**ABSTRACT LEVEL CLASSIFICATION**

**DDI In vivo PK**

**DDI In vitro PK**

**DDI Clinical**

**DDI PD**

**Drug-Nutrition Interaction** (Including Drug-food Interaction, Drug-Alcohol Interaction and Drug-Herb interaction) \* Take St. John’s Wort as a herb

**Single-Drug**

**Case Report**

**Non-Drug**

**SENTENCE LEVEL ANNOTATION**

* ***Summary:*** The typical fragment annotation thus consists of a tag of the form:

***\*\*[<Integer>][G|M|S]+[P|N][0-3][E[0|N |2|3]][-|+] ? [( ] [VV|VT|VC|V0]\* [DR|DE|DD|D0] \*[MI|MD|MM|MT|MS|MN|MA|M0]\* [ )]***

where *<****Integer****>* is the ordinal number of the fragment within its sentence, starting at 1.

* That is: Number, *Focus* indicator(s), followed by *Polarity*, then *Certainty* degree, followed by an *Evidence* indicator with one or more evidence codes, possibly followed by a *Direction* indicator, followed by Study Type; Interaction Type; and finally Mechanism.
* **Note:** The definition below is a Formal Grammar Specification of what an Annotation should look like. The square brackets, angular brackets, vertical lines (|) and Superscripts of the form  + ? \* are NOT part of the annotation itself.

Basically *[G|M|S]+*means “AT LEAST ONE of the letters G or M or S should occur. Possibly MORE THAN JUST ONE OF THEM”.

In contrast *[0-3]* means “EXACTLY ONE NUMBER BETWEEN 0 and 3 Must occur” while *[-|+] ?* means “ONE of the symbols – or + can occur. Possibly Both or None of them”. *[VV|VT|VC|V0] \** means “AT LEAST ONE if the code should occur, Either V0 or ONE/MORE THAN JUST ONE of THE OTHER CODES”.

**FRAGMENTATION**

**How to break the sentence:**

* Fragmentation should occur at each point in the sentence where the annotator perceives a change in any dimension.
* If there is no change, or important information (drug name) is missing, integrate the context as one fragment. In the context, the previous sentence is annotated as 11, while the end sentence is assigned full annotation tags.

**How to label the fragments:**

* Each fragment will be tagged with an ordinal number.
* The tag of the first fragment within a sentence starts with the number 1, the second with 2 etc.
* The tag of an un-fragmented sentence always starts with 1.

**EVERY ANNOTATION STARTS WITH \*\* (Immediately before the Fragment number)**

**DIMENSIONS FOR ANNOTATION:**

# Focus:

## Scientific (S)

* Any scientific content, findings and discovery.

e.g.

* + 1. Concurrent cimetidine did not cause a reduction in the AUC of the active desmethyl metabolite. \*\*1SN3E3-(V0DDMM)
    2. In the present study, we evaluate the contribution to tumorigenesis and the timing of b-catenin mutations in 202 sporadic colorectal tumors, including 48 small (<1cm) adenomas, 82 large adenomas, and 72 invasive cancers. \*\*1SP0EN(V0D0M0)
    3. We investigated the metabolism of pranlukast, a selective leukotriene agonist, and the potential for drug-drug interactions. \*\*1SP0E3(V0DRMM)
    4. Title = The influence of diltiazem hydrochloride on trough serum digoxin concentrations. \*\*1SP3E3(VVDDMM)

*As this is a title- it means that the paper is going to provide some evidence for whatever it is the title is saying. So E3 or E1, not E0. This sentence provides a pharmacokinetics evidence (serum concentration) for the interaction between diltiazem hydrochloride and digoxin, so E3.*

* For most sentences describing prospective or future study, **S** is assigned.

e.g.

* + 1. Diltiazem may therefore impair the clearance of other coadministered drugs that undergo hepatic oxidation. \*\*1SP2E1-(V0DRMM)
    2. It is recommended that femoxetine is given in reduced doses (e.g. 400 mg) when administered with cimetidine. \*\*1SP1EN-(V0DDM0)

## Generic (G)

* General state of knowledge and science outside the scope of the paper,
* The structure of the paper itself or the state of the world.
* Such statements are not usually based on scientific experiment, and may reflect an opinion or an observation that would have been as truthful, and probably as valid, if made by a layperson.

e.g.

* + 1. A review of the current literature on this topic is included. \*\*1GP3E1(VND0M0)

*It is not experimental evidence of any kind. If anything – it is E3 – reference to elsewhere in the paper, OR E1 – reference given but not very specific.*

* + 1. Thus, in this case, the chemistry of the product is similar to that of the signal molecules, \*\*1GP3E1(VND0M0)

but there is no complementary relationship to the signal sequences. \*\*2GN3E0(VND0M0)

*While this statement describes a scientific observation, it does not refer to any specific biological or medical entity; rather, it uses generic terms (“product”, “signal molecules” and “signal sequences”) making the whole statement generic.*

*The fragmentation occurs when there is a change of polarity from positive to negative.*

* + 1. This article suggests that medicine recycling may be a possibility (especially if manufacturers are mandated to blister-package and bar-code individual tablets and capsules). \*\*1GP2E3(VND0M0)

*This is not a scientific statement, but a statement of content of the article. Since the article itself is the evidence here we use the E3 code.*

* + 1. Although neuropathologic studies of autism are limited,

\*\*1GP3E1-(VND0M0)

reports of Purkinje and granule cell loss in Cblm (16) also suggest overlap with this neonatal infection paradigm. \*\*2SP2E2(VND0M0)

*The first fragment makes a claim only about the number of studies, not their scientific content. Therefore the focus is generic rather than scientific. As there is reference to “studies” but no explicit citation, that evidence is at level 1. The direction is negative since the number is said to be “limited”. The second fragment does discuss an explicit phenomenon and provides citation, hence the fragment is viewed as scientific, with evidence level 2. Because of the term “suggest” the confidence level is not as-high-as-can-be, but just “2”.*

## Methodology (M)

* That was used to execute an experiment or a study.

e.g.

Lidocaine hydrochloride 100 mg was administered intravenously over two minutes, and plasma lidocaine concentrations were determined before treatment and at various intervals for three hours. \*\*1MP3EN(VVDRM0)

*The statement describes what was done, using the past tense verb “was administered” and “was determined”. This indicates that the authors are reporting their own work, and makes it an evidence level of 3. The statement does not discuss results or conclusions – just the methodology used.*

## Both (e.g. SM)

* In some cases a fragment discussing Methodology may also discuss Science. In such cases the leftmost tag-letter will be M followed by S.

e.g.

* + 1. Treatment of human hepatocytes for 72 h with 2-200 microM TB produced concentration-dependent increases in CYP1A2, CYP2B6 and CYP3A4 mRNA levels, whereas treatment with BHT increased CYP2B6 and CYP3A4 mRNA levels. \*\*1SMP3EN+(VTDEM0)

*Here we have both methodology and experimental results described in such a way they cannot be readily separated. Hence, both Science (S) and Methodology (M) focus.*

* + 1. Future structural and functional studies will be necessary to understand precisely how She2p binds ASH1 mRNA and how interactions with She3p influence the formation of a functional localization complex. \*\*1[S|G]P0E0(VND0M0)

*While this is a statement with scientific contents it does not assert a completely scientific fact. Rather it makes an assertion about the necessity for further studies about a topic and finding further information. Therefore the focus is both S and G (Generic). Since it asks “how” questions, the level of certainty is 0, and as no evidence is provided, the level of evidence is also 0.*

# Polarity

## **P** (positive)

## **N** (negative)

* A fragment with any focus can be stated either positively or negatively. The next field in the tag sequence is thus either a ***P* (*positive*)** or an ***N* (*negative*)***.*

e.g.

* + 1. Title= Lack of pharmacokinetic interaction after administration of lansoprazole or omeprazole with prednisone. \*\*1SN3E3(V0DDM0)
    2. No influence of cimetidine was observed on the kinetics of single doses of femoxetine, \*\*1SN3E3(V0DDM0)

but after multiple doses the plasma concentration of femoxetine was significantly increased. \*\*2SP3E3+(VVDRM0)

*This sentence is fragmented because part is positive and part negative. A negative assertion “No influence”, stated as fact, with high confidence.*

* For statements that convey lack-of-knowledge, (e.g. “*It is still unknown whether*…”), the default assignment is ***P*.**

(The lack of knowledge in this case will be reflected with a certainty degree of ***0***, as explained in the next item*.*)

* + Every fragment should be annotated by its polarity, regardless of its focus, certainty, interaction-contents or direction.

# Certainty

* Indicates the level of certainty regarding the validity of an assertion made in a fragment.
  + Each fragment conveys a degree of certainty about the validity of the assertion it makes. The annotation will use a scale of 0-3 as a measure of certainty, for both positive and negative statements.

## 0

The lowest degree (**0**) represents **complete uncertainty**, that is, the fragment explicitly states that there is an uncertainty or lack of knowledge about a particular phenomenon—the author does not know (“it is unknown if…”, “it is unclear whether…”, how, “we evaluate/investigate…” etc.).

e.g.

* + 1. The influence of cimetidine on the pharmacokinetics of alprazolam and triazolam, two triazolobenzodiazepines metabolized by hepatic microsomal oxidation, was evaluated in a series of healthy volunteers. \*\*1SP0E3(VVDDMM)

*The ‘was evaluated in a series of healthy volunteers’, indicates the performance of an experiment and suggest that the evaluation has an experimental component, hence the evidence level E3. Since the sentence says that the influence of the cimetidine on other drugs is to be evaluated (and does not say that there is or that there isn’t such influence with any level of certainty) the certainty level is 0.*

* + 1. However, when morphine and nalbuphine are mixed together, the clinical interactions in different combining ratios on analgesic effect and adverse events are unknown. \*\*1[S|M]P0E0(VCDDM0)

*It can also be Methodology and Science because the beginning seems to describe a method.*

## **3**

The highest degree, (**3**), represents complete certainty (an accepted, known and/or proven fact).

e.g.

* + 1. Urinary digoxin clearance decreased from 223.5 +/- 35.7 ml/min to 153.4 +/- 17.5 ml/min (p less than 0.05). \*\*1SP3EN-(VVDRM0)
    2. A significant drug interaction between verapamil and digoxin, resulting in elevated serum digoxin concentrations, has been well documented in the medical literature. \*\*1SP3E1+(VVDDM0)
    3. The (AUC (0-infinity)) of norverapamil and the terminal half-life of verapamil did not significantly changed with lovastatin coadministration. \*\*1SN3E3(V0DDM0)

## **1** & **2**

Intermediate degrees: (**1**) represents a **low certainty**, while (**2**) is assigned to **high-likelihood** expressions that are still short of complete certainty.

e.g.

* + 1. Since ranitidine does not alter the pharmacokinetic profile of oral carbamazepine, \*\*1SN3E1(VVDDM0)

it is unlikely that the changes observed with cimetidine were due to increased carbamazepine absorption. \*\*2SP1E3+(V0DDM0)

*Fragmentation is motivated here by a change of strength of a statement (from a negative assertion with full confidence “does not alter” N3 to “unlikely” P1), and change in evidence support and in trend.*

* + 1. These results suggest that the effect of Cd was likely not caused by intracellular ROS generation, \*\*1SN2E3(VNDRM0)

but through interaction with the membrane receptors. \*\*2SP3E0(VND0M0)

*Fragmentation occurs due to change in polarity between first and second fragment. The occurrence of “likely not caused” in Fragment 1 implies that the assertion itself is uncertain, thus the 2 rating.*

* + 1. It is recommended that femoxetine is given in reduced doses (e.g. 400 mg) when administered with cimetidine. \*\*1SP2E3-(V0DDM0)
  + **Certainty in title** is typically indeed the highest possible (3) - as it is a bold statement, but sometimes the title is a question or a less confident statement. (Rarely but happens).

e.g.

* + 1. Effect of duration of lidocaine infusion and route of cimetidine administration on lidocaine pharmacokinetics. \*\*1SP3E3(VVDDM0)
    2. Title= Lack of pharmacokinetic interaction between rofecoxib and methotrexate in rheumatoid arthritis patients. \*\*1SN3E3(VVDDM0)
    3. Title = Quinidine-digoxin interaction: are the pharmacokinetics of both drugs altered? \*\*1SP0E1(V0DDM0)

*This title is an interrogative sentence. There is no evidence to support the interaction between the two drugs. So E1 is assigned.*

* + Usually methodology will have high certainty.

e.g.

After 14 days of concomitant therapy, steady-state trough digoxin concentrations were again determined, as well as creatinine clearances and urinary digoxin clearances. \*\*1MP3E3(VVDRM0)

*The statement describes what was done, using the past tense verb “were again determined”. This indicates that the authors are reporting their own work, and makes it an evidence level of 3. The statement does not discuss results or conclusions-just the methodology used. Therefore the tag M is used.*

* + When assigning tags, the annotator should not downgrade the certainty rating based on his/her own impression of the statement’s inaccuracy.
    - That is, as a rule of thumb, if a statement does not explicitly indicate any degree of uncertainty – it should be taken to convey complete certainty, and annotated with certainty level 3.
    - Statements should be tagged as uncertain if and only if the text itself contains language that supports this impression.
  + Our goal is to infer the certainty intended by the author.

Therefore, the tag should reflect the degree of certainty conveyed by the author’s statement about the scientific finding, rather than the annotator’s belief.

# Evidence

* + Indicates, for a fragment, regardless of its focus and certainty, if its assertion is supported by evidence.
  + The existence – or the lack of –evidence is denoted in the tag starting with the letter E. The letter is followed by one digit in the range [0-3], or letter N, indicating the type of evidence or its absence thereof:

## E0

There is no indication of evidence in the fragment whatsoever, or an explicit statement is made in the text about the lack of evidence.

e.g.

* + 1. We demonstrate that ICG-001 binds specifically to CBP \*\*1SP2E3(VND0M0)

but not the related transcriptional coactivator p300, \*\*2SN2E0(VND0M0)

thereby disrupting the interaction of CBP with beta-catenin.

\*\*3SP2E1-(VND0M0)

*First fragment: “We demonstrate” indicates that experiments performed by the authors support the statement E3.*

*The sentence is fragmented, due to change on polarity to negative (“but not”), and then again to positive-with a negative trend (“thereby disrupting”).*

*The last two fragments do not carry any indication of evidence, therefore the code becomes E0.*

* + 1. Abstract = Amodiaquine (AQ) metabolism to N-desethylamodiaquine (DEAQ) is the principal route of disposition in humans. \*\*1SP3E0(VTDRMM)

*Stated as a well-accepted fact, but with no indication for any evidence. Hence, E0.*

## E1

Evidence is hinted at but no explicit reference to it is provided, in one of the following forms:

a. The statement is well-known or common knowledge (e.g. “It is well known that…”).

b. The evidence is merely asserted to exist possibly in the preceding text, in prior experiments, or in other papers.

Note that the indirect implication of evidence may not be explicit in the fragment, but implied by a use of term referring to a previous fragment.

For instance, a sentence may begin with the fragment “Previous experiments show that…” followed by the fragment, “therefore, it is likely that …”. Both fragments are of evidence level 1; the first because it points to experiments without an explicit reference, and the second, because of the “therefore” term which uses the previous assertion as an indirect evidence.

e.g.

* + 1. Therefore, the mechanism of the single-dose carbamazepine-cimetidine interaction is probably metabolic inhibition, \*\*1SP2E1(V0DDMI)

although the exact pathway (or pathways) affected has not been identified. \*\*2GN3E0(VND0M0)

*The fact that they say “Therefore” means that they provided SOME kind of evidence in the previous sentence. At least E1 (if not E2-depending of what the previous sentence was…).*

* + 1. This may provide a novel combination strategy of opioid agonist and agonist-antagonist for postoperative pain management after gynaecologic surgery. \*\*1SP2E1(VCD0M0)

*The fact that they refer to “This” means that they showed something to support their claim in previous statements. Which makes it again – at least E1.*

* + 1. Thus, DHPLC analysis of Bat26 site may be a favorable method of detecting MSI-H status in gastric cancer, and be of clinical importance. \*\*1[M|S]P1E1(VND0M0)

*Again we have method and result intermingled and use MS. Also the word “Thus”* *suggests some evidence which has been mentioned in the previous discussion, so E1 is used.*

* + 1. At the present time, then, the available data would support the notion that b-catenin mutations are only rarely seen in sporadic colon cancer. \*\*1SP2E1-(VND0M0)

*The terms: “the available data” indicate that evidence is available, but there is no explicit reference to data produced by the authors (experiments) or to a paper presenting data produced by anyone else. Therefore the evidence is very indirect, and is indicated as E1.*

* + 1. The Wnt/beta-catenin pathway normally regulates expression of a range of genes involved in promoting proliferation and differentiation. \*\*1SP3E1(VND0M0)

*Stated as a well-accepted fact, but with no direct indication for any evidence.*

*Hence, E1.*

## E2

Evidence is not given within the sentence/fragment, but explicit reference is made to other papers (citations) to support the assertion.

e.g.

* + 1. Mechanisms underlying morphogenesis have been studied extensively in the unicellular yeast systems (Lew, 2003). \*\*1GP3E2(VND0M0)

*The explicit reference to Lew, 2003, provides evidence of type 2 (as defined in the guidelines) to the claim. Hence E2.*

* + 1. Neonatally infected rats are reported not to have inflammation (6–10) \*\*1SN2E2(VND0M0)

*Some uncertainty is expressed thus the P2. There is evidence in the form of references and this gives The E2 code.*

## E3

Descriptive evidence is provided, within the fragment, in one of the following forms:

a. A reference to experiments previously reported within the body of the paper by a direct description of the finding as an experimental results (e.g. “our data indicates…”, “… our results show”…)

b. A verb (typically in the past-tense) within the statement indicates an observation or an experimental finding which is described within the paper, (e.g. “We found that…”, “We see that…”, “The level of …increased over time…”).

e.g.

* + 1. These results show that cimetidine, unlike ranitidine, significantly inhibits the biotransformation of doxepin. \*\*1SP3E3(VNDDMI)

*“These results” suggests the existence of evidence, which is described in the context.*

* + 1. Since ranitidine does not alter the pharmacokinetic profile of oral carbamazepine, \*\*1SN3E1(VVDDM0)

it is unlikely that the changes observed with cimetidine were due to increased carbamazepine absorption. \*\*2SP1E3(V0DDM0)

*The change of polarity from negative to positive and the certainty level from complete certain to uncertain. In Fragment 1, “the pharmacokinetic profile” suggests the existence of evidence, but not where to find such evidence, and this leads to the E1 code.*

* Code E3 is given to authors’ suggestion, assumption, and recommendation inferred from the results of their results.

e.g.

1. Dose adjustment of pravastatin may be necessary with concomitant use of RTV and SQVsgc. \*\*1SP2E3(VVDDM0)
2. The overall results may help to explain high smoking rates in the MMT population and may account for reports of increased positive effects of methadone when the drugs are taken together. \*\*1SP2E3+(V0DDM0)

## EN

Evidence is provided as own experiment number (***EN***, Quantitative Evidence), such as values of PK/PD parameters, sample size, drug doses, treatment time.

e.g.

This was due to reductions in both renal clearance (from 105 +/- 39 to 84 +/- 15 ml/min) (p less than 0.05) and nonrenal clearance (from 130 +/- 38 to 88 +/- 20 ml/min) (p less than 0.01). \*\*1SP3EN-(VVD0M0)

*The statement describes the results of clinical PK study and the numerical values makes it an evidence level of EN.*

* The sentences of Methodology

e.g.

* + 1. During the control phase of the study, volunteers were administered digoxin 0.25 mg/d for 13 days, and subsequently judged to be at steady state by serial determinations of digoxin serum concentrations. \*\*1MP3EN(VVDRM0)

*The statement has the M (Methodology) tag as it describes a part of the clinical trail protocol used by the authors (as indicated by the use of the past-tense “were administered”). The drug dosage and time makes it EN.*

* + 1. Seven healthy male volunteers received sodium valproate (NaVPA, 200 mg) orally twice daily for 7 days, after which all drug intake ceased for 1 month. \*\*1MP3EN(V0DRM0)

# Direction/Trend

* The last (rightmost) part of the tag-vector for a fragment (BEFORE THE Parentheses with the interaction type and mechanism) indicates whether the assertion reports a qualitatively high/low level or an increase/decrease in a specific phenomenon, finding or activity.

## +

An increase or high-level is denoted by **+**

## -

A decrease or low is denoted by **-**.

e.g.

* + 1. The conclusion is that cimetidine impairs the elimination of chloroquine in healthy subjects. \*\*1SP3E3-(VVDDM0)

*A decrease/reduce trend is signaled by the word “impairs”.*

* + 1. Nitrendipine 20 mg daily led to a significant increase in plasma digoxin levels and in its area under the plasma concentration-time curve AUC (0-12) was 9.7 ng ml-1h when digoxin alone was given and 11.2 ng ml-1h on co-administration of the calcium antagonist. \*\*1SMP3EN+(VVDDM0)
    2. ICG-001 selectively blocked the beta-catenin-CBP interaction

\*\*1SP3E3-(VND0M0)

without interfering with the beta-catenin-p300 interaction.

\*\*2SN3E0-(VND0M0)

*Fragmentation at a conjunction term “without”. Here there is a change of polarity between the two fragments, from positive to negative. Note that the direction in both fragments is “-” since both “blocked” and “interfering” indicate a decline. The past tense of the first fragment “selectively blocked” indicates that this is an experimental report by the authors, and therefore obtains evidence level 3.*

* + 1. Omeprazole had no apparent effect on the mean (S)-warfarin plasma concentration (379 ng/ml with, versus 387 ng/ml without, omeprazole), \*\*1SN3EN(VVDDM0)

but caused a slight (12%) although statistically significant increase in the mean (R)-warfarin concentration from 490 to 548 ng/ml (95% confidence interval for difference of means: 28-88). \*\*2SP3EN+(V0DRM0)

## +/-

If both reduction and increase of the SAME phenomenon are said to be possible, we mark it as: +/-

e.g.

Abstract = Pharmacokinetic drug interactions may result in a decrease or increase in the oral bioavailability of some drugs. \*\*1GP2E0[+|-](VVD0M0)

*The word “may” conveys the uncertainty of the statement, without evidence support. So certainty level is 2, evidence E0. While the trend change of the oral bioavailability is either increase or decrease, so +|- is given.*

## None

There is no description of increase or reduction of anything – In which case we don’t put it.

e.g.

* + 1. “have little effect”—Positive polarity and no direction

*The Direction tag is introduced to separate the notion of positive/negative results and assertions (as captured by Polarity) from the level of the observed phenomenon itself.*

* + 1. Also, blocking the entry of Cd into the cells with manages did not diminish Cd-induced activation of MAPK/ERK. \*\*1SN3E3-(VTDDM0)

*This sentence indicates a negative experimental finding (“did not...” – negative polarity), about a negative trend (“diminish”). This is a case known as* ***double-negation****, and is typically hard to annotate, as it is not clear whether the phenomenon is actually present or not.*

*Separating Direction from Polarity provides a mechanical way to annotate and interpret the statement.*

*Moreover, this separation also provides means to indicate presence/absence of experimental findings (tagged as Polarity), regardless of whether these findings demonstrate the presence or the absence of the monitored phenomenon (the latter is captured by the Trend).*

* + Every indication of trend occurring in the text should be annotated.

# Study Type:

## In Vivo (*VV*)

Studies that are in vivo are those in which the pharmacokinetic entities of drugs are tested on humans through clinical trials.

* Besides PK parameters, dose adjustment, and treatment groups are also considered as important symbols of in vivo study.
* Serum/plasma concentration, urinary metabolic ratio, and oral clearance implies in vivo PK parameter.

e.g.

1. This investigation demonstrates that concomitant administration of diltiazem hydrochloride with digoxin results in significantly elevated steady-state trough digoxin concentrations (0.32 +/- 0.07 ng/ml increasing to 0.48 +/- 0.06 ng/ml, p less than 0.01). \*\*1SP3EN+(VVDDM0)

*The words “concomitant administration” and parameter “steady-state trough digoxin concentrations” indicate this is a pharmacokinetics study, so VV.* *And the numbers of the PK measurement indicate the performance of an experiment and suggest that the investigation has a strong numerical experimental evidence, hence the evidence level EN.*

1. However, renal and total clearance values for temafloxacin were reduced by 19%. \*\*1SP3EN-(VVDRM0)

*This statement describes the result of pharmacokinetics measurements, supported by the “clearance values”, with a decrease trend. And the word “renal” indicates this an in vivo study.*

## In Vitro (*VT*)

Studies that are in vitro are those in which the pharmacokinetic entities of drugs are tested on cell or human liver microsomes (HLM) models.

e.g.

1. The Dixon analysis showed that in both human liver microsomes and Supersomes CYP1A2 perazine potently and to a similar degree inhibited caffeine 3-N-demethylation (K(i) = 3.5 microM) and 1-N-demethylation (K(i) = 5 microM). \*\*1SP3EN(VTDDMI)

*The numerical values of the pharmacokinetics parameter K(i) indicate the result of an PK experiment, hence EN. Since the sentence mentions the drug metabolism inhibition is measured in “human liver microsomes and Supersomes”, VT is assigned for in vitro study type.*

1. The formation of DHTQ proceeds non-enzymatically, whereas that of DBAA requires NADPH. \*\* 1SP3E0(VTDRMM)

*“NADPH” implied in vitro study in test tube, so VT.*

## Clinical (*VC*)

Studies that are clinical are those in which the pharmacodynamic entities of drugs are tested in clinical trials.

* + - The difference between IN VIVO and CLINICAL study is the study endpoints. The IN VIVO studies present quantitative analysis of drugs, so the pharmacokinetic parameters are the main endpoints. While the symptom, sign, or change of diseases, adverse side effects, person-time, sample size, cox regression value, odd ratio, and hazard ratio are classified as CLINICAL endpoints.
    - Cohort studies, case control studies, and database studies are typical clinical studies.

e.g.

* + 1. The incidences and severity of dizziness, nausea, and vomiting were not significantly different. \*\*1SN3E3(VCD0M0)

*The symptoms “dizziness”, “nausea”, and “vomiting” indicate this statement describes the pharmacodynamics outcomes. Hence, VC.*

* + 1. The interaction between morphine and nalbuphine in PCA admixture on analgesia is additive. \*\*1SP3E3(VCDDMA)

## Multiple

Multiple study types are covered use the “|”(e.g. **VV|VC, or VV|VT|VC**)

e.g.

The effect of two different doses of nitrendipine on plasma digoxin levels, urinary recovery and systolic time intervals was investigated in 8 healthy volunteers. \*\*1SP0EN([VV|VC]DDM0)

*This is a statement describing what is going to be done in the clinical study. The under investigated parameters “plasma digoxin levels” and “urinary recovery” (pharmacokinetics in vivo parameters) and “systolic time intervals” (an echocardiographic parameter) indicate this is not only a PK in vivo study but also a PD clinical study. Hence, VV|VC. There is neither prediction of the outcome nor provided results, making no confidence, so certainty 0. These parameters and sample size indicate the performance of an experiment, so EN.*

## Don’t Know (*V0*)

We don't know which type of study is belonging to. For example, if there exists an endpoint, such as clearance but no information related to the route of drug intake, we cannot know whether it is an in vivo study or in vitro study.

e.g.

1. Then 0.25 mg digoxin b.d. was administered for two 1-week periods combined with nitrendipine 10 mg or 20 mg once daily. \*\*1MP3EN(V0DDM0)

*The statement has the M (Methodology) tag as it describes how the drugs are administered, which is a part of the protocol used by the authors. And the numbers of the drug dose and treatment period suggest evidence EN.*

*There is no endpoint or evidence that can indicate this is a PK in vivo or Clinical statement, hence V0.*

1. The wild type allele CYP2C9\*1 was the most active variant. \*\*1SP3E3(V0D0M0)

## No Study Type is Applicable (VN)

Studies are not drug interaction related.

e.g.

Therefore, the mechanism of the single-dose carbamazepine-cimetidine interaction is probably metabolic inhibition, \*\*1SP2E1(V0DDMI)

although the exact pathway (or pathways) affected has not been identified. \*\*2GN3E0(VND0M0)

*Due to the change of the polarity (from positive to negative “has not been”), this sentence is broken into to two fragments. “Therefore” in fragment 1, hints the indirect evidence existing possibly in the preceding text. So E1. While fragment 1 describes the possible mechanism (metabolic inhibition, so MI) of the drug interaction (“carbamazepine-cimetidine interaction”, so DD), no more information can help to indicate what study type it is. So V0 is given. In the second fragment, G (General focus) is given as this is a general description for the current research status. Hence, there is no applicable study type.*

# Interaction Type:

## Drug Related (*DR*)

* + Single drug study without mentioning the drug-drug interaction or drug-enzyme interaction.
  + When multiple drugs without interaction with each other, show up in one fragment, DR is still assigned.
  + Food, alcohol, herb medicine are not considered as drugs.

e.g.

* + 1. Total procainamide clearance (16.2, 14.1, and 13.7 ml/min/kg) did not differ significantly between the three trials, nor was there a significant change in area under the serum concentration curve for N-acetylprocainamide, the major metabolite. \*\*1SN3EN(VVDRM0)

*The words “did not” and “nor” indicate a negative polarity. And EN is given as this sentence states the numerical results of experiment done by the authors. “serum concentration curve” indicates this is a PK in vivo study, as “serum concentration” is measured in human. Through the whole sentence, only drug procainamide and its metabolite acetylprocainamide are mentioned. There is no drug interaction , so DR.*

* + 1. High pressure liquid chromatography analysis of plasma also verified compliance with cimetidine (mean level, 0.61 microgram/ml) and ranitidine (mean level, 0.36 microgram/ml) regimens. \*\*1[S|M]P3EN(VVDRM0)

## Drug Enzyme Related (*DE*)

When there is any interaction between drugs and enzymes.

e.g.

Verapamil is a substrate of both P-gp and CYP3A4. \*\*1SP3E1(V0DEM0)

*This statement indicates the relationship between drug “verapamil” and enzyme “CYP3A4”. Hence, DE.*

## Drug-Drug Interaction Related (*DD*)

Two drugs together can change endpoints than that of the single drug alone.

e.g.

Similarly, neither metoprolol nor atenolol had a significant effect on the systemic clearance, apparent oral clearance or other dispositional parameters of lignocaine. \*\*1SN3E3(VVDDM0)

*This sentence states how drug metoprolol and atenolol effect the PK parameters of drug lignocaine, respectively. There are two pairs of drug interaction, metoprolol vs. lignocaine, and atenolol vs. lignocaine. So DD.*

## Both

Two Interaction types in the sentence or fragment which cannot be fragmented any more, e.g. **(DD/DE)**

e.g.

Effect of saquinavir-ritonavir on cytochrome P450 3A4 activity in healthy volunteers using midazolam as a probe. \*\*1SP3E1(V0[DD|DE]M0)

*This sentence contains multiple interactions. DE can be found in “The effect of saquinavir-ritonavir” on enzyme “P450 3A4”, and “midazolam as a probe” to test the activity of enzyme P45 3A4. In turn, there is also interaction between midazolam and saquinavir-ritonavir, so DD.*

## No Drug (D0)

No drug or drug group is shown within the fragment.

e.g.

It has also shown that this interaction is sustained for at least several months. \*\*1GP3E3(VND0M0)

# Mechanism

Indicates the mechanism of how drugs interact with each other or with enzymes.

## Inhibition (*MI*)

The phenomenon of decreased drug metabolizing ability of the enzymes by several drugs.

e.g.

* + 1. The interaction of omeprazole with warfarin was attributed to a stereoselective inhibition of the hepatic metabolism of the less potent (R)-warfarin enantiomer. \*\*1SP3E3-(VVDD[MI|MM])

*This statement indicates the mechanism of drug interaction is omeprazole inhibiting (R)-warfarin through the metabolism pathway. The mechanism of this sentence includes MI and MM.*

* + 1. These results show that cimetidine, unlike ranitidine, significantly inhibits the biotransformation of doxepin. \*\*1SP3E3(V0DDMI)

## Induction (*MD*)

The phenomenon of increased drug metabolizing ability of the enzymes by several drugs.

e.g.

In concurrence with previous reports, we observed that paclitaxel potently induced CYP3A4 activity and expression in hepatocytes treated for 48-96 h. \*\*1[S|M]P3EN+(VTDEMD)

*The past tense “observed” indicates the authors are describing the results of their own experiments. The treatment time “48-96 h” not only makes the focus M, but also gives the evidence EN. There is a drug-enzyme interaction, paclitaxel vs. CYP3A4, so DE. And “induced” indicates the mechanism of the interaction is induction, so MD.*

## Metabolism (*MM*)

Drug metabolism is the biochemical modification of pharmaceutical substances respectively by specialized enzymatic systems.

e.g.

Title = CYP2B6, CYP3A4, and CYP2C19 are responsible for the in vitro N-demethylation of meperidine in human liver microsomes. \*\*1SP3E3(VTDEMM)

*This statement presents the interactions of CYP2B6 vs. meperidine, CYP3A4 vs. meperidine, and CYP2C19 vs. meperidine. So DE. The terms “in vitro”, “in human liver microsomes” indicate this is a PK in vitro, VT. “N-demethylation” indicates the metabolism pathway, so MM.*

## Transport (*MT*)

Indicates the drug-drug interaction is transporter-mediated.

e.g.

These results further supported the idea that OATP1B1 is a predominant transporter for the hepatic uptake of pitavastatin. \*\* 1SP3E1(V0DRMT)

*“These results” indicates there is a claim of evidence, but no explicit reference to it is provided. So E1. Study type cannot be determined by the limited description. But the mechanism of the interaction is transporting referring to “OATP1B1 is a predominant transporter for the hepatic uptake of pitavastatin”. Hence, MT.*

## Synergism *(MS)*

The effect produced with the two drugs is even greater than expected had the effect been additive.

e.g.

The combination of FW-04-806 and lapatinib showed synergistic reduction of HER2 expression and the downstream PI3K/Akt and Ras/MEK/ERK pathways, \*\*1SP3E3-(VTDDMS)

*“synergistic reduction” demonstrates the mechanism of the “combination of FW-04-806 and lapatinib” is MS.*

## Antagonism *(MN)*

The joint effect of two or more drugs such that the combined effect is less than the sum of the effects produced by each agent separately.

e.g.

Doxycycline in combination with doxorubicin or paclitaxel yielded therapeutic antagonism at all effect levels. \*\* 1SP3E3(V0DDMN)

*“antagonism” indicates the mechanism of drug interactions is MN.*

## Additive *(MA)*

The combined effect of two drugs is that expected based on the concentration-response curves for each drug given independently.

e.g.

Both ethanol and the two benzodiazepines significantly reduced critical flicker detection in themselves and, in combination, had additive effects.

\*\* 1SP3E3-(VCDRMA)

*MA is given due to the words “additive effects”.*

## BOTH

Both mechanisms are described use the “|” e.g. ***MI|MD***

e.g***.***

The interaction of omeprazole with warfarin was attributed to a stereoselective inhibition of the hepatic metabolism of the less potent (R)-warfarin enantiomer. \*\*1SP3E3-(VVDD[MI|MM])

*This statement indicates the mechanism of drug interaction is omeprazole inhibiting (R)-warfarin through the metabolism pathway. The mechanism of this sentence includes MI and MM.*

## No Mechanism is Applicable (M0)

No mechanism of drug is mentioned.

e.g.

High pressure liquid chromatography analysis of plasma also verified compliance with cimetidine (mean level, 0.61 microgram/ml) and ranitidine (mean level, 0.36 microgram/ml) regimens. \*\*1[S|M]P3EN(VVDRM0)

*Here we have both methodology and experimental results described in such a way they cannot be readily separated. Thus the MS focus. The word “plasma” and drug concentrations indicate this is a PK in vivo study, VV. Although two drugs mentioned, but no interaction between them can be found. So DR. No drug effect mechanism is investigated or mentioned. So M0.*