomedical evidence taxonomy oriented toward confidence assignment"

Contents

A The DIKB Evidence Taxonomy

DIKB curators categorize each evidence item into one of the evidence-types from the evidence-type taxonomy shown here. The evidence types in the taxonomy are arranged into parent and child classes of evidence. A child class inherits all of the properties of the parent class and adds some specific properties of its own. The taxonomy is shown here with child evidence-types at a deeper indent-level than its parent class.

Evidence Types

`[Statement]` *A statement:* A published artifact that is "...the basis for belief or disbelief; knowledge on which to base belief" see the term "evidence" in Wordnet version 3.0 [35]

`[Non_Traceable_Statement]` *A non-traceable, but possibly authoritative, statement:* A statement that does not explicitly refer to evidence items in justification of its assertion(s) or that refers to an evidence item that is not accessible to the curator (e.g. pre-market drug studies only accessible to drug-company or FDA researchers)

`[Non_traceable_Drug_Label_Statement]` *A non-traceable drug-label statement:* An assertion found in a drug label that does not provide any traceable citations for its evidence support

`[Traceable_Statement]` *A traceable statement:* A statement that provides citation to evidence support for justification of its assertion(s)

`[Traceable_Drug_Label_Statement]` *A traceable drug-label statement:* An assertion stated in a drug label that provides citations for its evidence support

`[EV_EX_Met_Enz_ID]` *A drug metabolism identification experiment:* An experiment conducted with biological tissues and/or chemical compounds in a laboratory designed to identify the specific enzymes responsible for the metabolism of a drug ([26], p. 25)

`[EV_EX_Met_Enz_ID_Cyp450]` *A CYP450 drug metabolism identification experiment:* A metabolic **enzyme** identification experiment specifically designed to identify the Cytochrome P-450 enzymes involved in the metabolism of a drug

`[EV_EX_Met_Enz_ID_Cyp450_Hum_Recom]` *A CYP450, recombinant, drug metabolism identification experiment with possibly NO probe enzyme inhibitor(s)*

`[EV_EX_Met_Enz_ID_Cyp450_Hum_Recom_Chem]` *A CYP450, recombinant, drug metabolism identification experiment using chemical inhibitors*

`[EV_EX_Met_Enz_ID_Cyp450_Hum_Recom_Antibody]` *A CYP450, recombinant, drug metabolism identification experiment using antibody inhibitors*

`[EV_EX_Met_Enz_ID_Cyp450_Hum_Microsome]` *A CYP450, human microsome, drug metabolism identification experiment:* A Cytochrome P-450 metabolic enzyme identification experiment using human liver microsomes that have been characterized for Cytochrome P-450 activity and possibly NO probe enzyme inhibitor(s)

`[EV_EX_Met_Enz_ID_Cyp450_Hum_Microsome_Chem]` *A CYP450, human microsome, drug metabolism identification experiment using chemical inhibitors*

`[EV_EX_Met_Enz_ID_Cyp450_Hum_Microsome_Antibody]` *A CYP450, human microsome, drug metabolism identification experiment using antibody inhibitors:*

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Evidence Types

`[EV_EX_Met_Enz_Inhibit]` *A metabolic enzyme inhibition experiment:* An experiment conducted with biological tissues and/or chemical compounds in a laboratory designed to determine whether or not a drug inhibits a specific drug-metabolizing enzyme

`[EV_EX_Met_Enz_Inhibit_Cyp450]` *A CYP450 metabolic enzyme inhibition experiment:* A metabolic **inhibition** experiment specifically designed to determine whether or not a drug inhibits a specific CYP450 enzyme

`[EV_EX_Met_Enz_Inhibit_Cyp450_Hum_Recom]` *A CYP450, recombinant, metabolic enzyme inhibition experiment:* A Cytochrome P-450 inhibition experiment using recombinant human enzymes

`[EV_EX_Met_Enz_Inhibit_Cyp450_Hum_Microsome]` *A CYP450, human microsome, metabolic enzyme inhibition experiment:* A Cytochrome P-450 metabolic enzyme inhibition experiment using human liver microsomes that have been characterized for Cytochrome P-450 activity

`[EV_Clinical_Trial]` *A clinical trial:* "a pre-planned clinical study of the safety, efficacy, or optimum dosage schedule of one or more diagnostic, therapeutic, or prophylactic drugs, devices, or techniques in humans selected according to predetermined criteria of eligibility and observed for predefined evidence of favorable and unfavorable effects." - (Medical Subject Headings (MeSH) [10] version 2008, concept code D016430, `Clinical Trial`)

`[EV_CT_DDI]` *A DDI clinical trial:* A study designed to quantify the pharmacokinetic and/or pharmacodynamic effects within study participants of a single drug in the presence of a purported precipitant.

`[EV_PK_DDI_NR]` *A non-randomized DDI clinical trial:* A pharmacokinetic DDI study where participants receive a drug in the presence of a purported precipitant (experimental group) or not (control group) but participants are not randomly assigned to experiment and control groups. This can include fixed-order studies where all participants are tested with placebo and precipitant after some period of washout

`[EV_PK_DDI_Par_Grps]` *A parallel groups DDI clinical trial:* A pharmacokinetic DDI study involving two groups of non-randomized participants where both groups receive the purported object drug while only one group receives the purported precipitant

`[EV_PK_DDI_RCT]` *A randomized DDI clinical trial:* A randomized, controlled, pharmacokinetic DDI study where participants receive a drug either in the presence of a purported precipitant (experimental group) or not (control group)

`[EV_CT_Pharmacokinetic]` *A pharmacokinetic clinical trial:* "A study of the process by which a drug is absorbed, distributed, metabolized, and eliminated by the body." (NCI Thesaurus [14] version 8, concept code C49663, `Pharmacokinetic Study`)

`[EV_CT_PK_Genotype]` *A genotyped pharmacokinetic clinical trial:* A drug pharmacokinetics study whose population consists of at least two groups known to posses distinct forms of some drug-metabolizing enzyme

`[EV_CT_PK_Phenotype]` *A phenotyped pharmacokinetic clinical trial:* A drug pharmacokinetics study whose population consists of at least two groups known to posses distinct drug metabolizing phenotypes

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Evidence Types

`[EV_Observation]` *An observation-based report:* An observation-based report of some occurrence

`[EV_Obs_ADE]` *An observation-based ADE report:* An observation-based report of an adverse drug event

`[EV_Obs_ADE_Public_Reported]` *An observation-based ADE report in a public reporting database:* An adverse event report on file in a public adverse event reporting database such as the FDA's Adverse Event Reporting System

`[EV_Obs_DI_CR]` *A published observation-based ADE report:* An published observation-based case-report of a drug interaction

`[EV_Obs_DI_CR_Evaluated]` *A published and evaluated observation-based ADE report:* An observation-based report of a drug interaction that has been evaluated by some assessment tool

`[EV_Retrospective]` *A retrospective study:* "Studies used to test etiologic hypotheses in which inferences about an exposure to putative causal factors are derived from data relating to characteristics of persons under study or to events or experiences in their past. The essential feature is that some of the persons under study have the disease or outcome of interest and their characteristics are compared with those of unaffected persons." (Medical Subject Headings (MeSH) [10] version 2008, concept code D012189, `Retrospective Studies`)

`[EV_PK_DDI_Retro]` *A retrospective DDI study:* A retrospective study looking at the change in patient exposure of a single drug in the presence of a purported precipitant using a retrospective set of clinical records

`[EV_Population_PK]` *A retrospective population PK study:* a "...study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug in question." ([25], p.1)

`[EV_Review]` *A review article:* A published analysis of the evidence supporting and/or refuting some topic

`[EV_Drug_Review]` *A drug review article:* A published analysis of research on the efficacy or safety of a drug, family of drugs, or drug therapy.

`[EV_DrugClinicalReview]` *An FDA clinical review:* An FDA-sponsored review of a drug's pre-market studies and adverse event reports.

B Inclusion Criteria and Required Actions for Evidence Types in the DIKB

Inclusion criteria specify the necessary attributes that an instance of an evidence type in the DIKB evidence taxonomy must meet for it to be used to support or refute a specific instance of an assertion type in the DIKB. This appendix lists all of the inclusion criteria along with specific actions that DIKB curators must take when linking evidence of a particular evidence type to an assertion instance. Unless stated otherwise, inclusion criteria and required actions apply to all sub-types of the evidence type that the criteria mentions. For example, the criteria and action that apply to the evidence taxonomy's `EV_CT_DDI` evidence type also apply to its sub-types `EV_PK_DDI_NR`, `EV_PK_DDI_Par_Grps`, and `EV_PK_DDI_RCT`.

B.1 Inclusion Criteria for Reviews (`EV_Review`) and Sub-classes

Though not encouraged, a statement in a published review (`EV_Review` and sub-classes) can be used as evidence for or against `inhibits`, `substrate-of`, `primary-clearance-enzyme`, `fraction-cleared-by`, `primary-clearance-mechanism`. The following inclusion criteria apply:

- the statement is non-ambiguous
- the review provides clearly cited references or is from an authoritative organization such as the Federal Drug Administration
- each cited reference meets the inclusion criteria for the evidence type it belongs to

B.2 Inclusion Criteria for Published Observation Reports (`EV_Obs_DI_CR`) and Sub-classes

Published observation reports that been evaluated by some assessment tool (`EV_Obs_DI_CR_Evaluated`) can be used as support that an interaction occurred between at least two of the active ingredients or metabolites mentioned in the report. The following inclusion criteria apply:

- the report contains sufficient pharmacokinetic data to establish that the reported interaction occured by pharmacokinetic mechanisms
- the report is not about an abnormal susceptibility to some active ingredient or metabolites peculiar to an individual, otherwise known as an idiosyncratic interaction
- the report contains enough information to apply the Drug Interaction P Scale (DIPS) [22] to evaluate the interaction claimed by the case report.
- the report receives a causation rating of at least "probable" according to the DIPS scale. This means that the interaction report establishes a probable level of causation for an interaction between the two drugs of interest in the report.

B.3 Inclusion Criteria for Pharmacokinetic Studies (`EV_CT_Pharmacokinetic`) and Sub-classes

Instances of the pharmacokinetic study evidence types (`EV_CT_Pharmacokinetic` and sub-classes) can be used as evidence for or against instances of the following assertion types:

`maximum-concentration` / `has-metabolite` / `primary-total-clearance-mechanism` / `bioavailability` / `first-pass-effect` / `fraction-absorbed` / `has-metabolite` / `substrate-of` / `primary--total-clearance-enzyme`

Instance of the EV_CT_PK_Genotype or EV_CT_PK_Phenotype evidence types can support or refute polymorphic--enzyme assertions. The following inclusion criteria apply to the EV_CT_Pharmacokinetic evidence type and sub-classes:

- The route of administration must stated.
- Study participants must not be exclusively under the age of 21 or over the age of 65.
- The study's design (dosing, duration, population size, and procedure for drug administration) should be sufficient to allow accurate measurements pharmacokinetic parameters.

Required Action(s):

- If evidence item's evidence-type is one of EV_CT_PK_Genotype or EV_CT_PK_Phenotype, then the curator must link a polymorphic-enzyme assertion as an assumption for the intended use of the evidence item.
- If an instance of the EV_CT_PK_Genotype or EV_CT_PK_Phenotype evidence types is being used to support or refute that an enzyme is polymorphic then the specific genotype of the enzyme must be noted in the description of evidence.

B.4 Inclusion Criteria for Pharmacokinetic DDI Studies (EV_CT_DDI) and Sub-classes

Pharmacokinetic drug-drug interaction (DDI) studies (EV_CT_DDI and sub-classes) can be used as evidence for or against increases-auc, inhibits, and substrate-of assertion instances. The following inclusion criteria apply:

- The route of administration must stated.
- If the study is to be used as evidence that the precipitant active ingredient or metabolite is, or is not, an **inhibitor** of an enzyme, ENZ, then ENZ must be the "primary total clearance enzyme" of the object active ingredient or metabolite used in the study.
- If the study is to be used as evidence that the object active ingredient or metabolite is, or is not, a **substrate** an enzyme, ENZ, then the precipitant must be an *in vivo selective* inhibitor of that ENZ.
- Study participants must not exclusively under the age of 21 or over the age of 65.
- The study's duration should be long enough for precipitant, and any of its known active metabolites, to effect enzyme pool.
- The study's design (dosing, duration, population size, and procedure for drug administration) should be sufficient to allow accurate measurements of AUC change.

Required Action(s):

- If the study is to be used as evidence that the an active ingredient or metabolite is, or is not, an **inhibitor** of an enzyme, ENZ, then the curator must link (as an assumption for the evidence item's usage) the assertion that ENZ is the primary-total-clearance-enzyme of the study's object active ingredient or metabolite.
- If the study is to be used as evidence that the object active ingredient or metabolite is, or is not, a substrate an enzyme, ENZ, then the curator must link the following assertions as assumptions for the evidence item's usage:
  - the study's precipitant is an in-viVo-selective-inhibitor-of-enzyme of 'ENZ. and,
  - the sole-PK-effect-alter-metabolic-clearance assertion indicating that the sole pharmacokinetic effect of the precipitant on the object drug is alteration of its metabolic clearance

B.5 Inclusion Criteria for Non-traceable Statements in Drug Product Labeling (Non_traceable_Drug_Label_Statement) and Sub-classes

An assertional statement found in a drug label that *does not* provide any traceable citations for its evidence support (Non_traceable_Drug_Label_Statement and sub-classes) can be used as evidence for or against inhibits, substrate-of, primary-clearance-enzyme, fraction-cleared-by, primary-clearance-mechanism. The following inclusion criteria apply:

- The labeling statement must be the most currently available for the drug
- The date of the label must be noted
- the statement cannot be accepted as evidence if its supporting evidence is based solely on non-human studies

Required Action(s):

- non-traceable and *ambiguous* author statements (such as "drug x did not increase the AUC of drug y" with no dosing or duration information) should be labeled as such.
- non-traceable, but *non-ambiguous*, author statements (such as "drug x, given at dose A, did not increase AUC of drug y, given at dose B for duration T") should be labeled as such

B.6 Inclusion Criteria for Drug Enzyme Inhibition Experiments (EV_EX_Met_Enz_Inhibit) and Sub-classes

A metabolic enzyme inhibition experiment (EV_EX_Met_Enz_Inhibit and sub-classes) can be used to support or refute an inhibition-constant assertion for an active ingredient or metabolite and some enzyme. An inhibition-constant assertion must be relevant to the concentration of the inhibitor as found in clinical practice. The system will ensure that this criteria is met while applying its inference algorithm to assertions in its knowledge-base. It will compare values for the maximum_concentration of the active ingredient or metabolite with its inhibition-constant values. Instances of the EV_EX_Met_Enz_Inhibit evidence type and its subtypes can also support or refute that an active ingredient or metabolite is known to affect an enzyme in such a way that the enzyme is permanantly removed from further participation in catalysis. The following inclusion criteria apply for all acceptible applications of these evidence types:

- The source of the enzymes must be either from human hepatocytes or human recombinant enzymes.
- NADPH must be added to the enzyme systems as part of the experiment when appropriate. In cases where no explicit statement in the evidence item mentions the use of NADPH, the curator is free to exercise judgement as to whether NADPH was added since it is considered standard protocol for studies during or after the year 2000.
- To support an inhibition-constant assertion for some active ingredient or metabolite and an enzyme, the substrate used in the experiment must be a *in vitro probe substrate* of the enzyme.
- Only K_i values, not $IC50$ or "percent of enzyme inhibited" values, can support an inhibition-constant assertion for some active ingredient or metabolite and an enzyme. The source describing the experiment must provide an appropriately derived K_i value.

Required Actions(s):

- If the study is being used to support or refute that an active ingredient or metabolite inhibits an enzyme, then the curator must link (as an assumption for the evidence item's usage) the assertion that the the substrate is an in-vitro-probe-substrate-of-enzyme of the target enzyme of the study.

B.7 Inclusion Criteria for Metabolic Enzyme Identification Experiments (EV_EX_Met_Enz_ID) and Sub-classes

A drug metabolism identification experiment (EV_EX_Met_Enz_ID and sub-classes) can be used to support or refute that an active ingredient or metabolite is a substrate of one or more enzymes. The following inclusion criteria apply:

- The source of the enzymes must be either from human hepatocytes or human recombinant enzymes.
- NADPH must be added to the enzyme system(s) as part of the experiment. In cases where no explicit statement in the evidence item mentions the use of NADPH, the curator is free to exercise judgement as to whether NADPH was added since it is considered standard protocol for studies conducted during or after the year 2000.
- Experiments that use antibody inhibitors cannot be applied as evidence for or against the affinity of the substrate of interest for the enzyme
- the inhibitor used to determine whether an active ingredient's or metabolite's metabolism is catalyzed by a specific enzyme must be an *in vitro selective* inhibitor of that ENZ.

Required Action(s):

- The curator must link an assertion that the inhibitor used in the experiment is an in-vitro-selective--inhibitor-of-enzyme as an assumption for the particular application of evidence.

C The Final Validation Set of Drug-drug Interactions and Non-interactions

The reference set of drug-drug interactions and non-interactions used to characterize the prediction accuracy of the DIKB using a wide range of *belief criteria* including criteria chosen by the DIKB's evidence-board. An "X" in the column labeled *DDI* indicates that one of the pharmaceutical entities in the first column is the victim of a metabolic-inhibition interaction. An "X" in the *Non-DDI* column indicates that no metabolic-inhibition interaction is known to occur between the the pharmaceutical entities in the first column. The arrows indicate the drug or drug metabolite that the validation set considers the victim of a metabolic inhibition interaction that occurs between the pair. Arrows with a line through them indicate which drug or drug metabolite should not be affected by a metabolic inhibition interaction involving the other drug in the pair.

† The noted interaction occurs by inhibition of the metabolic clearance of a parent compound.

†† The DIKB's evidence-base uses this study to supports an drug mechanism assertion that is not related to the drug/drug or drug/drug-metabolite pair.

§ The pair was accidentally excluded from the experiment due to a trascription error.

‡ The pair was excluded because a validation set interaction or non-interaction between the two pharmaceutical entities 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.

drug/drug or drug/metabolite pair	**DDI**	**Non-DDI**	**Source**
alprazolam - 1'-hydroxymidazolam			
alprazolam - 14-hydroxyclarithromycin			
alprazolam - 4-hydroxyalprazolam			
alprazolam - 4-hydroxymidazolam			
alprazolam - 4-hydroxytriazolam			
alprazolam - 6'-exomethylene-lovastatin			
alprazolam - 6'-exomethylene-simvastatin			
alprazolam - 6'-hydroxy-simvastatin			
alprazolam - 6'-hydroxymethyl-simvastatin			
alprazolam - 6'beta-hydroxy-lovastatin			
alprazolam - alpha-hydroxyalprazolam			
alprazolam - atorvastatin			
alprazolam - beta-hydroxy-lovastatin			
alprazolam - beta-hydroxy-simvastatin			
alprazolam - clarithromycin			
alprazolam - desacetyldiltiazem			
alprazolam - erythromycin ←	X		[50]
alprazolam - fluconazole			
alprazolam - fluvastatin			
alprazolam - itraconazole ←	X		[49]

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drug/drug or drug/metabolite pair	DDI	Non-DDI	Source
alprazolam - ketoconazole ←	X		[42], [19]
alprazolam - lovastatin			
alprazolam - midazolam			
alprazolam - N-demethyldesacetyl-diltiazem			
alprazolam - N-demethyldiltiazem			
alprazolam - N-desmethylrosuvastatin			
alprazolam - nefazodone ←	X		[20], [15]
alprazolam - ortho-hydroxy-atorvastatin			
alprazolam - para-hydroxy-atorvastatin			
alprazolam - pravastatin			
alprazolam - rosuvastatin			
alprazolam - simvastatin			
alprazolam - triazolam			
atorvastatin - 1'-hydroxymidazolam			
atorvastatin - 14-hydroxyclarithromycin			
atorvastatin - 4-hydroxyalprazolam			
atorvastatin - 4-hydroxymidazolam			
atorvastatin - 4-hydroxytriazolam			
atorvastatin - 6'-exomethylene-lovastatin			
atorvastatin - 6'-exomethylene-simvastatin			
atorvastatin - 6'-hydroxy-simvastatin			
atorvastatin - 6'-hydroxymethyl-simvastatin			
atorvastatin - 6'beta-hydroxy-lovastatin			
atorvastatin - alpha-hydroxyalprazolam			
atorvastatin - beta-hydroxy-lovastatin			
atorvastatin - beta-hydroxy-simvastatin			
atorvastatin - desacetyldiltiazem			
atorvastatin - erythromycin ←	X		[43]
atorvastatin - fluconazole			
atorvastatin - fluvastatin			
atorvastatin - lovastatin			
atorvastatin - N-demethyldesacetyl-diltiazem			
atorvastatin - N-demethyldiltiazem			
atorvastatin - N-desmethylrosuvastatin			
atorvastatin - nefazodone ←	X		[44]
atorvastatin - ortho-hydroxy-atorvastatin			
atorvastatin - para-hydroxy-atorvastatin			
atorvastatin - pravastatin			
atorvastatin - rosuvastatin			
atorvastatin - simvastatin			

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drug/drug or drug/metabolite pair	DDI	Non-DDI	Source
clarithromycin - 1'-hydroxymidazolam			
clarithromycin - 14-hydroxyclarithromycin			
clarithromycin - 4-hydroxyalprazolam			
clarithromycin - 4-hydroxymidazolam			
clarithromycin - 4-hydroxytriazolam			
clarithromycin - 6'-exomethylene-lovastatin			
clarithromycin - 6'-exomethylene-simvastatin			
clarithromycin - 6'-hydroxy-simvastatin			
clarithromycin - 6'-hydroxymethyl-simvastatin			
clarithromycin - 6'beta-hydroxy-lovastatin			
clarithromycin - alpha-hydroxyalprazolam			
clarithromycin - atorvastatin →	X		[3], [27]
clarithromycin - beta-hydroxy-lovastatin			
clarithromycin - beta-hydroxy-simvastatin ‡			
clarithromycin - desacetyldiltiazem			
clarithromycin - erythromycin			
clarithromycin - fluconazole ←	X		[1]
clarithromycin - fluvastatin			
clarithromycin - lovastatin			
clarithromycin - N-demethyldesacetyl-diltiazem			
clarithromycin - N-demethyldiltiazem			
clarithromycin - N-desmethylrosuvastatin			
clarithromycin - nefazodone			
clarithromycin - ortho-hydroxy-atorvastatin			
clarithromycin - para-hydroxy-atorvastatin			
clarithromycin - pravastatin →	X		[27]
clarithromycin - rosuvastatin			
clarithromycin - simvastatin ‡			
diltiazem - 1'-hydroxymidazolam			
diltiazem - 14-hydroxyclarithromycin			
diltiazem - 4-hydroxyalprazolam			
diltiazem - 4-hydroxymidazolam			
diltiazem - 4-hydroxytriazolam			
diltiazem - 6'-exomethylene-lovastatin			
diltiazem - 6'-exomethylene-simvastatin			
diltiazem - 6'-hydroxy-simvastatin			
diltiazem - 6'-hydroxymethyl-simvastatin			
diltiazem - 6'beta-hydroxy-lovastatin			
diltiazem - alpha-hydroxyalprazolam			
diltiazem - alprazolam			

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drug/drug or drug/metabolite pair	DDI	Non-DDI	Source
diltiazem - atorvastatin			
diltiazem - beta-hydroxy-lovastatin →	X		[4]
diltiazem - beta-hydroxy-simvastatin			
diltiazem - clarithromycin			
diltiazem - desacetyldiltiazem			
diltiazem - erythromycin			
diltiazem - fluconazole			
diltiazem - fluvastatin			
diltiazem - itraconazole			
diltiazem - ketoconazole			
diltiazem - lovastatin →	X		[7]
diltiazem - midazolam →	X		[5]
diltiazem - N-demethyldesacetyl-diltiazem			
diltiazem - N-demethyldiltiazem			
diltiazem - N-desmethylrosuvastatin			
diltiazem - nefazodone			
diltiazem - ortho-hydroxy-atorvastatin			
diltiazem - para-hydroxy-atorvastatin			
diltiazem - pravastatin ↛		X	[7]
diltiazem - rosuvastatin			
diltiazem - simvastatin →	X		[36]
diltiazem - triazolam →	X		[46]
erythromycin - 1'-hydroxymidazolam			
erythromycin - 14-hydroxyclarithromycin			
erythromycin - 4-hydroxyalprazolam			
erythromycin - 4-hydroxymidazolam			
erythromycin - 4-hydroxytriazolam			
erythromycin - 6'-exomethylene-lovastatin			
erythromycin - 6'-exomethylene-simvastatin			
erythromycin - 6'-hydroxy-simvastatin			
erythromycin - 6'-hydroxymethyl-simvastatin			
erythromycin - 6'beta-hydroxy-lovastatin			
erythromycin - alpha-hydroxyalprazolam			
erythromycin - beta-hydroxy-lovastatin			
erythromycin - beta-hydroxy-simvastatin →	X		[30]
erythromycin - desacetyldiltiazem			
erythromycin - fluconazole			
erythromycin - fluvastatin			
erythromycin - lovastatin			
erythromycin - N-demethyldesacetyl-diltiazem			

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drug/drug or drug/metabolite pair	DDI	Non-DDI	Source
erythromycin - N-demethyldiltiazem			
erythromycin - N-desmethylrosuvastatin			
erythromycin - nefazodone			
erythromycin - ortho-hydroxy-atorvastatin			
erythromycin - para-hydroxy-atorvastatin			
erythromycin - pravastatin			
erythromycin - rosuvastatin ↛		X	[11]
erythromycin - simvastatin →	X		[30]
fluconazole - 1'-hydroxymidazolam → †	X		[2]
fluconazole - 14-hydroxyclarithromycin ↛		X	[1]
fluconazole - 4-hydroxyalprazolam			
fluconazole - 4-hydroxymidazolam			
fluconazole - 4-hydroxytriazolam			
fluconazole - 6'-exomethylene-lovastatin			
fluconazole - 6'-exomethylene-simvastatin			
fluconazole - 6'-hydroxy-simvastatin			
fluconazole - 6'-hydroxymethyl-simvastatin			
fluconazole - 6'beta-hydroxy-lovastatin			
fluconazole - alpha-hydroxyalprazolam			
fluconazole - beta-hydroxy-lovastatin			
fluconazole - beta-hydroxy-simvastatin			
fluconazole - desacetyldiltiazem			
fluconazole - fluvastatin →	X		[29]
fluconazole - lovastatin			
fluconazole - N-demethyldesacetyl-diltiazem			
fluconazole - N-demethyldiltiazem			
fluconazole - N-desmethylrosuvastatin			
fluconazole - nefazodone			
fluconazole - ortho-hydroxy-atorvastatin			
fluconazole - para-hydroxy-atorvastatin			
fluconazole - pravastatin ↛		X	[29]
fluconazole - rosuvastatin ↛		X	[12]
fluconazole - simvastatin			
fluvastatin - 1'-hydroxymidazolam			
fluvastatin - 14-hydroxyclarithromycin			
fluvastatin - 4-hydroxyalprazolam			
fluvastatin - 4-hydroxymidazolam			
fluvastatin - 4-hydroxytriazolam			
fluvastatin - 6'-exomethylene-lovastatin			
fluvastatin - 6'-exomethylene-simvastatin			

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drug/drug or drug/metabolite pair	DDI	Non-DDI	Source
fluvastatin - 6'-hydroxy-simvastatin			
fluvastatin - 6'-hydroxymethyl-simvastatin			
fluvastatin - 6'beta-hydroxy-lovastatin			
fluvastatin - alpha-hydroxyalprazolam			
fluvastatin - beta-hydroxy-lovastatin			
fluvastatin - beta-hydroxy-simvastatin			
fluvastatin - desacetyldiltiazem			
fluvastatin - N-demethyldesacetyl-diltiazem			
fluvastatin - N-demethyldiltiazem			
fluvastatin - N-desmethylrosuvastatin			
fluvastatin - ortho-hydroxy-atorvastatin			
fluvastatin - para-hydroxy-atorvastatin			
fluvastatin - rosuvastatin			
itraconazole - 1'-hydroxymidazolam			
itraconazole - 14-hydroxyclarithromycin			
itraconazole - 4-hydroxyalprazolam			
itraconazole - 4-hydroxymidazolam			
itraconazole - 4-hydroxytriazolam			
itraconazole - 6'-exomethylene-lovastatin			
itraconazole - 6'-exomethylene-simvastatin			
itraconazole - 6'-hydroxy-simvastatin			
itraconazole - 6'-hydroxymethyl-simvastatin			
itraconazole - 6'beta-hydroxy-lovastatin			
itraconazole - alpha-hydroxyalprazolam			
itraconazole - atorvastatin →	X		[34]
itraconazole - beta-hydroxy-lovastatin →	X		[31]
itraconazole - beta-hydroxy-simvastatin ‡			
itraconazole - clarithromycin			
itraconazole - desacetyldiltiazem			
itraconazole - erythromycin ←	X		[28]
itraconazole - fluvastatin ↛		X	[31]
itraconazole - ketoconazole			
itraconazole - lovastatin →	X		[31]
itraconazole - N-demethyldesacetyl-diltiazem			
itraconazole - N-demethyldiltiazem			
itraconazole - N-desmethylrosuvastatin			
itraconazole - nefazodone			
itraconazole - para-hydroxy-atorvastatin §			
itraconazole - ortho-hydroxy-atorvastatin →	X		[34]
itraconazole - pravastatin →	X		[34]

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drug/drug or drug/metabolite pair	DDI	Non-DDI	Source
itraconazole - rosuvastatin →	X		[13]
itraconazole - simvastatin ‡			
ketoconazole - 1'-hydroxymidazolam			
ketoconazole - 14-hydroxyclarithromycin			
ketoconazole - 4-hydroxyalprazolam			
ketoconazole - 4-hydroxymidazolam			
ketoconazole - 4-hydroxytriazolam			
ketoconazole - 6'-exomethylene-lovastatin			
ketoconazole - 6'-exomethylene-simvastatin			
ketoconazole - 6'-hydroxy-simvastatin			
ketoconazole - 6'-hydroxymethyl-simvastatin			
ketoconazole - 6'beta-hydroxy-lovastatin			
ketoconazole - alpha-hydroxyalprazolam			
ketoconazole - atorvastatin			
ketoconazole - beta-hydroxy-lovastatin			
ketoconazole - beta-hydroxy-simvastatin			
ketoconazole - clarithromycin			
ketoconazole - desacetyldiltiazem			
ketoconazole - erythromycin			
ketoconazole - fluconazole			
ketoconazole - fluvastatin			
ketoconazole - lovastatin			
ketoconazole - N-demethyldesacetyl-diltiazem			
ketoconazole - N-demethyldiltiazem			
ketoconazole - N-desmethylrosuvastatin			
ketoconazole - nefazodone			
ketoconazole - ortho-hydroxy-atorvastatin			
ketoconazole - para-hydroxy-atorvastatin			
ketoconazole - pravastatin			
ketoconazole - rosuvastatin			
ketoconazole - simvastatin →	X		[9]
lovastatin - 1'-hydroxymidazolam			
lovastatin - 14-hydroxyclarithromycin			
lovastatin - 4-hydroxyalprazolam			
lovastatin - 4-hydroxymidazolam			
lovastatin - 4-hydroxytriazolam			
lovastatin - 6'-exomethylene-lovastatin			
lovastatin - 6'-exomethylene-simvastatin			
lovastatin - 6'-hydroxy-simvastatin			
lovastatin - 6'-hydroxymethyl-simvastatin			

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drug/drug or drug/metabolite pair	DDI	Non-DDI	Source
lovastatin - 6'beta-hydroxy-lovastatin			
lovastatin - alpha-hydroxyalprazolam			
lovastatin - beta-hydroxy-lovastatin			
lovastatin - beta-hydroxy-simvastatin			
lovastatin - desacetyldiltiazem			
lovastatin - fluvastatin			
lovastatin - N-demethyldesacetyl-diltiazem			
lovastatin - N-demethyldiltiazem			
lovastatin - N-desmethylrosuvastatin			
lovastatin - ortho-hydroxy-atorvastatin			
lovastatin - para-hydroxy-atorvastatin			
lovastatin - pravastatin			
lovastatin - rosuvastatin			
midazolam - 1'-hydroxymidazolam			
midazolam - 14-hydroxyclarithromycin			
midazolam - 4-hydroxyalprazolam			
midazolam - 4-hydroxymidazolam			
midazolam - 4-hydroxytriazolam			
midazolam - 6'-exomethylene-lovastatin			
midazolam - 6'-exomethylene-simvastatin			
midazolam - 6'-hydroxy-simvastatin			
midazolam - 6'-hydroxymethyl-simvastatin			
midazolam - 6'beta-hydroxy-lovastatin			
midazolam - alpha-hydroxyalprazolam			
midazolam - atorvastatin ‡			
midazolam - beta-hydroxy-lovastatin			
midazolam - beta-hydroxy-simvastatin ‡			
midazolam - clarithromycin ←	X		[21], [17]
midazolam - desacetyldiltiazem §			
midazolam - erythromycin ←	X		[39]
midazolam - fluconazole ←	X		[38], [2]
midazolam - fluvastatin			
midazolam - itraconazole ←	X		[40]
midazolam - ketoconazole ←	X		[40]
midazolam - lovastatin			
midazolam - N-demethyldesacetyl-diltiazem			
midazolam - N-demethyldiltiazem			
midazolam - N-desmethylrosuvastatin			
midazolam - nefazodone ← ††	X		[32]
midazolam - ortho-hydroxy-atorvastatin			

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drug/drug or drug/metabolite pair	DDI	Non-DDI	Source
midazolam - para-hydroxy-atorvastatin			
midazolam - pravastatin			
midazolam - rosuvastatin			
midazolam - simvastatin ‡			
midazolam - triazolam			
nefazodone - 1'-hydroxymidazolam			
nefazodone - 14-hydroxyclarithromycin			
nefazodone - 4-hydroxyalprazolam → †	X		[20]
nefazodone - 4-hydroxymidazolam			
nefazodone - 4-hydroxytriazolam			
nefazodone - 6'-exomethylene-lovastatin			
nefazodone - 6'-exomethylene-simvastatin			
nefazodone - 6'-hydroxy-simvastatin			
nefazodone - 6'-hydroxymethyl-simvastatin			
nefazodone - 6'beta-hydroxy-lovastatin			
nefazodone - alpha-hydroxyalprazolam			
nefazodone - beta-hydroxy-lovastatin			
nefazodone - beta-hydroxy-simvastatin →	X		[44]
nefazodone - desacetyldiltiazem			
nefazodone - fluvastatin			
nefazodone - lovastatin			
nefazodone - N-demethyldesacetyl-diltiazem			
nefazodone - N-demethyldiltiazem			
nefazodone - N-desmethylrosuvastatin			
nefazodone - ortho-hydroxy-atorvastatin			
nefazodone - para-hydroxy-atorvastatin			
nefazodone - pravastatin ↛		X	[44]
nefazodone - rosuvastatin			
nefazodone - simvastatin →	X		[44]
pravastatin - 1'-hydroxymidazolam			
pravastatin - 14-hydroxyclarithromycin			
pravastatin - 4-hydroxyalprazolam			
pravastatin - 4-hydroxymidazolam			
pravastatin - 4-hydroxytriazolam			
pravastatin - 6'-exomethylene-lovastatin			
pravastatin - 6'-exomethylene-simvastatin			
pravastatin - 6'-hydroxy-simvastatin			
pravastatin - 6'-hydroxymethyl-simvastatin			
pravastatin - 6'beta-hydroxy-lovastatin			
pravastatin - alpha-hydroxyalprazolam			

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drug/drug or drug/metabolite pair	DDI	Non-DDI	Source
pravastatin - beta-hydroxy-lovastatin			
pravastatin - beta-hydroxy-simvastatin			
pravastatin - desacetyldiltiazem			
pravastatin - fluvastatin			
pravastatin - N-demethyldesacetyl-diltiazem			
pravastatin - N-demethyldiltiazem			
pravastatin - N-desmethylrosuvastatin			
pravastatin - ortho-hydroxy-atorvastatin			
pravastatin - para-hydroxy-atorvastatin			
pravastatin - rosuvastatin			
rosuvastatin - 1'-hydroxymidazolam			
rosuvastatin - 14-hydroxyclarithromycin			
rosuvastatin - 4-hydroxyalprazolam			
rosuvastatin - 4-hydroxymidazolam			
rosuvastatin - 4-hydroxytriazolam			
rosuvastatin - 6'-exomethylene-lovastatin			
rosuvastatin - 6'-exomethylene-simvastatin			
rosuvastatin - 6'-hydroxy-simvastatin			
rosuvastatin - 6'-hydroxymethyl-simvastatin			
rosuvastatin - 6'beta-hydroxy-lovastatin			
rosuvastatin - alpha-hydroxyalprazolam			
rosuvastatin - beta-hydroxy-lovastatin			
rosuvastatin - beta-hydroxy-simvastatin			
rosuvastatin - desacetyldiltiazem			
rosuvastatin - N-demethyldesacetyl-diltiazem			
rosuvastatin - N-demethyldiltiazem			
rosuvastatin - N-desmethylrosuvastatin			
rosuvastatin - ortho-hydroxy-atorvastatin			
rosuvastatin - para-hydroxy-atorvastatin			
simvastatin - 1'-hydroxymidazolam			
simvastatin - 14-hydroxyclarithromycin			
simvastatin - 4-hydroxyalprazolam			
simvastatin - 4-hydroxymidazolam			
simvastatin - 4-hydroxytriazolam			
simvastatin - 6'-exomethylene-lovastatin			
simvastatin - 6'-exomethylene-simvastatin			
simvastatin - 6'-hydroxy-simvastatin			
simvastatin - 6'-hydroxymethyl-simvastatin			
simvastatin - 6'beta-hydroxy-lovastatin			
simvastatin - alpha-hydroxyalprazolam			

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drug/drug or drug/metabolite pair	DDI	Non-DDI	Source
simvastatin - beta-hydroxy-lovastatin			
simvastatin - beta-hydroxy-simvastatin			
simvastatin - desacetyldiltiazem			
simvastatin - fluvastatin			
simvastatin - lovastatin			
simvastatin - N-demethyldesacetyl-diltiazem			
simvastatin - N-demethyldiltiazem			
simvastatin - N-desmethylrosuvastatin			
simvastatin - ortho-hydroxy-atorvastatin			
simvastatin - para-hydroxy-atorvastatin			
simvastatin - pravastatin			
simvastatin - rosuvastatin			
triazolam - 1'-hydroxymidazolam			
triazolam - 14-hydroxyclarithromycin			
triazolam - 4-hydroxyalprazolam			
triazolam - 4-hydroxymidazolam			
triazolam - 4-hydroxytriazolam			
triazolam - 6'-exomethylene-lovastatin			
triazolam - 6'-exomethylene-simvastatin			
triazolam - 6'-hydroxy-simvastatin			
triazolam - 6'-hydroxymethyl-simvastatin			
triazolam - 6'beta-hydroxy-lovastatin			
triazolam - alpha-hydroxyalprazolam			
triazolam - atorvastatin			
triazolam - beta-hydroxy-lovastatin			
triazolam - beta-hydroxy-simvastatin			
triazolam - clarithromycin ←	X		[18]
triazolam - desacetyldiltiazem			
triazolam - erythromycin ←	X		[41]
triazolam - fluconazole ←	X		[47]
triazolam - fluvastatin			
triazolam - itraconazole ←	X		[45], [37]
triazolam - ketoconazole ←	X		[45], [48]
triazolam - lovastatin			
triazolam - N-demethyldesacetyl-diltiazem			
triazolam - N-demethyldiltiazem			
triazolam - N-desmethylrosuvastatin			
triazolam - nefazodone ←	X		[6]
triazolam - ortho-hydroxy-atorvastatin			
triazolam - para-hydroxy-atorvastatin			

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drug/drug or drug/metabolite pair	DDI	Non-DDI	Source
triazolam - pravastatin			
triazolam - rosuvastatin			
triazolam - simvastatin			
beta-hydroxy-simvastatin - 6'-hydroxymethyl-simvastatin			
beta-hydroxy-simvastatin - N-demethyldiltiazem			
beta-hydroxy-simvastatin - 14-hydroxyclarithromycin			
beta-hydroxy-simvastatin - 6'beta-hydroxy-lovastatin			
beta-hydroxy-simvastatin - para-hydroxy-atorvastatin			
beta-hydroxy-simvastatin - desacetyldiltiazem			
beta-hydroxy-simvastatin - 6'-hydroxy-simvastatin			
beta-hydroxy-simvastatin - 4-hydroxytriazolam			
beta-hydroxy-simvastatin - ortho-hydroxy-atorvastatin			
beta-hydroxy-simvastatin - 4-hydroxymidazolam			
beta-hydroxy-simvastatin - 6'-exomethylene-simvastatin			
beta-hydroxy-simvastatin - 6'-exomethylene-lovastatin			
beta-hydroxy-simvastatin - N-demethyldesacetyl-diltiazem			
beta-hydroxy-simvastatin - alpha-hydroxyalprazolam			
beta-hydroxy-simvastatin - 4-hydroxyalprazolam			
beta-hydroxy-simvastatin - beta-hydroxy-lovastatin			
beta-hydroxy-simvastatin - N-desmethylrosuvastatin			
beta-hydroxy-simvastatin - 1'-hydroxymidazolam			
beta-hydroxy-lovastatin - 6'-hydroxymethyl-simvastatin			
beta-hydroxy-lovastatin - N-demethyldiltiazem			
beta-hydroxy-lovastatin - 14-hydroxyclarithromycin			
beta-hydroxy-lovastatin - 6'beta-hydroxy-lovastatin			
beta-hydroxy-lovastatin - para-hydroxy-atorvastatin			
beta-hydroxy-lovastatin - desacetyldiltiazem			
beta-hydroxy-lovastatin - 6'-hydroxy-simvastatin			
beta-hydroxy-lovastatin - 4-hydroxytriazolam			
beta-hydroxy-lovastatin - ortho-hydroxy-atorvastatin			
beta-hydroxy-lovastatin - 4-hydroxymidazolam			
beta-hydroxy-lovastatin - 6'-exomethylene-simvastatin			
beta-hydroxy-lovastatin - 6'-exomethylene-lovastatin			
beta-hydroxy-lovastatin - N-demethyldesacetyl-diltiazem			
beta-hydroxy-lovastatin - alpha-hydroxyalprazolam			
beta-hydroxy-lovastatin - 4-hydroxyalprazolam			
beta-hydroxy-lovastatin - N-desmethylrosuvastatin			
beta-hydroxy-lovastatin - 1'-hydroxymidazolam			
6'-hydroxy-simvastatin - 6'-hydroxymethyl-simvastatin			
6'-hydroxy-simvastatin - N-demethyldiltiazem			

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drug/drug or drug/metabolite pair	DDI	Non-DDI	Source
6'-hydroxy-simvastatin - 14-hydroxyclarithromycin			
6'-hydroxy-simvastatin - 6'beta-hydroxy-lovastatin			
6'-hydroxy-simvastatin - para-hydroxy-atorvastatin			
6'-hydroxy-simvastatin - desacetyldiltiazem			
6'-hydroxy-simvastatin - 4-hydroxytriazolam			
6'-hydroxy-simvastatin - ortho-hydroxy-atorvastatin			
6'-hydroxy-simvastatin - 4-hydroxymidazolam			
6'-hydroxy-simvastatin - 6'-exomethylene-simvastatin			
6'-hydroxy-simvastatin - 6'-exomethylene-lovastatin			
6'-hydroxy-simvastatin - N-demethyldesacetyl-diltiazem			
6'-hydroxy-simvastatin - alpha-hydroxyalprazolam			
6'-hydroxy-simvastatin - 4-hydroxyalprazolam			
6'-hydroxy-simvastatin - N-desmethylrosuvastatin			
6'-hydroxy-simvastatin - 1'-hydroxymidazolam			
6'-hydroxymethyl-simvastatin - N-demethyldiltiazem			
6'-hydroxymethyl-simvastatin - 14-hydroxyclarithromycin			
6'-hydroxymethyl-simvastatin - 6'beta-hydroxy-lovastatin			
6'-hydroxymethyl-simvastatin - para-hydroxy-atorvastatin			
6'-hydroxymethyl-simvastatin - desacetyldiltiazem			
6'-hydroxymethyl-simvastatin - 4-hydroxytriazolam			
6'-hydroxymethyl-simvastatin - ortho-hydroxy-atorvastatin			
6'-hydroxymethyl-simvastatin - 4-hydroxymidazolam			
6'-hydroxymethyl-simvastatin - 6'-exomethylene-simvastatin			
6'-hydroxymethyl-simvastatin - 6'-exomethylene-lovastatin			
6'-hydroxymethyl-simvastatin - N-demethyldesacetyl-diltiazem			
6'-hydroxymethyl-simvastatin - alpha-hydroxyalprazolam			
6'-hydroxymethyl-simvastatin - 4-hydroxyalprazolam			
6'-hydroxymethyl-simvastatin - N-desmethylrosuvastatin			
6'-hydroxymethyl-simvastatin - 1'-hydroxymidazolam			
6'-exomethylene-simvastatin - N-demethyldiltiazem			
6'-exomethylene-simvastatin - 14-hydroxyclarithromycin			
6'-exomethylene-simvastatin - 6'beta-hydroxy-lovastatin			
6'-exomethylene-simvastatin - para-hydroxy-atorvastatin			
6'-exomethylene-simvastatin - desacetyldiltiazem			
6'-exomethylene-simvastatin - 4-hydroxytriazolam			
6'-exomethylene-simvastatin - ortho-hydroxy-atorvastatin			
6'-exomethylene-simvastatin - 4-hydroxymidazolam			
6'-exomethylene-simvastatin - 6'-exomethylene-lovastatin			
6'-exomethylene-simvastatin - N-demethyldesacetyl-diltiazem			
6'-exomethylene-simvastatin - alpha-hydroxyalprazolam			

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drug/drug or drug/metabolite pair	DDI	Non-DDI	Source
6'-exomethylene-simvastatin - 4-hydroxyalprazolam			
6'-exomethylene-simvastatin - N-desmethylrosuvastatin			
6'-exomethylene-simvastatin - 1'-hydroxymidazolam			
1'-hydroxymidazolam - N-demethyldiltiazem			
1'-hydroxymidazolam - 14-hydroxyclarithromycin			
1'-hydroxymidazolam - 6'beta-hydroxy-lovastatin			
1'-hydroxymidazolam - para-hydroxy-atorvastatin			
1'-hydroxymidazolam - desacetyldiltiazem			
1'-hydroxymidazolam - 4-hydroxytriazolam			
1'-hydroxymidazolam - ortho-hydroxy-atorvastatin			
1'-hydroxymidazolam - 4-hydroxymidazolam			
1'-hydroxymidazolam - 6'-exomethylene-lovastatin			
1'-hydroxymidazolam - N-demethyldesacetyl-diltiazem			
1'-hydroxymidazolam - alpha-hydroxyalprazolam			
1'-hydroxymidazolam - 4-hydroxyalprazolam			
1'-hydroxymidazolam - N-desmethylrosuvastatin			
4-hydroxymidazolam - N-demethyldiltiazem			
4-hydroxymidazolam - 14-hydroxyclarithromycin			
4-hydroxymidazolam - 6'beta-hydroxy-lovastatin			
4-hydroxymidazolam - para-hydroxy-atorvastatin			
4-hydroxymidazolam - desacetyldiltiazem			
4-hydroxymidazolam - 4-hydroxytriazolam			
4-hydroxymidazolam - ortho-hydroxy-atorvastatin			
4-hydroxymidazolam - 6'-exomethylene-lovastatin			
4-hydroxymidazolam - N-demethyldesacetyl-diltiazem			
4-hydroxymidazolam - alpha-hydroxyalprazolam			
4-hydroxymidazolam - 4-hydroxyalprazolam			
4-hydroxymidazolam - N-desmethylrosuvastatin			
4-hydroxytriazolam - N-demethyldiltiazem			
4-hydroxytriazolam - 14-hydroxyclarithromycin			
4-hydroxytriazolam - 6'beta-hydroxy-lovastatin			
4-hydroxytriazolam - para-hydroxy-atorvastatin			
4-hydroxytriazolam - desacetyldiltiazem			
4-hydroxytriazolam - ortho-hydroxy-atorvastatin			
4-hydroxytriazolam - 6'-exomethylene-lovastatin			
4-hydroxytriazolam - N-demethyldesacetyl-diltiazem			
4-hydroxytriazolam - alpha-hydroxyalprazolam			
4-hydroxytriazolam - 4-hydroxyalprazolam			
4-hydroxytriazolam - N-desmethylrosuvastatin			
6'beta-hydroxy-lovastatin - N-demethyldiltiazem			

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drug/drug or drug/metabolite pair	DDI	Non-DDI	Source
6'beta-hydroxy-lovastatin - 14-hydroxyclarithromycin			
6'beta-hydroxy-lovastatin - para-hydroxy-atorvastatin			
6'beta-hydroxy-lovastatin - desacetyldiltiazem			
6'beta-hydroxy-lovastatin - ortho-hydroxy-atorvastatin			
6'beta-hydroxy-lovastatin - 6'-exomethylene-lovastatin			
6'beta-hydroxy-lovastatin - N-demethyldesacetyl-diltiazem			
6'beta-hydroxy-lovastatin - alpha-hydroxyalprazolam			
6'beta-hydroxy-lovastatin - 4-hydroxyalprazolam			
6'beta-hydroxy-lovastatin - N-desmethylrosuvastatin			
6'-exomethylene-lovastatin - N-demethyldiltiazem			
6'-exomethylene-lovastatin - 14-hydroxyclarithromycin			
6'-exomethylene-lovastatin - para-hydroxy-atorvastatin			
6'-exomethylene-lovastatin - desacetyldiltiazem			
6'-exomethylene-lovastatin - ortho-hydroxy-atorvastatin			
6'-exomethylene-lovastatin - N-demethyldesacetyl-diltiazem			
6'-exomethylene-lovastatin - alpha-hydroxyalprazolam			
6'-exomethylene-lovastatin - 4-hydroxyalprazolam			
6'-exomethylene-lovastatin - N-desmethylrosuvastatin			
4-hydroxyalprazolam - N-demethyldiltiazem			
4-hydroxyalprazolam - 14-hydroxyclarithromycin			
4-hydroxyalprazolam - para-hydroxy-atorvastatin			
4-hydroxyalprazolam - desacetyldiltiazem			
4-hydroxyalprazolam - ortho-hydroxy-atorvastatin			
4-hydroxyalprazolam - N-demethyldesacetyl-diltiazem			
4-hydroxyalprazolam - alpha-hydroxyalprazolam			
4-hydroxyalprazolam - N-desmethylrosuvastatin			
alpha-hydroxyalprazolam - N-demethyldiltiazem			
alpha-hydroxyalprazolam - 14-hydroxyclarithromycin			
alpha-hydroxyalprazolam - para-hydroxy-atorvastatin			
alpha-hydroxyalprazolam - desacetyldiltiazem			
alpha-hydroxyalprazolam - ortho-hydroxy-atorvastatin			
alpha-hydroxyalprazolam - N-demethyldesacetyl-diltiazem			
alpha-hydroxyalprazolam - N-desmethylrosuvastatin			
14-hydroxyclarithromycin - N-demethyldiltiazem			
14-hydroxyclarithromycin - para-hydroxy-atorvastatin			
14-hydroxyclarithromycin - desacetyldiltiazem			
14-hydroxyclarithromycin - ortho-hydroxy-atorvastatin			
14-hydroxyclarithromycin - N-demethyldesacetyl-diltiazem			
14-hydroxyclarithromycin - N-desmethylrosuvastatin			
desacetyldiltiazem - N-demethyldiltiazem			

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drug/drug or drug/metabolite pair	DDI	Non-DDI	Source
desacetyldiltiazem - para-hydroxy-atorvastatin			
desacetyldiltiazem - ortho-hydroxy-atorvastatin			
desacetyldiltiazem - N-demethyldesacetyl-diltiazem			
desacetyldiltiazem - N-desmethylrosuvastatin			
N-demethyldesacetyl-diltiazem - N-demethyldiltiazem			
N-demethyldesacetyl-diltiazem - para-hydroxy-atorvastatin			
N-demethyldesacetyl-diltiazem - ortho-hydroxy-atorvastatin			
N-demethyldesacetyl-diltiazem - N-desmethylrosuvastatin			
N-demethyldiltiazem - para-hydroxy-atorvastatin			
N-demethyldiltiazem - ortho-hydroxy-atorvastatin			
N-demethyldiltiazem - N-desmethylrosuvastatin			
ortho-hydroxy-atorvastatin - para-hydroxy-atorvastatin			
ortho-hydroxy-atorvastatin - N-desmethylrosuvastatin			
para-hydroxy-atorvastatin - N-desmethylrosuvastatin			

D Generic and Trade-names for Drug Products Containing Active Pharmaceutical Ingredients in the DIKB

Below is a list of names for drug products containing active pharmaceutical ingredients in the DIKB. We compiled this list from `drugs@fda` [16], the FDA's "Orange Book" [23], and/or RxNorm [24]. Each drug product is 1) oral or injectable, 2) *not* a combined therapy (contained one active ingredient), and 3) present, as of Septemter 2007, in DRUGDEX Tradenames®.

```
'alprazolam':['ALPRAZOLAM', 'ALPRAZOLAM INTENSOL', 'NIRAVAM', 'XANAX', 'XANAX XR'],

'atorvastatin':['ATORVASTATIN','CADUET','LIPITOR'],

'clarithromycin':['CLARITHROMYCIN', 'CLARITHROMYCIN EXTENDED RELEASE',
   'BIAXIN', 'BIAXIN XL'],

'diltiazem':['DILTIAZEM', 'DILTIAZEM HYDROCHLORIDE', 'CARDIZEM','CARDIZEM CD',
  'CARDIZEM LA', 'CARDIZEM LYO-JECT', 'CARDIZEM MONOVIAL', 'CARDIZEM SR',
  'CARTIA', 'CARTIA XT', 'DILACOR XR', 'DILT', 'DILT-CD', 'DILT-XR', 'DILTIA XT',
  'DILTZAC',  'TAZTIA', 'TAZTIA XT', 'TECZEM', 'TIAMATE', 'TIAZAC'],

'erythromycin':['ERYTHROMYCIN',  'AKNEMYCIN', 'BRISTAMYCIN', 'E-SOLVE-2',
  'E-BASE', 'E-MYCIN', 'E-MYCIN E', 'E-SOLVE 2', 'E.E.S', 'E.E.S. 400 FILMTAB',
  'E.E.S. GRANULES', 'E.E.S.-200', 'E.E.S.-400', 'EMGEL', 'ERY-SOL', 'ERY-TAB',
  'ERYPED', 'ERYC', 'ERYC 125', 'ERYC SPRINKLES', 'ERYMAX', 'ERYPAR', 'ERYPED',
  'ERYTHROCIN', 'ERYTHROCIN STEARATE', 'ERYTHROMYCIN ESTOLATE ', 'ERYTHROMYCIN
   ETHYLSUCCINATE', 'ERYTHROMYCIN LACTOBIONATE', 'ERYTHROMYCIN STEARATE', 'ETHRIL
   250', 'ETHRIL 500', 'ERYZOLE', 'ILOSONE', 'ILOTYCIN', 'PCE', 'PCE BRAND OF
   ERYTHROMYCIN', 'PEDIAMYCIN', 'PEDIAMYCIN 400', 'ROBIMYCIN', 'ROMYCIN',
   'WYAMYCIN E', 'WYAMYCIN S'],

fluconazole':['FLUCONAZOLE', 'DIFLUCAN', 'DIFLUCAN IN DEXTROSE 5% IN PLASTIC
   CONTAINER', 'DIFLUCAN IN SODIUM CHLORIDE 0.9%', 'DIFLUCAN IN SODIUM CHLORIDE
   0.9% IN PLASTIC CONTAINER', 'FLUCONAZALE', 'FLUCONAZOLE IN DEXTROSE 5% IN
   PLASTIC CONTAINER', 'FLUCONAZOLE IN SODIUM CHLORIDE 0.9%', 'FLUCONAZOLE IN
   SODIUM CHLORIDE 0.9% IN PLASTIC CONTAINER'],

'itraconazole':['ITRACONAZOLE','SPORANOX','SPORANOX-PULSE'],
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'ketoconazole':['KETOCONAZOLE'],

'lovastatin':['LOVASTATIN', 'ADVICOR', 'ALTOPREV', 'MEVACOR'],

'midazolam':['MIDAZOLAM', 'MIDAZOLAM HYDROCHLORIDE', 'MIDAZOLAM HYDROCHLORIDE
   PRESERVATIVE FREE', 'VERSED'],

'pravastatin':['PRAVASTATIN', 'PRAVASTATIN SODIUM', 'PRAVACHOL'],

'rosuvastatin':['ROSUVASTATIN', 'CRESTOR'],

'simvastatin':['SIMVASTATIN', 'ZOCOR'],

'triazolam':['TRIAZOLAM', 'HALCION'],

'nefazodone':['NEFAZODONE', 'NEFAZODONE HYDROCHLORIDE', 'SERZONE']
```

Below is the pharmacologic actions specified in the 2007 Medical Subject Headings (MeSH) controlled vocabulary [10] for each drug products containing an active pharmaceutical ingredient present in the DIKB.

```
DRUGS = {'alprazolam':['ANTI-ANXIETY AGENTS', 'GABA MODULATORS', 'HYPNOTICS AND SEDATIVES'],
         'atorvastatin':['ANTICHOLESTEREMIC AGENTS','HYDROXYMETHYLGLUTARYL-COA REDUCTASE INHIBITORS'],
         'clarithromycin':['ANTI-BACTERIAL AGENTS', 'PROTEIN SYNTHESIS INHIBITORS',
                           'ERYTHROMYCIN/ANALOGS & DERIVATIVES'],
         'diltiazem':['ANTIHYPERTENSIVE AGENTS', 'CALCIUM CHANNEL BLOCKERS', 'CARDIOVASCULAR AGENTS',
                      'VASODILATOR AGENTS', 'ANISOLES', 'BENZAZEPINES', 'DIMETHYLAMINES'],
         'erythromycin':['ANTI-BACTERIAL AGENTS', 'GASTROINTESTINAL AGENTS', 'PROTEIN SYNTHESIS INHIBITORS'],
         'fluconazole':['ANTIFUNGAL AGENTS', 'TRIAZOLES'],
         'itraconazole':['ANTIFUNGAL AGENTS', 'ANTIPROTOZOAL AGENTS', 'KETOCONAZOLE/ANALOGS & DERIVATIVES'],
         'ketoconazole':['KETOCONAZOLE',  'ANTIFUNGAL AGENTS', 'IMIDAZOLES', 'PIPERAZINES'],
         'lovastatin':['ANTICHOLESTEREMIC AGENTS', 'HYDROXYMETHYLGLUTARYL-COA REDUCTASE INHIBITORS',
                       'HYDROXYMETHYLGLUTARYL COA REDUCTASES/ANTAGONISTS & INHIBITORS', 'NAPHTHALENES'],
         'midazolam':['ADJUVANTS, ANESTHESIA', 'ANESTHETICS, INTRAVENOUS', 'ANTI-ANXIETY AGENTS',
                      'GABA MODULATORS', 'HYPNOTICS AND SEDATIVES', 'AZEPINES', 'BENZODIAZEPINES'],
         'pravastatin':['ANTICHOLESTEREMIC AGENTS', 'HYDROXYMETHYLGLUTARYL-COA REDUCTASE INHIBITORS'],
```

```
'rosuvastatin':['HYDROXYMETHYLGLUTARYL-COA REDUCTASE INHIBITORS'],
'simvastatin':['ANTICHOLESTEREMIC AGENTS', 'HYDROXYMETHYLGLUTARYL-COA REDUCTASE INHIBITORS',
               'ANTILIPEMIC AGENTS', 'LOVASTATIN/ANALOGS & DERIVATIVES', 'NAPHTHALENES'],
'fluvastatin':['ANTICHOLESTEREMIC AGENTS', 'HYDROXYMETHYLGLUTARYL-COA REDUCTASE INHIBITORS'],
'triazolam':['ADJUVANTS, ANESTHESIA',  'ANTI-ANXIETY AGENTS', 'GABA MODULATORS', 'BENZAZEPINES',
             'BENZODIAZEPINES', 'TRIAZOLES', 'BENZODIAZEPINE TRANQUILIZERS'],
'nefazodone':['ANTIDEPRESSIVE AGENTS, SECOND-GENERATION']
}
```

E The DIKB's Rule-based Model of DDIs Occurring by Metabolite Inhibition

The listing starting on the next page is the complete set of rules that comprise the DIKB's model of DDIs occurring by metabolite inhibition at the time of this writing. Uppercase words within rule predicates represent assertion types with a defined semantics. For example, `1-is-an-IN-VITRO-SELECTIVE-INHIBITOR-of-2` contains the uppercase words `IN-VITRO-SELECTIVE-INHIBITOR` an assertion type defined in Appendix F.

E.1 Rules that Model Metabolic Inhibition

```
;; a necessary condition for being an 'in vitro
;; selective inhibitor' is that the agent is also
;; an inhibitor
(rule
 ((:IN (1-is-an-IN-VIVO-SELECTIVE-INHIBITOR-of-2 ?x ?y)))
 (rassert!
  (1-INHIBITS-2 ?x ?y)
  (nil
   (1-is-an-IN-VIVO-SELECTIVE-INHIBITOR-of-2 ?x ?y)
   )))

   ;; a necessary condition of some active ingredient
   ;; or compound having a primary total clearance
   ;; enzyme is that it is a substrate of that enzyme
   (rule
    ((:IN (primary-total-clearance-enzyme-of-1-is-2 ?x ?y)))
    (rassert!
     (1-is-substrate-of-2 ?x ?y)
     (nil
      (primary-total-clearance-enzyme-of-1-is-2 ?x ?y)
      )))
   ;; a necessary condition of some active ingredient
   ;; or compound having a primary total clearance
   ;; enzyme is that it is primarily cleared by metabolism
   (rule
   ((:IN (primary-total-clearance-enzyme-of-1-is-2 ?x ?y)))
    (rassert!
     (primary-total-clearance-mechanism-of-1-is-2 ?x 'METABOLIC-CLEARANCE)
      (nil
       (primary-total-clearance-enzyme-of-1-is-2 ?x ?y)
      )))
```

```
;; a rule that makes it a contradiction for an active ingredient
;; or compound to both permanently and not permanently deactivate the catalytic
;; function of an enzyme
(rule
 ((:IN
   (1-PERMANENTLY-DEACTIVATES-CATALYTIC-FUNCTION-of-2 ?drug1 ?enzyme))
  (:IN
   (1-DOES-NOT-PERMANENTLY-DEACTIVATES-CATALYTIC-FUNCTION-of-2
        ?drug1 ?enzyme)))
 (contradiction
   (eval (quotize (list
    '1-DOES-NOT-PERMANENTLY-DEACTIVATES-CATALYTIC-FUNCTION-of-2
        ?drug1 ?enzyme)))))

;; a rule for establishing that an active ingredient or metabolite
;; *does* inhibit an enzyme based on in vitro evidence
(rule
 ((:IN (INHIBITION-CONSTANT-of-1-for-2-is-3 ?x ?y ?k_i))
  (:IN
    (1-DOES-NOT-PERMANENTLY-DEACTIVATES-CATALYTIC-FUNCTION-of-2 ?x ?y))
  (:IN (MAXIMUM-IN-VIVO-CONCENTRATION-of-1-is-2 ?x ?c_max)
       :TEST (> (float (/ ?c_max ?k_i )) .1)))
 (rassert! (1-INHIBITS-2 ?x ?y)
           (nil
            ;;justifications
            (INHIBITION-CONSTANT-of-1-for-2-is-3 ?x ?y ?k_i)
            (1-DOES-NOT-PERMANENTLY-DEACTIVATES-CATALYTIC-FUNCTION-of-2
                                ?x ?y)
            (MAXIMUM-IN-VIVO-CONCENTRATION-of-1-is-2 ?x ?c_max)
            (accept-in-vitro-based-enzyme-modulation-assertions)
            )))
```

```
;; a rule for when a metabolic transformation is
;; inhibited by inhibition of a *known*
;; pathway. NOTE: This rule could explicitly ignore
;; inhibition a metabolite's own production itself
;; if a test were added to one of the antecedents:
;; :TEST (not (equal ?q ?y))
(rule
 ((:IN (1-has-metabolite-2-via-3 ?x ?y ?z))
  (:IN (1-INHIBITS-2 ?q ?z)))
 (rassert!
  (1-inhibits-transformation-of-2-to-3-via-4 ?q ?x ?y ?z)
  (nil
   (1-has-metabolite-2-via-3 ?x ?y ?z)
   (1-INHIBITS-2 ?q ?z)
   )))

;; a rule for when an active ingredient or metabolite, ?x, will
;; not inhibit the metabolic clearance  of another drug, ?z,
;; because ?x does not inhibit enzyme ?y's ability to catalyze
;; drug ?z
(rule
 ((:IN (1-DOES-NOT-INHIBIT-2 ?x ?y))
  (:IN (1-is-SUBSTRATE-OF-2 ?z ?y)))
 (rassert!
  (1-does-not-inhibit-the-metabolic-clearance-of-2-via-3 ?x ?z ?y)
  (nil
   (1-DOES-NOT-INHIBIT-2 ?x ?y)
   (1-is-SUBSTRATE-OF-2 ?z ?y)
   )))
```

```
;; a rule for when an active ingredient or metabolite, ?x, will
;; not inhibit the metabolic clearance  of another drug, ?z,
;; because ?z is not a substrate of enzyme ?y
(rule
 ((:IN (1-inhibits-2 ?x ?y))
  (:IN (1-is-not-a-substrate-of-2 ?z ?y)))
 (rassert!
  (1-does-not-inhibit-the-metabolic-clearance-of-2-via-3 ?x ?z ?y)
  (nil
   (1-inhibits-2 ?x ?y)
   (1-is-not-a-substrate-of-2 ?z ?y)
   )))

;; a rule for establishing that an active ingredient or metabolite
;; *does not* inhibit an enzyme based on in vitro evidence
(rule
 ((:IN (INHIBITION-CONSTANT-of-1-for-2-is-3 ?x ?y ?k_i))
  (:IN (1-DOES-NOT-PERMANENTLY-DEACTIVATES-CATALYTIC-FUNCTION-of-2 ?x ?y))
  (:IN (MAXIMUM-IN-VIVO-CONCENTRATION-of-1-is-2 ?x ?c_max)
       :TEST (<= (float (/ ?c_max ?k_i )) .1)))
 (rassert! (1-DOES-NOT-INHIBIT-2 ?x ?y)
           (nil
            ;;justifications
            (INHIBITION-CONSTANT-of-1-for-2-is-3 ?x ?y ?k_i)
            (1-DOES-NOT-PERMANENTLY-DEACTIVATES-CATALYTIC-FUNCTION-of-2 ?x ?y)
            (MAXIMUM-IN-VIVO-CONCENTRATION-of-1-is-2 ?x ?c_max)
            (accept-in-vitro-based-enzyme-modulation-assertions)
            )))
```

```
;; a rule for that makes it a contradiction for an active ingredient
;; or metabolite to both inhibit and not inhibit the catalytic
;; function of an enzyme
(rule
 ((:IN (1-INHIBITS-2 ?x ?y))
  (:IN (1-DOES-NOT-INHIBIT-2 ?x ?y)))
 (contradiction
  (eval (quotize (list
      '1-DOES-NOT-INHIBIT-2 ?drug1 ?enzyme)))))

;; a rule for that makes it a contradiction for an active ingredient
;; or compound to be  and *not* be a substrate of an enzyme
(rule
 ((:IN (1-is-substrate-of-2 ?drug ?enzyme))
  (:IN (1-is-not-substrate-of-2 ?drug ?enzyme)))
 (contradiction
  (eval (quotize (list
                   '1-is-not-substrate-of-2 ?drug ?enzyme)))))
```

```
;; Some, possibly negligible, inhibition of
;; metabolic clearance of active ingredient or
;; metabolite ?z by active ingredient or metabolite
;; ?x due to ?x's inhibition of enzyme ?y's ability
;; to catalyze ?z. NOTE: this test ignores cases
;; where a drug INHIBITS itself
(rule
 ((:IN (1-INHIBITS-2 ?x ?y))
  (:IN (1-is-SUBSTRATE-OF-2 ?z ?y)
       :TEST (not (equal ?x ?z))))
 (rassert!
  (1-INHIBITS-METABOLIC-CLEARANCE-of-2-via-3 ?x ?z ?y)
  (nil
   (1-INHIBITS-2 ?x ?y)
   (1-is-SUBSTRATE-OF-2 ?z ?y)
   )))
```

```
;; A more significant inhibition of metabolic clearance
;; that should lead to a greater *minimum* increase in AUC
;; than the 1-INHIBITS-METABOLIC-CLEARANCE-of-2-via-3 assertion captures.
;; This models the effect of inhibiting an enzyme that is responsible
;; for .25 of a drug's total clearance by requiring inhibition of an enzyme
;; responsible for at least .50 of a drug's *metabolic* clearance when that
;; form of clearance is responsible for at least .50 of the drug's
;; *total* clearance
(rule
 ((:IN
   (1-inhibits-metabolic-clearance-of-2-via-3 ?x ?z ?y)
   :TEST (not (equal ?x ?z)))
  (:IN
   (PRIMARY-TOTAL-CLEARANCE-MECHANISM-of-1-is-2 ?z
                                                'METABOLIC-CLEARANCE))
  (:IN
   (PRIMARY-METABOLIC-CLEARANCE-ENZYME-of-1-is-2 ?z ?y)))
 (rassert!
  (1-inhibits-3-the-primary-metabolic-enzyme-of-2 ?x ?z ?y)
  (nil
   ;;justifications
   (1-inhibits-metabolic-clearance-of-2-via-3 ?x ?z ?y)
   (PRIMARY-TOTAL-CLEARANCE-MECHANISM-of-1-is-2 ?z
                                                'METABOLIC-CLEARANCE)
   (PRIMARY-METABOLIC-CLEARANCE-ENZYME-of-1-is-2 ?z ?y)
   )))
```

```
;; This rule models inhibition of metabolic clearance that should lead to
;; a greater *minimum* increase in AUC than the
;; 1-INHIBITS-3-the-primary-metabolic-enzyme-of-2 assertion captures.
;; If one enzyme is responsible for at least .50  of the
;; metabolic clearance of a drug and another drug fully INHIBITS that enzyme
;; then, one would expect at least at least a .50 decrease in clearance and,
;; subsequently, at least a 2-fold increase in AUC.
(rule
 ((:IN
   (1-inhibits-metabolic-clearance-of-2-via-3 ?x ?z ?y)
   :TEST (not (equal ?x ?z)))
  (:IN
   (PRIMARY-TOTAL-CLEARANCE-ENZYME-of-1-is-2 ?z ?y)))
 (rassert!
  (1-inhibits-3-the-primary-total-clearance-enz-of-2 ?x ?z ?y)
  (nil
   ;;justifications
   (1-inhibits-metabolic-clearance-of-2-via-3 ?x ?z ?y)
   (PRIMARY-TOTAL-CLEARANCE-ENZYME-of-1-is-2 ?z ?y)
   )))
```

```
;; This rule models inhibition of metabolic clearance that should lead to
;; a greater *maximum* increase in AUC than the
;; inhibit-primary-tot-clearance-enz assertion captures.
;; It predicts a drastic increase in AUC for active
;; ingredients that undergo a high degree first-pass metabolism
(rule
 ((:IN
   (1-inhibits-3-the-primary-total-clearance-enz-of-2 ?x ?z ?y))
  (:IN
   (FIRST-PASS-EFFECT-on-1-is-2 ?z 'HIGH)))
 (rassert!
  (met-inhibit-drug-w-high-first-pass ?x ?z ?y)
  (nil
   ;;justifications
   (1-inhibits-3-the-primary-total-clearance-enz-of-2 ?x ?z ?y)
   (FIRST-PASS-EFFECT-on-1-is-2 ?z 'HIGH)
   )))

;; a rule defining some, possibly negligible, inhibition
;; of clearance for a pceut-entity-of-concern
(rule
 ((:IN
   (1-inhibits-metabolic-clearance-of-2-via-3 ?x ?z ?y))
  (:IN
   (1-is-PCEUT-ENTITY-OF-CONCERN ?z)))
 (rassert!
  (first-level-metabolic-inhibition-of-pceut-entity-of-concern ?x ?z ?y)
  (nil
   ;;justifications
   (1-inhibits-metabolic-clearance-of-2-via-3 ?x ?z ?y)
   (1-is-PCEUT-ENTITY-OF-CONCERN ?z)
   )))
```

```
;; rules defining when the inhibition of a pceut-entity-of-concern
;; clearance should lead to a more significant increase in AUC
;; than that captured by
;; first-level-metabolic-inhibition-of-pceut-entity-of-concern
;; assertions
(rule
 ((:IN
   (1-inhibits-3-the-primary-metabolic-enzyme-of-2 ?x ?z ?y))
  (:IN
   (1-is-PCEUT-ENTITY-OF-CONCERN ?z)))
 (rassert!
  (second-level-metabolic-inhibition-of-pceut-entity-of-concern ?x ?z ?y)
  (nil
   ;;justifications
   (1-inhibits-3-the-primary-metabolic-enzyme-of-2 ?x ?z ?y)
   (1-is-PCEUT-ENTITY-OF-CONCERN ?z)
   )))

(rule
 ((:IN
   (1-inhibits-3-the-primary-total-clearance-enz-of-2 ?x ?z ?y))
  (:IN (1-is-PCEUT-ENTITY-OF-CONCERN ?z)))
 (rassert!
  (second-level-metabolic-inhibition-of-pceut-entity-of-concern ?x ?z ?y)
  (nil
   ;;justifications
   (1-inhibits-3-the-primary-total-clearance-enz-of-2 ?x ?z ?y)
   (1-is-PCEUT-ENTITY-OF-CONCERN ?z)
   )))
```

E.2 Rules for Linking Metabolites to Active Ingredients and Ancestor Compounds

```
;; a rule linking an parent compound to an metabolite
(rule
 ((:IN (1-has-metabolite-2-via-3 ?x ?y ?z)))
 (rassert!
  (1-is-ANCESTOR-OF-2 ?x ?y)
  (nil
   (1-has-metabolite-2-via-3 ?x ?y ?z)
   )))


   (rule
    ((:IN (1-has-metabolite-2-via-3 ?x ?y ?z)))
    (rassert!
     (1-is-SUBSTRATE-OF-2 ?x ?z)
     (nil
      (1-has-metabolite-2-via-3 ?x ?y ?z)
      )))


   ;; a rule linking the catalysis of the formation of a
   ;; metabolite to parent compounds
   (rule
    ((:IN (1-CONTROLS-FORMATION-of-2 ?enz ?x))
     (:IN (1-HAS-METABOLITE-2 ?y ?x)))
    (rassert!
     (1-has-metabolite-2-via-3 ?y ?x ?enz)
     (nil
      (1-CONTROLS-FORMATION-of-2 ?enz ?x)
      (1-HAS-METABOLITE-2 ?y ?x)
      )))
```

```
;; a rule linking an ancestor compound to an metabolite
(rule
 ((:IN (1-has-metabolite-2-via-3 ?x ?y ?e))
  (:IN (1-is-ANCESTOR-OF-2 ?z ?x)))
 (rassert!
  (1-is-ANCESTOR-OF-2 ?z ?y)
  (nil
   (1-has-metabolite-2-via-3 ?x ?y ?e)
   (1-is-ANCESTOR-OF-2 ?z ?x)
   )))
```

E.3 Modeling the Effect of Inhibition Through a Graph of Catalytic Reactions

All of these rules assume that alternate clearance pathways are not saturated.

```
;; inhibition of the formation of a metabolite
;; upstream affects the formation of all metabolites
;; downstream
(rule
 ((:IN
   (1-inhibits-transformation-of-2-to-3-via-4 ?q ?x ?m1 ?enz))
  (:IN
   (1-is-ANCESTOR-OF-2 ?m1 ?m2)))
 (rassert!
  (1-INHIBITS-transformation-of-2-to-3-via-4-upstream ?q ?x ?m2 ?enz)
  (nil
   (1-INHIBITS-transformation-of-2-to-3-via-4 ?q ?x ?m1 ?enz)
   (1-is-ANCESTOR-OF-2 ?m1 ?m2)
   )))
```

```
;; if the formation of two different metabolites, M1
 ;; and M2, from the same agent, X, is catalyzed by
 ;; *different* enzymes then, the effect on M2 of
 ;; modulating the clearance of X by inhibiting or
 ;; inducing the catalytic function of one of the
 ;; enzymes will be an non-ambiguous increase or
 ;; decrease
 (rule
  ((:IN (1-has-metabolite-2-via-3 ?x ?m1 ?enz1))
   (:IN (1-has-metabolite-2-via-3 ?x ?m2 ?enz2)
    :TEST (and (not (equal ?m1 ?m2))
               (not (equal ?enz1 ?enz2))
               (not (equal ?enz1 'UNKNOWN)))))
  (assume!
    (eval
     (quotize
       (list
       'effect-on-1-of-modulating-the-clearance-of-2-via-3-is-non-ambiguous
              ?m2 ?x ?enz1)))
                'default-inference-assumption))
```

```
;; If the effect on some metabolite, M1, of
;; modulating the clearance of its parent compound,
;; X, by inhibiting or inducing the catalytic
;; function of some enzyme, E, is an unambiguous
;; increase or decrease and if M1 has a metabolite,
;; M2, and the transformation of M1 to M2 is
;; controlled by a different enzyme than E then,
;; then an increase or decrease in X will effect an
;; non-ambiguous increase M2
(rule
 ((:IN
   (effect-on-1-of-modulating-the-clearance-of-2-via-3-is-non-ambiguous
      ?m1 ?x ?enz1))
  (:IN (1-has-metabolite-2-via-3 ?m1 ?m2 ?enz2)
   :TEST (and (not (equal ?enz1 ?enz2))
              (not (equal ?enz1 'UNKNOWN)))))
 (assume!
  (eval
   (quotize
     (list
     'effect-on-1-of-modulating-the-clearance-of-2-via-3-is-non-ambiguous
             ?m2 ?x ?enz1)))
     'default-inference-assumption))
```

```
(rule
 ((:IN (effect-on-1-of-modulating-the-clearance-of-2-via-3-is-non-ambiguous
                                ?m ?x ?enz))
  (:IN (1-inhibits-2 ?q ?enz)))
 (rassert!
  (1-effects-an-increase-in-2-by-reducing-clearance-of-3-via-4
                                  ?q ?m ?x ?enz)
  (nil
   (effect-on-1-of-modulating-the-clearance-of-2-via-3-is-non-ambiguous
                                       ?m ?x ?enz)
   (1-inhibits-2 ?q ?enz)
   )))
```

```
;; The effect of an increased formation of a parent
;; compound, X, on some metabolite, M1, due to
;; reduced clearance by an alternate pathway is to
;; increase formation of M2 when the enzymes
;; involved in the formation of M1 and M2 are both
;; different then the enzyme whose inhibition caused
;; an increase in X
(rule
 (
  (:IN
    (1-effects-an-increase-in-2-by-reducing-clearance-of-3-via-4
      ?q ?m1 ?x ?enz1))
  (:IN (1-has-metabolite-2-via-3 ?m1 ?m2 ?enz2)
   :TEST (and (not (equal ?enz1 ?enz2))
              (not (equal ?enz1 'UNKNOWN))))
  (:IN
   (effect-on-1-of-modulating-the-clearance-of-2-via-3-is-non-ambiguous
     ?m2 ?x ?enz1)))
 (rassert!
  (1-effects-an-increase-in-2-by-reducing-clearance-of-3-via-4
     ?q ?m2 ?x ?enz1)
  (nil
   (1-effects-an-increase-in-2-by-reducing-clearance-of-3-via-4
      ?q ?m1 ?x ?enz1)
   (1-has-metabolite-2-via-3 ?m1 ?m2 ?enz2)
   (effect-on-1-of-modulating-the-clearance-of-2-via-3-is-non-ambiguous
     ?m2 ?x ?enz1)
   )))
```

```
;; Ambiguous and non-ambiguous effects are mutually
;; exclusive. Since an non-ambiguous effect is the
;; default assumption, it is retracted
(rule
 ((:IN
    (effect-on-1-of-2-reducing-the-clearance-of-3-via-4-is-ambiguous
      ?m ?q ?x ?z))
  (:IN
    (effect-on-1-of-modulating-the-clearance-of-2-via-3-is-non-ambiguous
     ?m ?x ?z)))
 (rretract!
    (effect-on-1-of-modulating-the-clearance-of-2-via-3-is-non-ambiguous
      ?m ?x ?z)
       default-inference-assumption))


;; If the effect of reducing the clearance of
;; metabolite is uncertain for a given metabolite,
;; it will be so for all metabolites downstream in
;; the metabolic pathway
(rule
 (
  (:IN
   (effect-on-1-of-2-reducing-the-clearance-of-3-via-4-is-ambiguous
     ?m1 ?q ?x ?enz))
  (:IN (1-is-ancestor-of-2 ?m1 ?m2)))
 (rassert!
  (effect-on-1-of-2-reducing-the-clearance-of-3-via-4-is-ambiguous
     ?m2 ?q ?x ?enz)
  (nil
   (effect-on-1-of-2-reducing-the-clearance-of-3-via-4-is-ambiguous
     ?m1 ?q ?x ?enz)
   (1-is-ancestor-of-2 ?m1 ?m2)
   )))
```

```
;; It is a contradiction to have an ambiguous effect and a clearly
;; identified effect
(rule
 (
  (:IN
    (effect-on-1-of-2-reducing-the-clearance-of-3-via-4-is-ambiguous
      ?m ?q ?x ?z))
  (:IN
    (1-effects-an-increase-in-2-by-reducing-clearance-of-3-via-4
      ?q ?m ?x ?z)))
 (contradiction
    (eval
      (quotize
         (list '1-effects-an-increase-in-2-by-reducing-clearance-of-3-via-4
            ?q ?m ?x ?z)))))
```

```
;; If the formation of two different metabolites
;; from the same agent are catalyzed by *the same enzyme*
;; then the effect of inhibiting the enzyme
;; on both metabolites is ambiguous. This is because
;; there is both an increase in parent compound due
;; to removal of one clearance pathway and a
;; decrease in the ability of the enzyme formation
;; of child compound
(rule
 ((:IN (1-has-metabolite-2-via-3 ?x ?m1 ?z))
  (:IN (1-has-metabolite-2-via-3 ?x ?m2 ?z) :TEST (not (equal ?m1 ?m2)))
  (:IN (1-inhibits-2 ?q ?z)))
 (rassert!
  (effect-on-1-of-2-reducing-the-clearance-of-3-via-4-is-ambiguous
     ?m2 ?q ?x ?z)
  (nil
   (1-has-metabolite-2-via-3 ?x ?m1 ?z)
   (1-has-metabolite-2-via-3 ?x ?m2 ?z)
   (1-inhibits-2 ?q ?z)
   )))
```

```
;; If it is not known if the formation of two
;; different metabolites from the same agent are
;; catalyzed by *the same enzyme* then the effect of
;; inhibiting the enzyme on both metabolites is
;; ambiguous. This is because there might be both an
;; increase in parent compound due to removal of one
;; clearance pathway and a decrease in the ability
;; of the enzyme formation of child compound
(rule
 ((:IN (1-has-metabolite-2-via-3 ?x ?m1 ?z))
  (:IN (1-has-metabolite-2-via-3 ?x ?m2 'UNKNOWN)
     :TEST (not (equal ?m1 ?m2)))
  (:IN (1-inhibits-2 ?q ?z)))
 (rassert!
  (effect-on-1-of-2-reducing-the-clearance-of-3-via-4-is-ambiguous
     ?m2 ?q ?x ?z)
  (nil
   (1-has-metabolite-2-via-3 ?x ?m1 ?z)
   (1-has-metabolite-2-via-3 ?x ?m2 'UNKNOWN)
   (1-inhibits-2 ?q ?z)
     )))
```

```
;; The effect of an increased formation of a parent
;; compound on a metabolite due to reduced clearance
;; of an alternate pathway is unclear if the same
;; enzyme is inhibited in both the alternate pathway
;; and the formation of the metabolite
(rule
 ((:IN
   (1-effects-an-increase-in-2-by-reducing-clearance-of-3-via-4
     ?q ?m1 ?x ?enz))
  (:IN (1-has-metabolite-2-via-3 ?m1 ?m2 ?enz)))
 (rassert!
  (effect-on-1-of-2-reducing-the-clearance-of-3-via-4-is-ambiguous
     ?m2 ?q ?x ?enz)
  (nil
   (1-effects-an-increase-in-2-by-reducing-clearance-of-3-via-4
     ?q ?m1 ?x ?enz)
   (1-has-metabolite-2-via-3 ?m1 ?m2 ?enz)
   )))
```

```
;; The effect of an increased formation of a parent
;; compound on a metabolite due to reduced clearance
;; of an alternate pathway is unclear if is not
;; known whether or not the same enzyme is inhibited
;; in both the alternate pathway and the formation
;; of the metabolite
(rule
 ((:IN
    (1-effects-an-increase-in-2-by-reducing-clearance-of-3-via-4
     ?q ?m1 ?x ?enz))
  (:IN (1-has-metabolite-2-via-3 ?m1 ?m2 'UNKNOWN)))
 (rassert!
  (effect-on-1-of-2-reducing-the-clearance-of-3-via-4-is-ambiguous
     ?m2 ?q ?x ?enz)
  (nil
   (1-effects-an-increase-in-2-by-reducing-clearance-of-3-via-4
    ?q ?m1 ?x ?enz)
   (1-has-metabolite-2-via-3 ?m1 ?m2 'UNKNOWN)
    )))
```

E.4 Rules for Disjunctive Cases

A set of rules to for the disjunctive case where an active ingredient is ancestor to a compound that interacts with another active ingredient or metabolite.

```
(rule
 ((:IN (1-is-an-ACTIVE-INGREDIENT ?x))
  (:IN (1-is-ANCESTOR-OF-2  ?x ?y))
  (:IN (1-INHIBITS-3-the-primary-metabolic-enzyme-of-2
                                                ?y ?z ?enz)))
 (rassert!
  (active-ingredient-1-is-ancestor-to-2-and-2-interacts-with-3
                                                    ?x ?y ?z)
  (nil
   (1-is-an-ACTIVE-INGREDIENT ?x)
   (1-is-ANCESTOR-OF-2  ?x ?y)
   (1-INHIBITS-3-the-primary-metabolic-enzyme-of-2
                                           ?y ?z ?enz)
   )))


(rule
 ((:IN (1-is-an-ACTIVE-INGREDIENT ?x))
  (:IN (1-is-ANCESTOR-OF-2  ?x ?y))
  (:IN (1-inhibits-metabolic-clearance-of-2-via-3
                                         ?y ?z ?enz)))
 (rassert!
  (active-ingredient-1-is-ancestor-to-2-and-2-effects-an-interaction-with-3
                                             ?x ?y ?z)
  (nil
   (1-is-an-ACTIVE-INGREDIENT ?x)
   (1-is-ANCESTOR-OF-2  ?x ?y)
   (1-inhibits-metabolic-clearance-of-2-via-3
                                        ?y ?z ?enz)
   )))
```

A set of rules to for the disjunctive case where an active ingredient is ancestor to a compound that is the victim of an interaction with another active ingredient or metabolite.

```
(rule
 ((:IN (1-is-an-ACTIVE-INGREDIENT ?x))
  (:IN (1-is-ANCESTOR-OF-2  ?x ?z))
  (:IN (1-inhibits-3-the-primary-metabolic-enzyme-of-2
                                              ?y ?z ?enz)))
 (rassert!
  (active-ingredient-1-is-ancestor-to-2-and-2-is-affected-by-3
                                                 ?x ?z ?y)
  (nil
   (1-is-an-ACTIVE-INGREDIENT ?x)
   (1-is-ANCESTOR-OF-2  ?x ?z)
   (1-inhibits-3-the-primary-metabolic-enzyme-of-2 ?y ?z ?enz)
   )))

(rule
 ((:IN (1-is-an-ACTIVE-INGREDIENT ?x))
  (:IN (1-is-ANCESTOR-OF-2  ?x ?z))
  (:IN (1-inhibits-metabolic-clearance-of-2-via-3 ?y ?z ?enz)))
 (rassert!
  (ACTIVE-INGREDIENT-1-is-ancestor-to-2-and-2-is-affected-by-3
                                                   ?x ?z ?y)
  (nil
   (1-is-an-ACTIVE-INGREDIENT ?x)
   (1-is-ANCESTOR-OF-2  ?x ?z)
   (1-inhibits-metabolic-clearance-of-2-via-3 ?y ?z ?enz)
   )))
```

F Definitions for Each Assertion Type Used in the DIKB's Rule-base

F.1 The `primary-total-clearance-mechanism` Assertion

The "primary total clearance mechanism" of some active pharmaceutic ingredient or metabolite, `X`, is the pharmacokinetic process that accounts for more than 50% of `X`'s clearance from the body. The DIKB's structured vocabulary lists four possible clearance processes:

1. `Biliary_Excretion` - Excretion of unchanged active pharmaceutic ingredient or metabolite, be it a `complex`, `protein`, or `small molecule`, via the bile and feces
2. `Exhalation_Excretion` - Excretion of unchanged active ingredient or metabolite, be it a `complex`, `protein`, or `small molecule`, via the lungs
3. `Renal_Excretion` - Excretion of unchanged active pharmaceutic ingredient or metabolite, be it a `complex`, `protein`, or `small molecule`, via the kidneys
4. `Metabolic_Clearance` - Elimination from the body of an active ingredient or metabolite, be it a `complex`, `protein`, or `small molecule`, by transformation through the biochemical reactions and pathways to substances that are inactive and/or excreted by the body

F.2 The `bioavailability` Assertion

This assertion specifies the proportion of an active pharmaceutical ingredient's dose that reaches systemic circulation. This assertion does not apply to drug metabolites. When the DIKB's `evidence-model` exports this assertion it takes the maximum bioavailability entry found in all of the evidence items in the `evidence-for` list belonging to a given `Assertion` instance.

This value is mapped to the following discrete categories:

- `LOW`: $[0.0, .20]$
- `MEDIUM`: $(.201, .50]$
- `HIGH`: $(.501, 1]$

The motivation for choosing these categories is based on simple conjectures about what the maximum increase in AUC can be at various bioavailability levels. For example, a drug with a bioavailability of 50% should only be able to experience an approximate 2-fold increase in AUC if whatever is blocking the drug from entering systemic is completely removed. The maximum possible magnitude increase at the 20% level is approximately 5-fold while there is no limit for drugs with bioavailability values near zero.

Like the `maximum_concentration` assertion, `bioavailability` depends on statistical inference rather than logical induction and all drugs have some bioavailability value. Therefore, no `evidence-against` items need be collected. When different formulations of a drug have different bioavailability values (e.g. extended vs normal release) each assertion instance must refer to the dose and formulation of the pharmaceutical preparation that is associated with the bio-availability value.

F.3 The `first-pass-effect` Assertion

The `first-pass-effect` assertion is a qualitative statement of the degree to which an active pharmaceutic ingredient is cleared from the body before entering systemic circulation. At the time of this writing the focus is on the degree of first-pass metabolism an active pharmaceutic ingredient undergoes in the liver and gut wall before a drug reaches systemic circulation. As more becomes known about transporter proteins (e.g. P-glycoprotein) separate rules might be created to model effects on modulation of their activity. This assertion does not apply to metabolites.

This value is mapped to the following discrete categories:

- `LOW`: [0.0, .50]
- `MEDIUM`: (.501, .80]
- `HIGH`: (.801, 1]

The motivation for choosing these categories is based on simple conjectures about what the maximum increase in AUC can be at various first-pass-effect levels. For example, an active pharmaceutic ingredient with a first-pass effect of 50% should only be able to experience an approximate 2-fold increase in AUC if the first-pass effect is completely removed. The maximum possible magnitude increase at the 80% level is approximately 5-fold while there is no limit for drugs with first-pass effect values near 100%.

Establishment: There are two ways that to derive a value for this assertion:

1. The value might be found in the results of a mass-balance study
2. If quantitative values are known for both the bioavailability, F, of and percent of active pharmaceutic ingredient absorbed, f_{abs}, then first pass effect can be calculated as:

$$1 - \frac{F}{f_{abs}} \tag{1}$$

This is a quantitative assertion that requires statistical inference. Some drugs or drug metabolits might have no first-pass effect (e.g. pharmaceutical entities with no clearance by metabolism) so it is logical to seek evidence against this assertion as well as supporting evidence.

F.4 The `fraction-absorbed` Assertion

This assertion is a quantitative statement of the fraction of an active ingredient's dose that gets absorbed in the gastro-intestinal tract. Such an estimate might be obtained from a study focusing on gut wall absorption. The quantitative values are maintained by the system but, they are also mapped to the following qualitative levels:

- `LOW`: $[0.0, .50]$
- `HIGH`: $(.501, 1]$

In many cases there will be no quantitative data for either the fraction of active pharmaceutic ingredient that is absorbed, its bioavailability, or both. However, one can often find, or derive, a reasonable qualitative estimate that falls within the range of either of these levels. This assertion does not apply to metabolites.

This is a quantitative assertion that requires statistical inference. Some drugs might not be absorbed in the GI tract (e.g. drugs for which there are only IV formulations) so it is logical to seek evidence against this assertion as well as supporting evidence.

F.5 The `maximum-concentration` Assertion

This assertion specifies the maximum concentration (C_{max}), in grams/liter, that the an active pharmaceutic ingredient or metabolite is known to reach. For active pharmaceutical ingredients, it is linked to the particular dose, in grams, of active pharmaceutic ingredients that was given in the study. For drug metabolites, it is linked to the particular dose in grams of the metabolite's ancestor active pharmaceutic ingredient that was given in the study. When the DIKB's `evidence-model` exports this assertion it takes the maximum C_{max} value entry found in all of the evidence items in the `evidence-for` list belonging to a given `Assertion` instance.

When different formulations of a drug have different maximum concentration values (e.g. extended vs normal release) each assertion instance must refer to the dose and formulation of the drug that is associated with the value being entered.

This assertion, depends on statistical inference rather than logical induction and all pharmaceutical entities will have some C_{max} value. Therefore, no `evidence-against` items need be collected.

F.6 The `inhibits` Assertion

An active pharmaceutic ingredient or metabolite, X, is said to be a `inhibit` some enzyme, E, if X effects a measurable reduction in the catalytic function of E *in vivo*.

F.7 The `does-not-inhibit` Assertion

If an active pharmaceutic ingredient or metabolite, X *does not* effect a measurable reduction in the catalytic function of some enzyme E *in vivo* then the `X does-not-inhibit E` assertion applies.

F.8 The `in-vitro-selective-inhibitor-of-enzyme` Assertion

The FDA has provided a list of preferred and acceptable inhibitors for *in vitro* studies in [26], Appendix C-1, Table 2, and the CDER Web page on drug interactions [8]. In the DIKB, these chemicals are assumed to be *in vitro* selective inhibitors of they enzymes that they are listed with in these sources.

F.9 The `in-viVo-selective-inhibitor-of-enzyme` Assertion

The FDA has provided a list of preferred and acceptable inhibitors for *in vivo* studies in [26], Appendix A, Table 2, and the CDER Web page on drug interactions [8]. In the DIKB, these chemicals are assumed to be *in vivo* selective inhibitors of they enzymes that they are listed with in these sources.

Applying this assertion to some metabolite or active pharmaceutic ingredient, X, and enzyme, ENZ, implies that X `inhibits` ENZ.

F.10 The `substrate-of` Assertion

An active pharmaceutic ingredient or metabolite, X, is said to be a `substrate-of` some enzyme, E, if E catalyzes the transformation of the X to a metabolite, M. This assertion does not imply any quantitative information such as contribution E makes relative to other enzymes that catalyze the same reaction.

F.11 The `in-vitro-probe-substrate-of-enzyme` Assertion

The FDA has provided a list of preferred and acceptable chemical substrates for *in vitro* studies in [26], Table 3, and the CDER Web page on drug interactions [8]. In the DIKB, the principle chemicals involved in these reactions are *in vitro* probe substrates of the enzymes they are listed.

F.12 The `is-not-substrate-of` Assertion

Let X be an active pharmaceutic ingredient or metabolite and E some enzyme. If E does not catalyze the transformation of X to any known metabolite of X then the assertion `X is-not-substrate-of E` applies.

F.13 The `primary-total-clearance-enzyme` Assertion

The "primary total clearance enzyme" of some active pharmaceutic ingredient or metabolite, `X`, is the enzyme, `ENZ`, responsible for 50% or more of the active pharmaceutic ingredient or metabolite's total clearance from the body. In other words, if at least 50% of `X` is cleared from the body by metabolic reactions catalyzed by `ENZ` then `ENZ` is the "primary total clearance enzyme" of `X`. This assertion can be established by any of the following methods:

1. `ENZ` is polymorphic and a well-designed *in vivo* polymorphic pharmacokinetic study shows that `ENZ` is responsible for 50% or more of `X`'s clearance
2. a well-designed clinical trial investigating the pharmacokinetics of drug `X` in the presence of drug `Y` shows an increase in the AUC of `X` of at least 2-fold. NOTE: 1) drug `Y` must have no measurable effect on `X`'s clearance by renal clearance, biliary clearance, or exhalation, and 2) drug `Y` must be a *selective* inhibitor of `ENZ`

Applying this assertion to some metabolite or active pharmaceutic ingredient, X, and enzyme, ENZ, implies that:

- X is a `substrate-of` ENZ
- the `primary-total-clearance-mechanism` of X is metabolism

The current DIKB policy is that any enzyme that the FDA considers a drug or drug metabolite to be a probe-substrate of *in vivo* should be labeled its *primary total clearance enzyme*. The FDA has provided a list of preferred and acceptable probe substrates for *in vivo* studies in [26], Appendix A, Table 2, and the CDER Web page on drug interactions [8]. In the DIKB, these chemicals are assumed to be *in vivo* probe substrates of the enzymes that they are listed with in these sources.

F.14 The `primary-metabolic-clearance-enzyme` Assertion

The "primary metabolic clearance enzyme" of some active pharmaceutic ingredient or metabolite, `X`, is the enzyme, `ENZ`, responsible for 50% of the active pharmaceutic ingredient or metabolite's total *metabolic* clearance from the body.

F.15 The `inhibition-constant` Assertion

Some *in vitro* inhibition studies provide an inhibition constant, K_i, or a value that can converted to one. This assertion is the continuous value derived from such studies. When the DIKB's `evidence-model` exports this assertion it takes the minimum all K_i values in the `evidence-for` list belonging to a given `Assertion` instance. When the DIKB's prediction rules are ran, this assertion is combined with the `maximum_concentration` assertion for the (see Section F.5), C_{max}, and the `permanently_deactivates_catalytic_function` assertion (Section F.22) to derive an estimate of the clinical relevance of the observed *in vitro* inhibition.

The DIKB labels a drug or drug metabolite an *in vivo* inhibitor for some drug metabolizing enzyme at the concentrations it is expected to reach during drug therapy if the following relationship holds:

$$\frac{C_{max}}{K_i} > 0.1 \tag{2}$$

Where C_{max} is the maximum observed concentration the inhibitor has reached in patients at normal, therapeutic, doses and K_i is an inhibition constant derived from a well-designed *in vitro* enzyme inhibition experiment involving the inhibitor. This relationship applies to inhibition of members of the Cytochrome P-450 enzyme family and is not applicable if the inhibitor is thought to permanently remove the affected enzyme from further participation in catalysis by any means. The basis for this relationship can be found in a recent FDA guidance that recommends that a clinically relevant effect from competitive enzyme inhibition be considered possible if the following relationship holds (see [26], p.33):

$$\frac{[I]}{K_i} > 0.1 \tag{3}$$

Where $[I]$ is the estimated concentration of the inhibitor at the enzyme binding site.

It is important to note that K_i values can vary depending on the system of enzymes used in each study. In fact, there can be a greater than 10-fold difference between the K_i found in recombinant enzyme systems compared to the K_i derived from human liver microsomes. Thus, the DIKB requires that the enzyme system used in the study from which a K_i is taken be noted in case there will be a need to distinguish K_i value by the enzyme system from which they were derived.

Like the `maximum_concentration` assertion, `inhibition_constant` depends on statistical inference rather than logical induction. Unlike the `maximum_concentration`, the value does not exist for some pharmaceutical entities. Therefore, it is logical to collect `evidence-against` items.

F.16 The `has-metabolite` Assertion

If an active pharmaceutic ingredient or metabolite, X, can be chemically altered to produce another compound, M, via a single chemical reaction possibly involving some enzyme, E, then, metabolite M is considered a metabolite of X and the assertion `(X has-metabolite M)` is applicable.

F.17 The `controls-formation-of` Assertion

If an active pharmaceutic ingredient or metabolite, X, can be chemically altered to produce another compound, M, via a single chemical reaction that requires catalysis by some enzyme, E then, E controls the formation of M and the assertion `(E controls-formation-of M)` is applicable.

F.18 The `polymorphic-enzyme` Assertion

A `polymorphic-enzyme` enzyme is an enzyme that has multiple drug-catalysis phenotypes due to genetic polymorphisms. By default, the DIKB assumes all enzymes to be *non*-polymorphic.

F.19 The `pceut-entity-of-concern` Assertion

A "pceut-entity-of-concern" is an active pharmaceutic ingredient or metabolite for which even a small change in the system concentration would be of concern to a clinician. We assume that the criteria for a drug to meet this definition will vary for valid reasons between different groups of experts but use the following criteria in the current DIKB:

- active pharmaceutic ingredient or metabolites for which therapeutic drug monitoring is required
- active pharmaceutic ingredient or metabolites for which the ratio between the toxic systemic concentration of the agent and the concentration at which the agent is therapeutic is less than or equal to 2.0.

F.20 The `sole-PK-effect-alter-metabolic-clearance` Assertion

This assertion is a required assumption of evidence from a clinical pharmacokinetic DDI study involving a non-polymorphic enzyme when a curator applies the study as support for the `primary-total-clearance-enzyme` assertion (see Section F.13). It asserts that the sole pharmacokinetic effect of an active pharmaceutic ingredient or metabolite, `Y`, on an active pharmaceutic ingredient or metabolite, `X`, is alteration of `X`'s metabolic clearance. In other words, it asserts that `Y` has no measurable effect on `X`'s clearance by renal, biliary, exhalation, or efflux transport processes.

F.21 The `permanently_deactivates_catalytic_function` Assertion

This assertion specifies that an active pharmaceutical ingredient or metabolite is known to affect an enzyme in such a way that the enzyme is permanently removed from further participation in catalysis. For example, this assertion is applicable for the *slowly reversible* and *irreversible* inhibition mechanisms as discussed in detail in Levy *et al* [33]. This assertion is also applicable if there is any other mechanism by which the active pharmaceutic ingredient or metabolite could permanently remove the enzyme from further participation in catalysis.

When the DIKB's *evidence-model* asserts that some active pharmaceutical ingredient or metabolite, `X`, is an inhibitor of some enzyme, `Y`, and the `permanently_deactivate_catalytic_function` assertion contains no value, the system will assert the `does_not_permanently_deactivate_catalytic_function` assertion by default reasoning.

F.22 The `does_not_permanently_deactivate_catalytic_function` Assertion

This is the inverse of the `permanently_deactivates_catalytic_function` assertion (Section F.21). When the DIKB's *evidence-model* asserts that some active pharmaceutical ingredient or metabolite, `X`, is an inhibitor of some enzyme,

`Y`, and the `permanently_deactivates_catalytic_function` assertion contains no value, the system will assert the `does_not_permanently_deactivate_catalytic_function` assertion by default reasoning.

G A Belief Criteria Questionnaire

Questionnaire to establish belief criteria

Each assertion type in the DIKB is listed below in its own section along with DIKB evidence types that can support or refute the assertion. You can assume that all evidence, no matter what type, meets the minimum criteria for quality that we have defined in the DIKB inclusion criteria. Your task is to reflect on your experience and decide which evidence types, or combinations of evidence types, provide information you consider trustworthy for making decisions about the safe use of a drug.

For each assertion type, please list the evidence type(s) whose information. or data, that you would consider believable. For example, there are three evidence type that can support the general assertion regarding the bioavailability of some drug 'X'. Read each evidence type and ask yourself if you trust the validity of a claim about a drug's bioavailability when the information comes from such a study. Then, note which, if any, study types you would find trustworthy. If more than one evidence type meets your belief criteria then list them all separating each evidence type with a comma or and 'OR'. If some combination of the available evidence types would eliminate your doubt in an assertion then, list that combination separating each evidence type with an 'AND'.

If there is no combination of the available evidence types that would relieve your doubt as to the validity of a particular assertion then you can leave your response blank.

the bioavailability of active ingredient 'X'
1.A non-traceable drug-label statement
2.A non-traceable (but possibly authoritative) statement
3.A pharmacokinetic clinical trial
Your belief criteria:

the primary_total_clearance_mechanism of active ingredient or metabolite 'X'

1.A non-traceable drug-label statement

2.A non-traceable (but possibly authoritative) statement

3.A pharmacokinetic clinical trial

Your belief criteria:

the maximum_concentration of active ingredient or metabolite 'X'

1.A non-traceable drug-label statement

2.A non-traceable (but possibly authoritative) statement

3.A pharmacokinetic clinical trial

Your belief criteria:

active ingredient or metabolite 'X' is a substrate_of enzyme 'E'

1.A non-traceable drug-label statement

2.A non-traceable (but possibly authoritative) statement

3.A CYP450, recombinant, drug metabolism identification experiment using

chemical inhibitors

4.A CYP450, recombinant, drug metabolism identification experiment using antibody inhibitors

5.A CYP450, recombinant, drug metabolism identification experiment (possibly NO probe enzyme inhibitor(s))

6.A CYP450, human microsome, drug metabolism identification experiment using antibody inhibitors

7.A CYP450, human microsome, drug metabolism identification experiment using chemical inhibitors

8.A CYP450, human microsome, drug metabolism identification experiment (possibly NO probe enzyme inhibitor(s))

9.A randomized DDI clinical trial

10.A genotyped pharmacokinetic clinical trial

11. A phenotyped pharmacokinetic clinical trial

12. A non-randomized DDI clinical trial

Your belief criteria:

active ingredient or metabolite 'X' is is_not_a_substrate_of enzyme 'E'

1.A non-traceable drug-label statement

2.A non-traceable (but possibly authoritative) statement

3.A CYP450, recombinant, drug metabolism identification experiment using chemical inhibitors

4.A CYP450, recombinant, drug metabolism identification experiment using antibody inhibitors

5.A CYP450, recombinant, drug metabolism identification experiment (possibly NO probe enzyme inhibitor(s))

6.A CYP450, human microsome, drug metabolism identification experiment using

antibody inhibitors

7.A CYP450, human microsome, drug metabolism identification experiment using chemical inhibitors

8.A CYP450, human microsome, drug metabolism identification experiment (possibly NO probe enzyme inhibitor(s))

9.A randomized DDI clinical trial

10.A genotyped pharmacokinetic clinical trial

11. A phenotyped pharmacokinetic clinical trial

12. A non-randomized DDI clinical trial

Your belief criteria:

active ingredient or metabolite 'X' has_metabolite 'M'

1.A non-traceable drug-label statement

2.A non-traceable (but possibly authoritative) statement

3.A pharmacokinetic clinical trial

4.A drug metabolism identification experiment

5.A CYP450, recombinant, drug metabolism identification experiment using chemical inhibitors

6.A CYP450, recombinant, drug metabolism identification experiment using antibody inhibitors

7.A CYP450, recombinant, drug metabolism identification experiment (possibly NO probe enzyme inhibitor(s))

8.A CYP450, human microsome, drug metabolism identification experiment using chemical inhibitors

9.A CYP450, human microsome, drug metabolism identification experiment using antibody inhibitors

10. A CYP450, human microsome, drug metabolism identification experiment (possibly NO probe enzyme inhibitor(s))

Your belief criteria:

enzyme 'E' controls_formation_of metabolite 'M'

1.A non-traceable drug-label statement

2.A non-traceable (but possibly authoritative) statement

3.A CYP450, recombinant, drug metabolism identification experiment using chemical inhibitors

4.A CYP450, recombinant, drug metabolism identification experiment using antibody inhibitors

5.A CYP450, recombinant, drug metabolism identification experiment (possibly NO probe enzyme inhibitor(s))

6.A CYP450, human microsome, drug metabolism identification experiment using chemical inhibitors

7.A CYP450, human microsome, drug metabolism identification experiment using antibody inhibitors

8.A CYP450, human microsome, drug metabolism identification experiment (possibly NO probe enzyme inhibitor(s))

9.A randomized DDI clinical trial

10.A genotyped pharmacokinetic clinical trial

11.A phenotyped pharmacokinetic clinical trial

12. A non-randomized DDI clinical trial

Your belief criteria:

the first_pass_effect of active ingredient 'X'

1.A non-traceable drug-label statement

2.A non-traceable (but possibly authoritative) statement

3.A study of the process by which a drug is absorbed, distributed,
metabolized,and eliminated by the body.

Your belief criteria:

the fraction_absorbed of active ingredient 'X'

1.A non-traceable drug-label statement

2.A non-traceable (but possibly authoritative) statement

3.A study of the process by which a drug is absorbed, distributed,
metabolized, and eliminated by the body.

Your belief criteria:

active ingredient or metabolite 'X' increases_auc of active ingredient or metabolite 'Y'

1.A non-traceable drug-label statement

2.A non-traceable (but possibly authoritative) statement

3.A randomized DDI clinical trial

4.A non-randomized DDI clinical trial

Your belief criteria:

an inhibition_constant for an active ingredient or metabolite 'X' and some enzyme 'E'

1.A non-traceable drug-label statement

2.A non-traceable (but possibly authoritative) statement

3.A CYP450, recombinant, metabolic enzyme inhibition experiment

4.A CYP450, human microsome, metabolic enzyme inhibition experiment

Your belief criteria:

active ingredient or metabolite 'X' inhibits enzyme 'E'

1.A non-traceable drug-label statement

2.A non-traceable (but possibly authoritative) statement

3.A CYP450, human microsome, metabolic enzyme inhibition experiment

4.A CYP450, recombinant, metabolic enzyme inhibition experiment

5.A randomized DDI clinical trial

6.A non-randomized DDI clinical trial

Your belief criteria:

active ingredient or metabolite 'X' does_not_inhibit enzyme 'E'

1.A non-traceable drug-label statement

2.A non-traceable (but possibly authoritative) statement

3.A CYP450, human microsome, metabolic enzyme inhibition experiment

4.A CYP450, recombinant, metabolic enzyme inhibition experiment

5.A randomized DDI clinical trial

6.A non-randomized DDI clinical trial

Your belief criteria:

enzyme 'E' is the primary_total_clearance_enzyme of active ingredient or metabolite 'X'

1.A non-traceable drug-label statement

2.A non-traceable (but possibly authoritative) statement

3.A randomized DDI clinical trial

4.A genotyped pharmacokinetic clinical trial

5.A phenotyped pharmacokinetic clinical trial

6.A non-randomized DDI clinical trial

Your belief criteria:

enzyme 'E' is the primary_metabolic_clearance_enzyme of active ingredient or metabolite 'X'

1.A non-traceable drug-label statement

2.A non-traceable (but possibly authoritative) statement

3.A CYP450, human microsome, drug metabolism identification experiment using
chemical inhibitors

4.A CYP450, human microsome, drug metabolism identification experiment using
antibody inhibitors

5.A CYP450, recombinant, drug metabolism identification experiment using
chemical inhibitors

6.A CYP450, recombinant, drug metabolism identification experiment using
antibody inhibitors

7.A CYP450, recombinant, drug metabolism identification experiment (possibly
NO probe enzyme inhibitor(s))

8. A CYP450, recombinant, drug metabolism identification experiment (possibly NO probe enzyme inhibitor(s))

9.A randomized DDI clinical trial

10. A genotyped pharmacokinetic clinical trial

11. A phenotyped pharmacokinetic clinical trial

12. A non-randomized DDI clinical trial

Your belief criteria:

References

[1] Abbott. Biaxin filmtab (clarithromycin) tablet, film coated. FDA-approved drug product labeling, 03 2007. Last accessed on DailyMed 05/29/2008.

[2] J. Ahonen, K. T. Olkkola, and P. J. Neuvonen. Effect of route of administration of fluconazole on the interaction between fluconazole and midazolam. *Eur J Clin Pharmacol*, 51(5):415–419, 1997.

[3] G. W. Amsden, O. Kuye, and G. C. Wei. A study of the interaction potential of azithromycin and clarithromycin with atorvastatin in healthy volunteers. *J Clin Pharmacol*, 42(4):444–449, 2002.

[4] N. E. Azie, D. C. Brater, P. A. Becker, D. R. Jones, and S. D. Hall. The interaction of diltiazem with lovastatin and pravastatin. *Clin Pharmacol Ther*, 64(4):369–377, 1998.

[5] J. T. Backman, K. T. Olkkola, K. Aranko, J. J. Himberg, and P. J. Neuvonen. Dose of midazolam should be reduced during diltiazem and verapamil treatments. *Br J Clin Pharmacol*, 37(3):221–225, 1994.

[6] R. H. Barbhaiya, U. A. Shukla, P. D. Kroboth, and D. S. Greene. Coadministration of nefazodone and benzodiazepines: Ii. a pharmacokinetic interaction study with triazolam. *J Clin Psychopharmacol*, 15(5):320–326, 1995.

[7] Biovail. cardizem (diltiazem hydrochloride) tablet, coated. FDA-approved drug product labeling, 04 2006. Last accessed on DailyMed 05/29/2008.

[8] CDER Web page on drug interactions. Internet. `http://www.fda.gov/Cder/drug/drugInteractions/`. Last accessed 04/29/2008.

[9] E. Chung, A. N. Nafziger, D. J. Kazierad, and J. S. Jr Bertino. Comparison of midazolam and simvastatin as cytochrome p450 3a probes. *Clin Pharmacol Ther*, 79(4):350–361, 2006.

[10] M. H. Coletti and H. L. Bleich. Medical Subject Headings Used to Search the Biomedical Literature. *J Am Med Inform Assoc*, 8(4):317–323, 2001.

[11] K. J. Cooper, P. D. Martin, A. L. Dane, M. J. Warwick, A. Raza, and D. W. Schneck. The effect of erythromycin on the pharmacokinetics of rosuvastatin. *Eur J Clin Pharmacol*, 59(1):51–56, 2003.

[12] K. J. Cooper, P. D. Martin, A. L. Dane, M. J. Warwick, D. W. Schneck, and M. V. Cantarini. The effect of fluconazole on the pharmacokinetics of rosuvastatin. *Eur J Clin Pharmacol*, 58(8):527–531, 2002.

[13] K. J. Cooper, P. D. Martin, A. L. Dane, M. J. Warwick, D. W. Schneck, and M. V. Cantarini. Effect of itraconazole on the pharmacokinetics of rosuvastatin. *Clin Pharmacol Ther*, 73(4):322–329, 2003.

[14] S. de Coronado, M. W. Haber, N. Sioutos, M. S. Tuttle, and L. W. Wright. NCI Thesaurus: using science-based terminology to integrate cancer research results. *Medinfo*, 11(Pt 1):33–37, 2004.

[15] C. L. DeVane, J. L. Donovan, H. L. Liston, J. S. Markowitz, K. T. Cheng, S. C. Risch, and L. Willard. Comparative CYP3A4 inhibitory effects of venlafaxine, fluoxetine, sertraline, and nefazodone in healthy volunteers. *J Clin Psychopharmacol*, 24(1):4–10, 2004.

[16] drugs@fda website. Internet. `http://www.fda.gov/cder/drugsatfda/datafiles/ default.htm`. Last accessed 03/01/2006.

[17] J. C. Gorski, D. R. Jones, B. D. Haehner-Daniels, M. A. Hamman, E. M. Jr O'Mara, and S. D. Hall. The contribution of intestinal and hepatic CYP3A to the interaction between midazolam and clarithromycin. *Clin Pharmacol Ther*, 64(2):133–143, 1998.

[18] D. J. Greenblatt, L. L. von Moltke, J. S. Harmatz, M. Counihan, J. A. Graf, A. L. Durol, P. Mertzanis, S. X. Duan, C. E. Wright, and R. I. Shader. Inhibition of triazolam clearance by macrolide antimicrobial agents: in vitro correlates and dynamic consequences. *Clin Pharmacol Ther*, 64(3):278–285, 1998.

[19] D. J. Greenblatt, C. E. Wright, L. L. von Moltke, J. S. Harmatz, B. L. Ehrenberg, L. M. Harrel, K. Corbett, M. Counihan, S. Tobias, and R. I. Shader. Ketoconazole inhibition of triazolam and alprazolam clearance: differential kinetic and dynamic consequences. *Clin Pharmacol Ther*, 64(3):237–247, 1998.

[20] D. S. Greene, D. E. Salazar, R. C. Dockens, P. Kroboth, and R. H. Barbhaiya. Coadministration of nefazodone and benzodiazepines: Iii. a pharmacokinetic interaction study with alprazolam. *J Clin Psychopharmacol*, 15(6):399–408, 1995.

[21] B. Gurley, M. A. Hubbard, D. K. Williams, J. Thaden, Y. Tong, W. B. Gentry, P. Breen, D. J. Carrier, and S. Cheboyina. Assessing the clinical significance of botanical supplementation on human cytochrome

P450 3A activity: comparison of a milk thistle and black cohosh product to rifampin and clarithromycin. *J Clin Pharmacol*, 46(2):201–213, 2006.

[22] JR Horn, PD Hansten, and LN Chan. Proposal for a new tool to evaluate drug interaction cases. *Ann Pharmacother*, 41(4):674–80, 2007.

[23] Internal Authorship. Electronic Orange Book. Internet. `http://www.fda.gov/ cder/ob/`. Last accessed 06/01/2008.

[24] Internal Authorship. RxNorm. Internet. `http://www.nlm.nih.gov/research/umls/rxnorm/index.html`. Last accessed 06/01/2008.

[25] Internal Authorship. FDA guidance for industry - population pharmacokinetics. Technical report, Federal Drug Administration, 1999.

[26] Internal Authorship. FDA guideline: Drug interaction studies – study design, data analysis, and implications for dosing and labeling. Internet, September 2006. `http://www.fda.gov/Cber/gdlns/interactstud.htm`. Last accessed 09/25/2006.

[27] T. A. Jacobson. Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. *Am J Cardiol*, 94(9):1140–1146, 2004.

[28] Janssen. sporanox (itraconazole) capsule. FDA-approved drug product labeling, 01 2008. Last accessed on DailyMed 05/16/2008.

[29] T. Kantola, J. T. Backman, M. Niemi, K. T. Kivisto, and P. J. Neuvonen. Effect of fluconazole on plasma fluvastatin and pravastatin concentrations. *Eur J Clin Pharmacol*, 56(3):225–229, 2000.

[30] T. Kantola, K. T. Kivisto, and P. J. Neuvonen. Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. *Clin Pharmacol Ther*, 64(2):177–182, 1998.

[31] K. T. Kivisto, T. Kantola, and P. J. Neuvonen. Different effects of itraconazole on the pharmacokinetics of fluvastatin and lovastatin. *Br J Clin Pharmacol*, 46(1):49–53, 1998.

[32] Y. W. Lam, C. L. Alfaro, L. Ereshefsky, and M. Miller. Pharmacokinetic and pharmacodynamic interactions of oral midazolam with ketoconazole, fluoxetine, fluvoxamine, and nefazodone. *J Clin Pharmacol*, 43(11):1274–1282, 2003.

[33] René H. Levy, Kenneth E. Thummel, William F. Trager, Philip D. Hansten, and Michel Eichelbaum, editors. *Metabolic Drug Interactions - Kenneth E. Thummel and Kent L. Kunze and Danny D. Shen*, chapter "Metabolically-Based Drug-Drug Interactions: Principles and Mechanisms". Lippincott, Williams, and Wilkens, 2000.

[34] A. L. Mazzu, K. C. Lasseter, E. C. Shamblen, V. Agarwal, J. Lettieri, and P. Sundaresen. Itraconazole alters the pharmacokinetics of atorvastatin to a greater extent than either cerivastatin or pravastatin. *Clin Pharmacol Ther*, 68(4):391–400, 2000.

[35] George A. Miller. WordNet: a lexical database for English. *Commun. ACM*, 38(11):39–41, 1995.

[36] O. Mousa, D. C. Brater, K. J. Sunblad, and S. D. Hall. The interaction of diltiazem with simvastatin. *Clin Pharmacol Ther*, 67(3):267–274, 2000.

[37] P. J. Neuvonen, A. Varhe, and K. T. Olkkola. The effect of ingestion time interval on the interaction between itraconazole and triazolam. *Clin Pharmacol Ther*, 60(3):326–331, 1996.

[38] K. T. Olkkola, J. Ahonen, and P. J. Neuvonen. The effects of the systemic antimycotics, itraconazole and fluconazole, on the pharmacokinetics and pharmacodynamics of intravenous and oral midazolam. *Anesth Analg*, 82(3):511–516, 1996.

[39] K. T. Olkkola, K. Aranko, H. Luurila, A. Hiller, L. Saarnivaara, J. J. Himberg, and P. J. Neuvonen. A potentially hazardous interaction between erythromycin and midazolam. *Clin Pharmacol Ther*, 53(3):298–305, 1993.

[40] K. T. Olkkola, J. T. Backman, and P. J. Neuvonen. Midazolam should be avoided in patients receiving the systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther*, 55(5):481–485, 1994.

[41] J. P. Phillips, E. J. Antal, and R. B. Smith. A pharmacokinetic drug interaction between erythromycin and triazolam. *J Clin Psychopharmacol*, 6(5):297–299, 1986.

[42] J. Schmider, J. Brockmoller, G. Arold, S. Bauer, and I. Roots. Simultaneous assessment of CYP3A4 and CYP1A2 activity in vivo with alprazolam and caffeine. *Pharmacogenetics*, 9(6):725–734, 1999.

[43] P. H. Siedlik, S. C. Olson, B. B. Yang, and R. H. Stern. Erythromycin coadministration increases plasma atorvastatin concentrations. *J Clin Pharmacol*, 39(5):501–504, 1999.

[44] Teva. nefazodone hydrochloride (Nefazodone Hydrochloride) tablet. FDA-approved drug product labeling, 11 2006. Last accessed on DailyMed 05/29/2008.

[45] A. Varhe, K. T. Olkkola, and P. J. Neuvonen. Oral triazolam is potentially hazardous to patients receiving systemic antimycotics ketoconazole or itraconazole. *Clin Pharmacol Ther*, 56(6 Pt 1):601–607, 1994.

[46] A. Varhe, K. T. Olkkola, and P. J. Neuvonen. Diltiazem enhances the effects of triazolam by inhibiting its metabolism. *Clin Pharmacol Ther*, 59(4):369–375, 1996.

[47] A. Varhe, K. T. Olkkola, and P. J. Neuvonen. Fluconazole, but not terbinafine, enhances the effects of triazolam by inhibiting its metabolism. *Br J Clin Pharmacol*, 41(4):319–323, 1996.

[48] L. L. von Moltke, D. J. Greenblatt, J. S. Harmatz, S. X. Duan, L. M. Harrel, M. M. Cotreau-Bibbo, G. A. Pritchard, C. E. Wright, and R. I. Shader. Triazolam biotransformation by human liver microsomes in vitro: effects of metabolic inhibitors and clinical confirmation of a predicted interaction with ketoconazole. *J Pharmacol Exp Ther*, 276(2):370–379, 1996.

[49] N. Yasui, T. Kondo, K. Otani, H. Furukori, S. Kaneko, T. Ohkubo, T. Nagasaki, and K. Sugawara. Effect of itraconazole on the single oral dose pharmacokinetics and pharmacodynamics of alprazolam. *Psychopharmacology (Berl)*, 139(3):269–273, 1998.

[50] N. Yasui, K. Otani, S. Kaneko, T. Ohkubo, T. Osanai, K. Sugawara, K. Chiba, and T. Ishizaki. A kinetic and dynamic study of oral alprazolam with and without erythromycin in humans: in vivo evidence for the involvement of CYP3A4 in alprazolam metabolism. *Clin Pharmacol Ther*, 59(5):514–519, 1996.