

Accelerating PKPD Analysis with Automated DDI Variable Creation: A SAS-Based Approach.

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ABSTRACT

Creating time-varying drug-drug interaction (DDI) variables is essential but often time-consuming in PKPD dataset construction. Our SAS-based standardized script automates this process, leveraging a continuously updated internal database of drug lists and potencies, curated by our DDB clinical experts. This has led to substantial efficiency and quality gains.

INTRODUCTION

Drug-drug interaction (DDI) occurs when two or more drugs react with each other when taken simultaneously. This can in turn impact the overall therapeutic effect and safety of the treatment (as these can cause unexpected side effects). This is crucial in PK-PD analysis because understanding these interactions allows for optimized drug combinations and helps identify potential adverse effects in patients taking multiple medications.

Cytochrome P450 enzymes are essential for the metabolism of many medications, with the two most significant enzymes being CYP3A4 and CYP2D6. Cytochrome P450 enzymes can be inhibited or induced by drugs, resulting in clinically significant drug-drug interactions that can cause unanticipated adverse reactions or therapeutic failures. So, it is important to code DDI as accurately as possible. Our automated process handles many challenges in the DDI extraction process. For e.g., names of drugs in CM or ADCM are not consistently reported (for e.g., combination of drugs can be represented using “;” or “and” or “+”), creating a challenge while searching for appropriate DDI. Each drug has a different potency, and the potency can be different when given together with other drugs. Provisions in the script are also made to dynamically change the window of induction/inhibition to consider the half-life and lag effect of a drug.

Here is a list of a subset of these challenges

- Lag effects of a Drug and Lack of usage of appropriate Interaction Time Window
- Incomplete Documentation or Missing data
- Inconsistencies in Drug Names captured in the dataset
- Identifying relevant drugs of interest from multiple sources
- Multiple versions in WHODrug formats in CM dataset
- Need for repeated review of changes in guidelines

We will explore some of these challenges and probable solutions included in our automated process.

IMPORTANT CONSIDERATIONS IN DDI

LAG EFFECTS OF A DRUG AND LACK OF USAGE OF APPROPRIATE INTERACTION TIME WINDOW

Depending on the pharmacokinetics or half-life of the drugs involved, we might need to consider a specific time window for interaction analysis (e.g., only considering interactions when both drugs are present within a certain period). Effects of a drug on the enzyme can linger in the body long after it has been stopped depending on the half-life of the drug. E.g., "The induction of CYP3A4 by rifampicin takes around six days to develop and 11 days to disappear" ^{(a)(c)}. Mostly this window only affects Inducers primarily, but there can be a provision in the code to dynamically consider additional days even for inhibitors.

The induction period of a drug is the time it takes for a drug to increase the production of a cytochrome P450 (CYP450) enzyme. The half-life of a drug is the time it takes for a drug's active substance in the body to reduce by half. Depending on the pharmacokinetics or half-life of the drugs involved, we might need to consider a specific time window for interaction analysis (slightly bigger window than the actual conmed dates).

This information is very important to accurately capture DDI information. So, we need to provide some option to expand the period of conmed using some DELTA (correction factor or window of DDI consideration) variable that will be provided to us by the modelers or Subject Matter Experts, if not, programmers should prompt the modelers for this window information. But, if no information is provided, by default DELTA value can be considered as 0 or no changes to the existing information of start and stop date times of conmeds are observed.

INCOMPLETE DOCUMENTATION OR MISSING DATA

Not all concomitant medications or their complete details (e.g., start and stop dates, dose amounts, frequencies etc.) are consistently reported. Missing data can result in underestimating the prevalence and impact of DDIs. Handle missing values appropriately, either by imputing missing data or excluding relevant time points from the analysis.

Some of the missing information can be addressed using best judgement or assumptions listed below

- If the Start Date is partial like YYYY or YYYY-MM, we can use the first month and first day of the month etc. and append it to the partial information to get a good estimate of Start Date.
- Similarly, if the End Date is partial like YYYY or YYYY-MM, we can use the last month and last date of the year or last date of the month etc., to get an exhaustive period when co-medication may have been taken.
- We can also make provisions for considering Leap Year information while filling the missing months or dates. E.g., if the CMSTDTC was 2024-02, we can fill it as 2024-02-29 as 2024 is a leap year.
- If CMENDTC is missing completely or blank and another CM column, like CMENRF or CMENRTPT or CMONGO etc. has the value ONGOING or AFTER, we can fill the CMENDTC as the date on which the script is being run or the last date of the year when the script is being run to be consistent and exhaustive in the conmed date range.

INCONSISTENCIES IN DRUG NAMES CAPTURED IN THE DATASET

Drugs may be recorded using various terminologies (e.g., brand names, generic names, or free-text descriptions or using synonyms/alternate names etc.). Some countries mandate the inclusion of specific details alongside the scientific name, such as salt forms or stereochemistry due to regulatory labeling requirements.

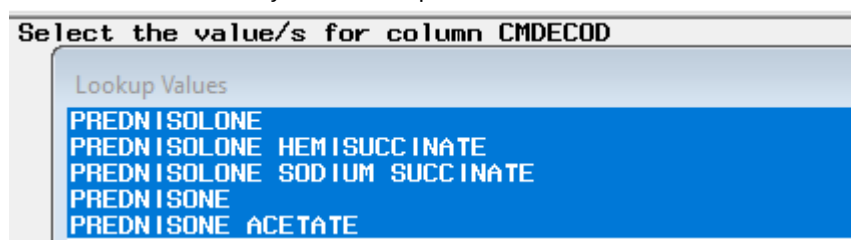
Example:

Different salt form and release profile: Metoprolol succinate (slowly over time) vs. Metoprolol tartrate (immediate-release formulation). Both contain the same active ingredient, metoprolol.

Alternate names/ Synonyms: Prednisolone sodium hemisuccinate is also known as Meticortelone Soluble.

Prodrug vs active drug listed: Sometimes prodrug is listed sometimes active drug is listed in the CM/ADCM. Unless we have an extensive list of these drugs, we may miss out on some of these during analysis. Prednisone is a prodrug, meaning it chemically changes in your body after you swallow it. It then turns into its active form, prednisolone.

We can have various ways of these captured in the CM/ADCM dataset.



So, searching for the drugs using an exact, specific search string will make us miss more drugs from the source CM/ADCM matching a criterion. To resolve this use partial searches instead of exact search on the drug list from CM/ADCM and carefully validate these by a SME (subject matter expert). Also, making the use of ATC codes or other universal codes mapping a drug

to CM/SUPPCM mandatory in the upcoming studies will help ease some of the burden of these variations in which different drugs are logged.

IDENTIFYING RELEVANT DRUGS OF INTEREST FROM MULTIPLE SOURCES

Knowledge of the most important drugs metabolized by cytochrome P450 enzymes, as well as the potency of these drugs, can help minimize the possibility of adverse drug reactions and interactions. But finding a well-documented list of these drugs and their potencies is hard. Even though FDA provides a list of most common drugs and their relevant induction/inhibition effects on the CYP enzymes, it is not complete. Likewise, other providers like D1DB repository/Flockhart Table/drug bank etc., also provide a list of these drugs and their potencies for the various enzymes. But again, that is not exhaustive. Care should be taken first to compile a master list of drugs and their potencies and their effects on the enzymes as that is more important before jumping into any programming for standardization. Also, periodically this list must be reviewed and updated if more drug interactions are found with regards to the respective CYP enzymes of interest.

MULTIPLE VERSIONS IN WHODRUG FORMATS IN CM DATASET

WHO Drug Global dictionary is an industry standard for coding conmeds. Every year constant updates or discussions happen to accommodate new regulatory requirements or improve data granularity. The WHODrug Global B3/C3 formats are updates to the previous B2/C2 formats used in drug coding and classification (use of the B3 format is required in submissions of studies starting after 15th March 2019.). Studies are conducted over many years and may have different WHODrug global versions to code conmeds and there is no explicit requirement to recode earlier studies or legacy ones. When pooling studies of a sponsor together and analyzing the data, we should be aware that the earlier studies could have used prior formats of WHODrug standards and may not adhere to latest formats. This can complicate standardization, mapping, and identification of potential interactions as it increases the complexity in the approach used to pull the drugs from the dataset.

For e.g., "In the B2/C format, the generic names were displayed by appending 'w/' followed by the substance name, whereas in the B3/C3 format, the generic name is separated by a semicolon (;) when multi-ingredient generic names of drugs are captured in the CM dataset" ^(b).

POTENTIAL SOLUTION FOR INCONSISTENCIES IN DRUG NAMES

FUNCTIONS TO FILTER DATA

There is a potential issue of finding typos and/or marketed drug names also being included with generic names in CM datasets. So, to minimize these inadvertent data inconsistencies or other challenges with legacy studies, we should try searching for partial strings in both variables CMDECOD and CMTRT individually.

To search for drugs in the CM/SUPPCM dataset, we need to use partial strings and pattern matching and searching within strings. We can use either of two choices of functions for this (There could be more but listing two potential options here). In SAS, both the PRXMATCH and INDEX functions are used for pattern matching and searching within strings, but they serve different purposes and have different strengths.

- **Use INDEX** when we need to perform simple substring searches and prioritize performance.
- **Use PRXMATCH** when we need to perform complex pattern matching with regular expressions.

The INDEX function returns the position of the substring if it is found, or 0 if it is not found. We use INDEX along with UPCASE/LOWCASE to search for partial drug information in CM: CMDECOD/CM: CMTRT.

```
data result;
  set example;
  if index(UPCASE(CMDECOD), 'ASPIRIN') > 0 then output result;
run;
```

In this example, INDEX is used to search for the substring "ASPIRIN" within the CMDECOD variable. The UPCASE function is used to make the search case insensitive. This approach is simple and efficient for finding the presence of "aspirin" in any part of the string.

Similarly, in any programming language, a "where" statement is typically used to filter data based on a condition before it is processed, essentially creating a subset of data that meets specific criteria, while an "if" statement is used to execute a block of code only if a condition is true within the code flow, making decisions based on the current data state. We need to know when to use one over the other. Ideally in a large dataset, if both the statements are being evaluated in the same vein, then

prefer to go with “where” to filter the conditions as it deals with a smaller data thereby making it faster in processing and execution time.

ADDITIONAL FUNCTIONS TO CLEAN DATA ISSUES

There could be different regional spellings for the same drug and sometimes inadvertent typos could be present for the drug names. E.g., Sulphate versus Sulfate. We can overcome some of these issues by exploring few additional functions.

Usage of

- **SOUNDEX** ^{(d)(e)} (converts a character string into a phonetic code. This helps in matching names that sound similar but may be spelled differently)
- **COMPED** ^{(d)(e)} (returns a numerical value representing the edit distance)
- **DIFFERENCE** ^(e) (returns the difference between the SOUNDEX values of two strings. This function is useful for comparing the phonetic similarity of two strings directly) etc.

Please note that these functions can also be used for safety analysis where we usually encounter data entry errors or regional differences in spellings in the AE dataset. So, the usage of these can be explored in use cases far beyond the DDI variable creation.

Sample exploration of SOUNDEX function is presented below:

```
data names;
  input name $30.;
  soundex_code = soundex(name);
  datalines;
anemia
anaemia
anemya
Anemic
Anemiaically
Cetirizine hydrochloride
Cetzine
Cetsine
cetirizine
isavuconazonium
isavuconazonium sulphate
isavuconazonium sulfate
isavuconazole
;
run;

proc print data=names;
run;
```

Obs	name	soundex_code
1	anemia	A55
2	anaemia	A55
3	anemya	A55
4	Anemic	A552
5	Anemiaically	A5524
6	Cetirizine hydrochloride	C3625362463
7	Cetzine	C325
8	Cetsine	C325
9	cetirizine	C3625
10	isavuconazonium	I2125255
11	isavuconazonium sulphate	I21252552413
12	isavuconazonium sulfate	I21252552413
13	isavuconazole	I212524

ADDITIONAL EXPLORATION AREAS

DDIs depend on variables like patient metabolism, timing of doses, and co-morbid conditions, which are often absent in SDTM: CM. This limits the dataset’s ability to capture context-sensitive interactions. Whenever data is captured in every study, there should be more efforts put in to capture accurate dose information like amount and dose times all the time.

In the future, we should try to improve CM/SUPPCM, in such a way that we can map the records in CM/SUPPCM using a common key variable between EX/EC and CM/SUPPCM to map the accurate doses and their times of main drug to the concomitant drug. There should be robust efforts put in to accurately capture concomitant medication’s doses all the time.

CONCLUSION

As illustrated in this document, automation is key to improve the efficiencies in the process of creating time-varying DDI variables to understand the overall therapeutic effect and safety of the treatment. Streamlining the process through automation, it not only accelerates the speed of dataset delivery, but also improves the quality of the output dataset.

APPENDIX A

RATIONALE BEHIND DDI TIME-VARIABLE CREATION: PURPOSE AND AUTOMATION CONSIDERATIONS

The reason behind the interest to explore and look at concomitant medications drug effects in the pharmacometrics analysis would be to understand more regarding the following -

- Do moderate/strong CYP3A4 or other CYP inhibitors lead to higher investigational drug exposures?
- Do moderate/strong CYP3A4 or other CYP inducers lead to lower investigational drug exposures?
- Do acid-reducing agents (ARAs) or proton pump inhibitors (PPIs) lead to higher or lower investigational drug exposure?
- How do drug transporters like Human breast cancer resistance protein (BCRP) affect some of the analysis (tumor related)?

When we say the automation looks at drug-drug interaction, essentially, we are thinking on the above lines based on IB (investigational brochure) or characteristics of the investigational drug, whether it has some basis to believe for us to explore along those lines as drug-drug interactions affect the drug metabolism (including key PPK parameters like clearance etc.) in turn affecting the drug exposure.

Directly we are not looking at individual or combinational drugs and their effects on the investigational drug but indirectly we are assessing these. The reason we are saying indirect exploration of DDI is because these are actually looked at from the perspective of how these medications inhibit or induce the cytochrome P450 (CYP) enzymes in the liver, which are responsible for metabolizing many drugs in the body, meaning they can significantly affect how other drugs are processed and potentially lead to harmful drug interactions when taken together; Essentially, they have a significant impact on the metabolism of other drugs due to their potential CYP activity.

"Of all the different CYP proteins that are present in the human body, six of them are involved in the metabolism of 90% of drugs. These proteins are CYP1A2, CYP2C9, CYP2D6, CYP3A4, and CYP3A5. The most important are CYP3A4 and CYP2D6" ^(f).

So, in the creation of time-varying DDI variables, we are essentially interested in creating time-varying categorical variables of (CYP3A or CYP2D6, two most prominent CYP enzymes that affect majority of drug metabolism) and PPI/ARA. Depending on the investigational drug characteristics, we could also look at other CYP's of interest.

The automation has provision to feed in respective drugs/enzymes of interest. Currently we have factored in the following DDI list that will be output as time-varying CYP3A (strong, moderate, weak), CYP2D6 (strong, moderate, weak), PPI (binary variable indicating proton-pump inhibitor drugs from the CM/SUPPCM/ADCM), ARA (binary variable indicating acid reducing agent drugs from the CM/SUPPCM/ADCM) that will be looked at by the modelers. In specific tumor related studies, we also have provisions for considering BCRP inhibitors.

Administration of a CYP3A inducer/inhibitor within X days (DELTA window X, will be provided by the modeler based on half-life of the drug) prior to the PK sample will be identified for potential drug-drug interaction (DDI) assessment. Administration of a PPI, H2 blockers or antacid within X days prior to investigational drug administration will also be considered during DDI assessment.

SAMPLE OUTPUT VALUE CODES

CxxxINDW (0=absence of weak CYP3A inducers; 1=presence of weak CYP3A inducers;)

CxxxINDM (0=absence of moderate CYP3A inducers; 1=presence of moderate CYP3A inducers;)

CxxxINDS (0=absence of strong CYP3A inducers; 1=presence of strong CYP3A inducers;)

where xxx is 3A4 or 2D6 (most popular two CYP's that affect more than 80% of all metabolisms among all CYP enzymes)

Similarly, inhibitor variables are

CxxxINHw (0=absence of weak CYP3A inhibitors; 1=presence of weak CYP3A inhibitors;)

CxxxINHm (0=absence of moderate CYP3A inhibitors; 1=presence of moderate CYP3A inhibitors;)

CxxxINHs (0=absence of strong CYP3A inhibitors; 1=presence of strong CYP3A inhibitors;)

PPI (0=absence of PPI; 1=presence of PPI;)

H2A (0=absence of H2-Blockers; 1=presence of H2-Blockers;)

Although the automation outputs different binary time-varying variables mapped to unique time per subject, sometimes these could be explored using single categorical variable for inhibition and induction for the analysis using the following categorization -

CYPxxxID (0=absence or presence of weak CYP3A inducers; 1= moderate CYP3A inducers and 2= strong CYP3A inducers)

CYPxxxIH (0=absence or presence of weak CYP3A inhibitors; 1= moderate CYP3A inhibitors and 2= strong CYP3A inhibitors)

There are provisions to expand the results accordingly for further analysis.

APPENDIX B

SAMPLE SCREENSHOT OF SOME OF THE OUTPUTS

VERIFY_THESE with values of 1 - Please confirm with the sponsor and/or modeler if okay to map them under the given potency and DDI variables

Potency Classification	Search String	Standardized Medication Name	Unique Subject Identifier	Start Date/Time of Medication	End Date/Time of Medication	Study Day of Start of Medication	Study Day of End of Medication	End Relative to Reference Period	VERIFY_THESE
Strong Inhibitor	CLARITHROMYCIN	CLARITHROMYCIN	M A S K E D	2023-03-13		210	.	AFTER	0
Strong Inhibitor	IDELALISIB	IDELALISIB		2018-01-05	2021	-1900	-444		0
Strong Inhibitor	CLARITHROMYCIN	CLARITHROMYCIN		2023-12-04	2023-12-08	189	193		0
Strong Inhibitor	IDELALISIB	IDELALISIB		2014-10-22	2015-05-08	-2842	-2644		0
Strong Inhibitor	VORICONAZOLE	VORICONAZOLE		2023-04-04	2023-04-06	35	37		0
Strong Inhibitor	CLARITHROMYCIN	CLARITHROMYCIN		2023-09-19	2023-09-24	386	391		0
Strong Inhibitor	RITONAVIR	NIRMATRELVIR;RITONAVIR	S K	2022-07-19	2022-07-23	183	187		1
Strong Inhibitor	RITONAVIR	NIRMATRELVIR;RITONAVIR		2022-07-19	2022-07-23	183	187		1
Strong Inhibitor	IDELALISIB	IDELALISIB	E D	2022-09-30	2022-10-17	103	120		0
Strong Inhibitor	IDELALISIB	IDELALISIB	I	2021-11-23	2021-12-10	-21	-4		0
Strong Inhibitor	IDELALISIB	IDELALISIB		2023-09-08		459	.		0
Strong Inhibitor	RITONAVIR	NIRMATRELVIR;RITONAVIR	N F O	2023-11-02	2023-11-06	79	83		1
Strong Inhibitor	RITONAVIR	NIRMATRELVIR;RITONAVIR		2023-11-02	2023-11-06	79	83		1
Strong Inhibitor	IDELALISIB	IDELALISIB		2018-11-23	2020-04-13	-1713	-1206		0
Strong Inhibitor	IDELALISIB	IDELALISIB		2023-08-01	2023-11-27	-125	-7		0
Strong Inhibitor	IDELALISIB	IDELALISIB		2022-10	2023-05	.	22		0
Strong Inhibitor	IDELALISIB	IDELALISIB		2022-12-08	2023-01-19	-102	-60		0
Strong Inhibitor	CLARITHROMYCIN	CLARITHROMYCIN LACTOBIONATE		2023-09-28	2023-10-03	67	72		1
Strong Inhibitor	IDELALISIB	IDELALISIB		2014-09-30	2016-05	-3352	-2743		0
Strong Inhibitor	CLARITHROMYCIN	CLARITHROMYCIN LACTOBIONATE		2023-12-18	2023-12-24	113	119		1

Potency Classification	Search String	Standardized Medication Name	Unique Subject Identifier	Start Date/Time of Medication	End Date/Time of Medication	Study Day of Start of Medication	Study Day of End of Medication	End Relative to Reference Period	VERIFY_THESE
Moderate Inhibitor	CIPRO	CIPROFLOXACIN HYDROCHLORIDE;FLUOCINOLONE ACETONIDE	masked	2023-08-07	2023-08-12	90	95		1
Moderate Inhibitor	CIPRO	CIPROFLOXACIN		2023-08-19	2023-08-19	102	102		1
Moderate Inhibitor	CIPROFLOXACIN	CIPROFLOXACIN HYDROCHLORIDE;FLUOCINOLONE ACETONIDE		2023-08-07	2023-08-12	90	95		1
Moderate Inhibitor	APREPITANT	FOSAPREPITANT		2023-05-20	2023-05-20	76	76		1
Moderate Inhibitor	APREPITANT	FOSAPREPITANT		2023-04-03	2023-04-03	34	34		1

NOTE: Fosaprepitant is a weak CYP3A4 inhibitor whereas aprepitant is a moderate CYP3A4 inhibitor. Using a validation step by the SME or the sponsor we can effectively negate the wrong classification of potencies in extreme cases (False Positive)

VERIFY_THESE with values of 1 - Please confirm with the sponsor and/or modeler if okay to map them under the given potency and DDI variables

Potency Classification	Search String	Standardized Medication Name	Unique Subject Identifier	Start Date/Time of Medication	End Date/Time of Medication	Study Day of Start of Medication	Study Day of End of Medication	End Relative to Reference Period	VERIFY_THESE
Weak Inhibitor	CANNABIS	CANNABIS SATIVA FRUIT; CITRUS X AURANTIIUM UNRIPE FRUIT; MAGNOLIA OFFICINALIS BARK; PRUNUS SPP. SEED; RHEUM SPP. ROOT WITH STEM	masked	2023-09-06	2023-09-15	-9		1	1
Weak Inhibitor	CANNABIS SATIVA	CANNABIS SATIVA FRUIT; CITRUS X AURANTIIUM UNRIPE FRUIT; MAGNOLIA OFFICINALIS BARK; PRUNUS SPP. SEED; RHEUM SPP. ROOT WITH STEM		2023-09-06	2023-09-15	-9		1	1
Weak Inhibitor	CIMETIDIN	CIMETIDINE		2023-08-29	2023-09-15	-17		1	1
Weak Inhibitor	CIMETIDINE	CIMETIDINE		2023-08-29	2023-09-15	-17		1	0
Weak Inhibitor	AMLODIPIN	LEVAMLODIPINE BESILATE		2023-06-10	2023-08-23	33		107	1
Weak Inhibitor	AMLODIPINE	LEVAMLODIPINE BESILATE		2023-06-10	2023-08-23	33		107	1

NOTE: IN OUR AUTOMATED PROCESS THE DDI LIST NOT ONLY ENCOMPASSES CYP ENZYMES BUT ALSO H2 BLOCKERS AND PROTON PUMP INHIBITORS (PPIS) AS WELL.

SAMPLE OUTPUT WITH TIME-VARYING DDI VARIABLES

ID	TIME	C3A4INDW	C3A4INDM	C3A4INDS	C3A4INHW	C3A4INHM	C3A4INHS	PPI	H2A
1	0	1	1	0	0	0	0	0	0
1	1	1	1	0	0	0	0	0	0
1	3	1	1	0	0	0	0	0	0
1	8	1	1	0	0	0	0	0	0
1	20	1	1	0	0	0	0	0	0
1	32	1	1	0	0	0	0	1	0
1	44	1	1	0	0	0	0	1	0
1	56	1	1	0	0	0	0	1	0
1	68	1	1	0	0	0	0	1	0
1	80	1	1	0	0	0	0	1	0

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- (d) Paulette S., Paul W., West N. et al. 2007. Fuzzy Matching using the COMPGED Function
- (e) <https://studysas.blogspot.com/2024/09/sas-functions-soundex-compged-and-their.html>
- (f) <https://www.ncbi.nlm.nih.gov/books/NBK557698/>

DISCLAIMER

All the drug names provided in this document are for the purposes of illustration and education only and does not constitute a commercial endorsement or promotion of any specific product, service, or company.

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RECOMMENDED READING

Few relevant links for future reading

- <https://pmc.ncbi.nlm.nih.gov/articles/PMC8657965/>
- <https://pmc.ncbi.nlm.nih.gov/articles/PMC4287283/>

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