**Drug-drug interaction validation guideline for TAC 2018 challenge**

# Overview

The goal is to derive semantically structured drug-drug interaction (DDI) knowledge from natural language texts. The texts are “sentences” extracted from the drug interactions, contraindications, precautions & warnings, and certain other sections of the drug labels in Dailymed. (Some of them are sentence fragments, run-on sentences, and/or subsection titles due to punctuation/parsing idiosyncrasies.) The validation/judging/coding tool presents the sentences one at a time, together with the label drug name. The human coder/judge must first decide if the sentence asserts one or more DDI’s (known, possible, potential, or any other level of certainty). If it does, the coder must choose between three interaction types: Pharmacodynamic (PD), Pharmacokinetic (PK), or Unspecified. Then the coder must identify the text fragments/substrings which support such coding: the “precipitant” represents the concomitant drug, substance, or class; the “trigger” is a clue to the interaction type; and, for PD interactions, the “specific interaction” (SI) represents the resulting (usually pathological) medical condition. Finally, for PK interactions, the coder must select a subtype according to an FDA picklist provided by the tool.

# Parsing of Triggers & Precipitants

## Triggers

Triggers capture the words that lead to the interpretation of a specific type of interaction.

Capture the minimal text necessary – this is because the competitors are judged based on word matching, the longer the text, the more difficult it is for them to match.

Drug names (label drug or precipitant) should not be included in the trigger.

PD specific interactions *in general* should not be included in the trigger; however, sometimes this rule must be stretched or broken if there is no better option. (See examples in PD subsection below.)

Modifiers that do not substantively change the meaning (*vis a vis* interaction type) should not be included in the trigger; e.g., the trigger “increase plasma concentrations” usually signifies a PK interaction and is sufficient to do so at the FDA picklist’s level of granularity (see PK section below). Therefore modifiers such as “sometimes”, “substantially”, “can”, “may” and the like should not be included.[[1]](#footnote-1)

Since the context is drug-drug interaction, the co-administration of two drugs is assumed, so words like “coadministration”, “given with”, “concomitantly”, “Co-administration”, “concomitant” on their own are generally not considered as triggers unless there is no other choice; e.g.,

***text:*** “Do not coadminister aliskiren with VASOTEC in patients with diabetes .”

***trigger:*** Do not coadminister

***precipitant:*** aliskiren

If the desired trigger phrase words are interspersed with drug names or other unwanted words, the latter can be replaced by the wildcard “ | “; e.g., “increase ~~measurable~~ plasma concentration” 🡺 “increase | plasma concentrations”.

Non-content “stopwords” or “noisewords” such as “of”, “the”, “in”, “with” and the like are best dealt with downstream and should not be replaced by “ | “ unless some other adjacent word justifies it; e.g., “increase ~~in measurable~~ plasma concentration” 🡺 “increase | plasma concentrations” but “increase in plasma concentrations” is ok as is

A given text may indicate multiple DDI’s within and across triggers as well as interaction types and precipitants. Multiple triggers that all point to the same precipitant, interaction type, PK subtype (if any), and PD specific interaction (if any) can be lumped together with “ ; “ separators. Otherwise they must be paired up with those other values to preserve the meaning of the text and coded as separate interactions. (See examples in the Interaction Types section below.)

## Precipitants

Precipitants capture the words representing

* single drugs, substances, or drug/substance classes, which are
* distinct from the label drug and its surrogates such as abbreviations, generic/trade name equivalents, and general classes when they clearly refer to the label drug itself, and that
* interact with the label drug.

A given text may indicate multiple precipitants. Each should be encoded as a separate DDI of the appropriate type, PK subtype (if any), and PD specific interaction (if any); i.e., no “ ; “ lumping of precipitants.

Parenthetical synonyms and abbreviations should be treated as distinct precipitants and therefore coded as separate DDI’s. Do not include the parentheses unless they are part of the name.

The tool is case-sensitive but case variants do not have to be encoded redundantly. Encode the case of the occurrence which is best grammatically joined to the trigger; e.g.

***text:*** “HMG-CoA reductase inhibitors : Atorvastatin ? Atorvastatin Titrate atorvastatin dose carefully …”

***trigger:*** Titrate | dose

***precipitant:*** atorvastatin

Otherwise encode the case of the first occurrence.

Drug classes can be precipitants, but do not encode them if the syntax clearly indicates that they are stated merely as descriptive subsection headers (e.g. “HMG-CoA reductase inhibitors” in the foregoing example) or refer to the label drug.

Route of administration qualifiers (oral, parenteral, intravenous, etc.) should be included as stated in the text, but NOT specific doses, schedules, etc.

Combination “/” drug precipitants AND their components should be coded as separate DDI’s; e.g.,

***text:*** “HIV-1 protease inhibitor: Tipranavir/ritonavir ? Saquinavir Combining saquinavir with tipranavir/ritonavir is not recommended.”

***trigger:*** not recommended

***precipitant 1:*** tipranavir

***precipitant 2:*** ritonavir (entered as a separate DDI)

***precipitant 3:*** tipranavir/ritonavir (entered as a separate DDI)

# Interaction types

## Pharmacodynamic (PD)

PD interactions can be thought of as the effect of the drug combination *on the organism* (as opposed to PK which are drug-drug effects *on each other*). For our purposes PD interactions are distinguished by one or more “specific interactions” (SI; disorder or other biomedical result of the DDI) that can be extracted from the text.

SI’s also need to be as “trimmed” down to minimal strings because the goal is to facilitate matching to controlled terminologies. “Hedging” words (modifiers) such as “serious”, “life-threatening”, “potential”, “risk” and the like should usually be excluded or, if necessary, used as trigger words. Each SI should convey a single *result* of the DDI, usually a pathological condition; e.g., in “Drug X may increase blood pressure …” the SI is “increase blood pressure” because “blood pressure” alone is a normal function, not a *result* of the DDI or a pathological condition.

General terms like “symptoms”, “toxicity”, and “adverse reactions” alone do not count as SI’s. In the absence of more specific information, code such DDI’s as “Unspecified interactions.”

SI’s *in general* should not include trigger words; however, sometimes the trigger may have to “share” all or part of an SI because there is no better trigger substring available; e.g.,

***text:*** Potentiation occurs with ganglionic or peripheral adrenergic blocking drugs.

***precipitant 1:*** ganglionic | adrenergic blocking drugs

***precipitant 2:*** peripheral adrenergic blocking drugs (entered as a separate DDI)

***trigger:*** Potentiation

***SI:*** Potentiation

[A better SI would be “Potentiation of X” where X is the label drug, but this is not available in the text.]

***text:*** “In some patients, the administration of an NSAID can reduce the diuretic, natriuretic, and antihypertensive effect of loop, potassium-sparing, and thiazide diuretics.”

***precipitant:*** NSAID

***trigger:*** reduce | effect

***SI:*** reduce | diuretic | effect ; reduce | natriuretic | effect ; reduce | antihypertensive effect

***text:*** “ALDACTONE reduces the vascular responsiveness to norepinephrine .”

***precipitant:*** norepinephrine

***trigger:*** reduces | responsiveness

***SI:*** reduces the vascular responsiveness

SI’s *in general* should not include drug names (label drug or precipitant); however, sometimes this rule must be excepted to obtain a specific enough SI; e.g.,

***text:*** Methotrexate and other drugs may reduce the effect of LASIX .

***precipitant:*** Methotrexate

***trigger:*** reduce the effect

***SI:*** reduce the effect of LASIX

Some of these examples raise another issue: PD interactions with triggers such as “potentiate” and “reduce the effect” (especially with SI’s that include drug names) may tempt coders to code them instead as Pharmacokinetic (PK) interactions. However, in the absence of a more PK-specific trigger, these should be interpreted as drug-drug agonism/antagonism which is PD, even if PK keywords are mentioned elsewhere in the text; e.g.,

***text:*** Methotrexate and other drugs that , like LASIX , undergo significant renal tubular secretion may reduce the effect of LASIX .

***precipitant:*** Methotrexate

***trigger:*** reduce the effect

***SI:*** reduce the effect of LASIX

If the direction (increased/decreased) of the effect is not evident (“reduce” in the foregoing), it is too nonspecific to be a PD SI, so code the DDI as Unspecified; e.g.,

***text:*** “Monitor diuretic effects when furosemide is coadministered with aliskiren .”

***precipitant:*** furosemide

***trigger:*** Monitor

If, in the same text and for the same precipitant, there is a distinct Pharmacokinetic (PK) interaction indicated, code it as a separate interaction; e.g.,

***text:*** “Coadministration is not recommended.Increased concentrations of indinavir may result in nephrolithiasis.”

***precipitant:*** indinavir

***PD trigger:*** result in

***PD SI:*** nephrolithiasis

***PK trigger:*** Increased concentrations (entered as separate DDI)

***PK type:*** C54357: INCREASED CONCOMITANT DRUG LEVEL (entered as separate DDI)

However, if, in the same text and for the same precipitant, there is also a distinct nonspecific trigger (e.g., “not recommended” in the foregoing example), do NOT code it as a separate Unspecified interaction and avoid including it in the PD or PK triggers unless clearly needed.[[2]](#footnote-2)

If, for a given precipitant, there are multiple triggers and/or multiple specific interactions, they can be lumped together with the “ ; “ separator and coded as one interaction, as long as the meaning of the text is preserved; e.g.,

***text:*** In isolated cases , intravenous administration of LASIX within 24 hours of taking chloral hydrate may lead to flushing , sweating attacks , restlessness , nausea , increase in blood pressure and tachycardia .

***precipitant:*** chloral hydrate

***trigger:*** lead to

***SI:*** flushing ; sweating attacks ; restlessness ; nausea ; increase in blood pressure ; tachycardia~~.~~

***text:*** “In some patients, co-administration of an NSAID can increase the risk of bleeding and/or dyspepsia.” [[3]](#footnote-3)

***precipitant:*** NSAID

***trigger:*** increase the risk

***SI:*** bleeding ; dyspepsia

However, distinct trigger-effect pairings should be split into separate interactions; e.g.,

***text:*** “In some patients, the co-administration of an NSAID can increase the risk of bleeding while exacerbating dyspepsia.”

***precipitant:*** NSAID

***trigger 1:*** increase the risk

***SI 1:*** bleeding

***trigger 2:*** exacerbating (entered as separate DDI)

***SI 2:*** dyspepsia (entered as separate DDI)

## Pharmacokinetic (PK)

PK interactions can be thought of as the effect of the two drugs in combination *on each other* (as opposed to PD which are effects *on the organism*). PK effects can be thought of as the convenient acronym ADME: absorption, distribution, metabolism, elimination. For our purposes PK interactions must subtyped and coded according to an FDA picklist supplied by the tool which specifies

* Whether the effect is on the DRUG (label drug or its surrogates such as generic name or class) or the CONCOMITANT DRUG (precipitant);
* Whether the effect is DECREASED or INCREASED;
* Which PK parameter (AUC, Cmax, half-life, level, and Tmax) is affected.



PK trigger keywords signifying concentration, absorption, metabolism, clearance, excretion, etc., can be coded with the “LEVEL” terms in the picklist. However, be aware that the INCREASED/DECREASED direction might be reversed from the text (e.g. “decreased metabolism” normally means INCREASED LEVEL).

***text:*** “treatment with phenytoin leads to decrease intestinal absorption “

***precipitant:*** phenytoin

***PK trigger:*** decrease intestinal absorption

***PK type:*** C54356: DECREASED DRUG LEVEL

***text:*** Lithium generally should not be given with diuretics because they reduce lithium's renal clearance and add a high risk of lithium toxicity.

***precipitant:*** diuretics

***PK trigger:*** reduce | renal clearance

***PK type:*** C54355: INCREASED DRUG LEVEL

Multiple specific PK subtype interactions for the same drug/precipitant should be coded as separate interactions; e.g.,

***text:*** “Drug X and Labe l Drug increase each other’s plasma levels”

***precipitant:*** Drug X

***PK trigger 1:*** increase | plasma levels

***PK type 1:*** C54355: INCREASED DRUG LEVEL

***PK trigger 2:*** increase | plasma levels (entered as separate DDI)

***PK type 2:*** C54357: INCREASED CONCOMITANT DRUG LEVEL (entered as separate DDI)

If there are multiple triggers for the same specific PK subtype interaction, they can all be lumped together with “ ; “ separators as one interaction (per drug/precipitant); e.g.,

***text:*** “Oral administration of nitroglycerin markedly decreases the first-pass metabolism of dihydroergotamine and subsequently increases its oral bioavailability .”

***precipitant:*** dihydroergotamine

***PK trigger:*** decreases | metabolism ; increases | bioavailability

***PK type:*** C54357: INCREASED CONCOMITANT DRUG LEVEL

However, distinct trigger-subtype pairings should be split into separate interactions; e.g.,

***text:*** “Drug X increases Label Drug’s AUC and elevates Cmax”

***precipitant:*** Drug X

***PK trigger 1:*** increases | AUC

***PK type 1:*** C54605: INCREASED DRUG AUC

***PK trigger 2:*** elevates Cmax (entered as separate DDI)

***PK type 2:*** C54602: INCREASED DRUG CMAX (entered as separate DDI)

If there is a distinct PD interaction indicated for the same drug/precipitant, code it as a separate PD interaction; e.g.,

***text:*** “Strong CYP3A4 inducers decrease exposure to rivaroxaban and may increase the risk of thromboembolic events .”

***precipitant:*** CYP3A4 inducers

***PK trigger:*** decrease exposure

***PK type:*** C54356: DECREASED DRUG LEVEL

***PD trigger:*** increase the risk (entered as separate DDI)

***PD SI:*** thromboembolic events (entered as separate DDI)

As stated in the PD section, triggers such as “potentiate” and “reduce the effect” in the absence of a more PK-specific trigger should be interpreted as drug-drug agonism/antagonism and coded as PD if there is a specific interaction. If there is not, code the DDI as Unspecified.Triggers involving dosage adjustments (e.g., “reduce the dose”) should be encoded as PK.

***text:*** “Since the concomitant administration of warfarin with amiodarone increases the INR by 100 % after 3 to 4 days , reduce the dose of the anticoagulant by one-third to one-half , and monitor INR closely .

***precipitant:*** warfarin

***PD trigger:*** increases the INR

***PD SI:*** increases the INR

***PK trigger:*** reduce the dose (entered as separate DDI)

***PK type:*** C54357: INCREASED CONCOMITANT DRUG LEVEL (entered as separate DDI)

## Unspecified Interactions

General warnings of risk and against combining the label drug with a precipitant should be coded as Unspecified Interactions as long as there is a clear trigger and precipitant in the text; e.g.,

***text:*** “Lithium generally should not be given with diuretics.”

***trigger:*** should not be given

***precipitant:*** diuretics

For a given text/precipitant, the text must not otherwise qualify for coding as a PD or PK interaction. That is, do not code additional “Unspecified” interactions for the same text/precipitant that have a PD or PK interaction, and do not include such triggers in the PD or PK interactions coding; e.g. “Lithium should not be given with diuretics …” in the example on the previous page.

However, a given text may suggest DDI’s for multiple precipitants which should be coded independently as PD, PK, or Unspecified, as appropriate. Be careful not to lump triggers inappropriately; i.e. restrict them to the specific DDI being encoded.

General terms like “symptoms”, “toxicity”, and “adverse reactions” do not count as specific interactions for a PD interaction. In the absence of more specific interactions, code such DDI’s as “Unspecified interaction.”

If there are multiple triggers for the same precipitant’s Unspecified interaction, they can all be lumped together with “ ; “ separators and coded as a single Unspecified interaction.

## No Interaction

Code as “No Interaction” those texts where

* The text does not represent a DDI, OR
* No precipitant (non-label) drug, substance, or class is explicitly mentioned, OR
* The “trigger” is absent, neutral, ambiguous, or negative (i.e. suggests that there is NO interaction), or suggests that the evidence is unclear or unknown. Note that the trigger must exist in the text; label section headings don’t count and will be rejected by the online coding tool.
1. This could depend on the particular modifier and interaction type. Ongoing QA will be informative. [↑](#footnote-ref-1)
2. This is a new convention so it’s not the case for our training set, but we include it here for implementation in post-processing rules and filters. Given enough examples of absent validated coding, systems can learn to ignore less specific interactions in texts with a PD or PK DDI for the same precipitant. [↑](#footnote-ref-2)
3. Some examples in this document are “made up” for purposes of illustration. [↑](#footnote-ref-3)