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Programming in the World of PK: Guidance for the Beginner

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ABSTRACT

The first time one produces Pharmacokinetic (PK) and Pharmacodynamic (PD) analysis outputs can be challenging, even for an experienced programmer. The process is more complex than the process for importing and analysing CRF data and includes tasks performed by a pharmacokineticist. Experience has shown that this, together with a lack of knowledge of PK modelling can lead to numerous aspects being overlooked at the programming level causing issues further down the line that could have easily been avoided with some basic prior knowledge. The aim of this poster is to provide a checklist of common pitfalls and problems to look out for including some common data issues; to enable a programmer with little PK/PD experience to work with the data proactively and efficiently to avoid unnecessary re-work that can lead to overburn and delays in timelines.

INTRODUCTION

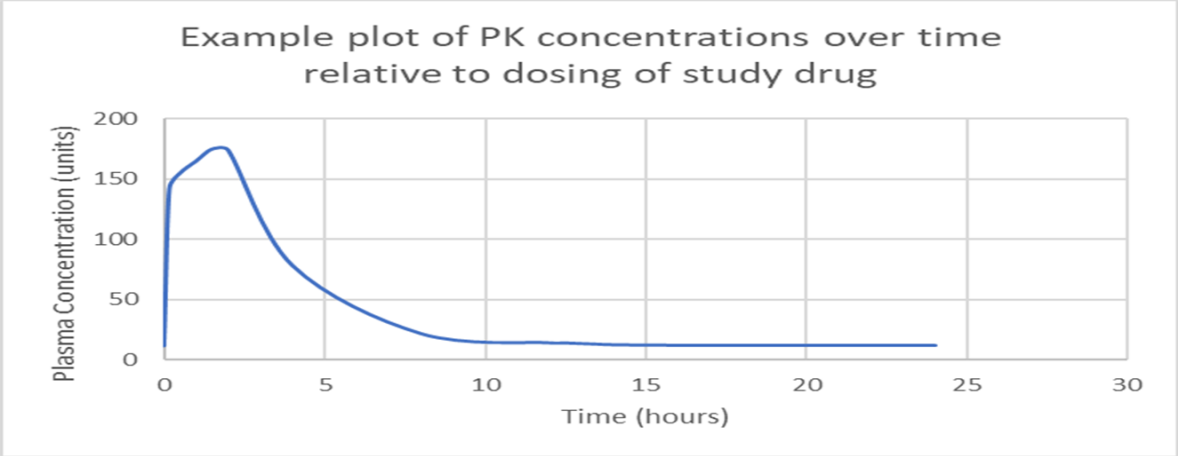
Working on a study with a predominant PK/PD component for the first time as a programmer can be daunting given the complex nature of the process. PK analysis can play an important part in assessing the safety of a drug and at what dosing level. Typically these are Early Phase clinical pharmacology studies such as first in human, food effect, bioequivalence and drug-drug interaction studies which may be required as part of the early development of a compound. Some basic prior knowledge of the process and an understanding of potential challenges can make the process more efficient and reduce potential re-work.

Throughout the rest of this paper it is assumed that the data is required in CDISC SDTM and ADaM format.

ABOUT PK/PD DATA

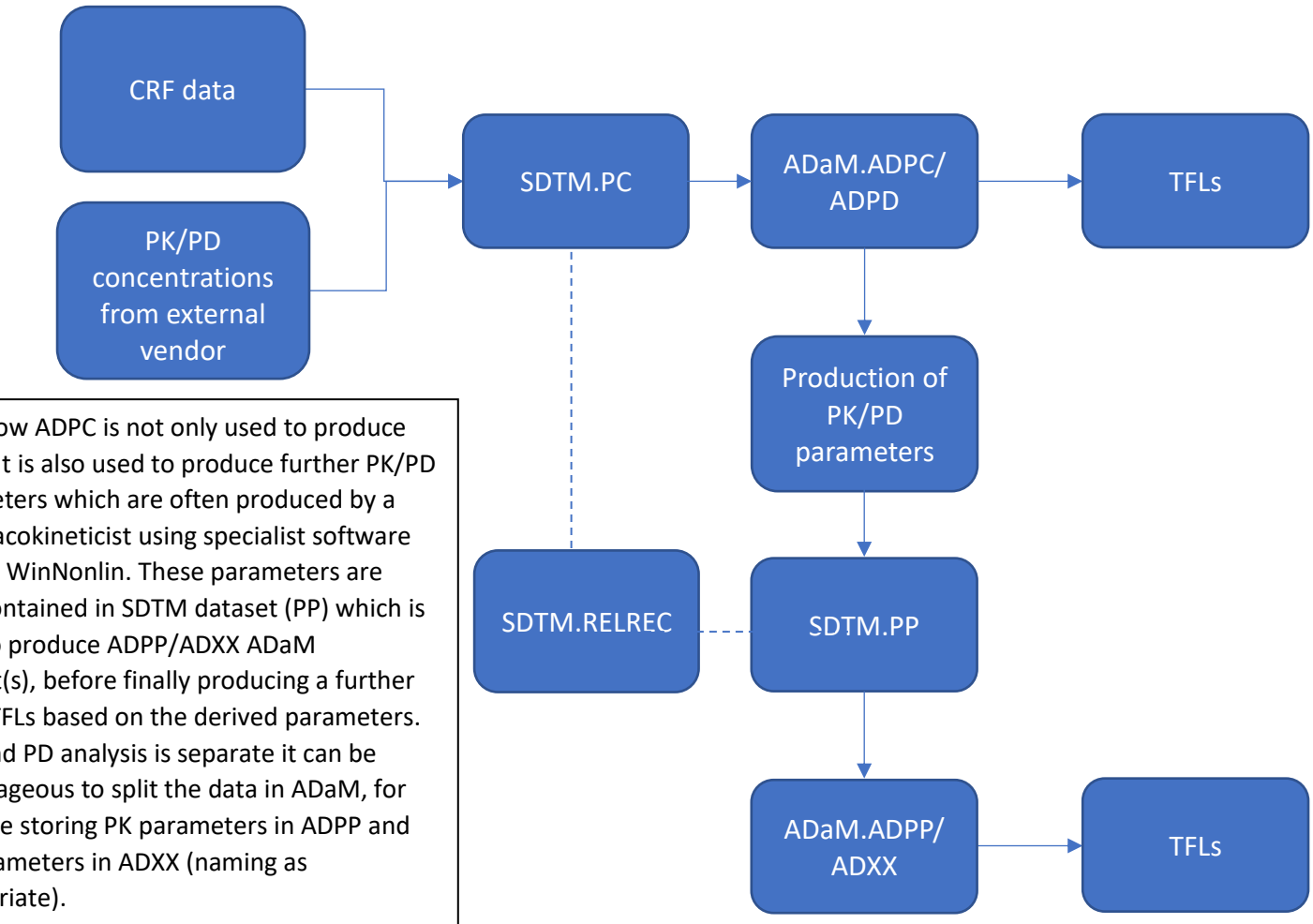
Pharmacokinetics is the study of how a drug moves through the body. It tells us what happens to the drug from entry in the body to the time of excretion whilst, in contrast, Pharmacodynamics is the study of the effect the drug has on the body such as a decrease in blood pressure.

Typically PK is assessed by measuring the concentration of the drug in the body over time. This may be represented by blood, plasma, serum or even urine/faecal concentrations reported at pre-dose and post-dose timepoints, see example plot below. Concentrations in blood are usually provided at a specific time point e.g., 2 hours post-dose, whilst urine concentrations are provided over a collection interval e.g. 0-2 hours post-dose.



Analysis of these concentrations can vary greatly between studies, a study may simply require the production of the SDTM.PC dataset, whilst another may require the production of SDTM.PC and ADaM.ADPC/ADPD with the addition of SDTM.PP and ADaM.ADPP/ADXX. ADPC/ADPD will contain the concentration data and sometimes parameters derived by the programmer, PP will contain the parameters derived by the pharmacokineticist and ADPP/ADXX will contain the parameters from PP and sometimes parameters derived by the programmer.

FLOW OF DATA



Note how ADPC is not only used to produce TFLs but is also used to produce further PK/PD parameters which are often produced by a pharmacokineticist using specialist software such as WinNonlin. These parameters are then contained in SDTM dataset (PP) which is used to produce ADPP/ADXX ADaM dataset(s), before finally producing a further set of TFLs based on the derived parameters. If PK and PD analysis is separate it can be advantageous to split the data in ADaM, for example storing PK parameters in ADPP and PD parameters in ADXX (naming as appropriate).

THE SAP

It is important to ensure specific details relating to the PK/PD analysis are outlined in the SAP. Clarity early in the study will help reduce the risk of re-work further down the line. For a programmer dealing with PK/PD data for the first time, there are aspects in the SAP that they may not know to look out for. The following is a non-exhaustive list of areas in the SAP that a programmer should pay particular attention to and from my experience, may be overlooked:

- *Does the SAP contain rules for handling values that are below the lower limit of quantification (LLOQ)?*
    - The lower limit of quantification is the lower limit of an assay for a specific analyte, this LLOQ value is used when the concentration is too low to be quantified, you may see the data reported as BLQ (below level of quantification), <XX where XX is the LLOQ value. The SAP should outline how to handle values reported as BLQ for use in analysis, different rules can apply for tables, figures, listings and the production of PK/PD parameters which can require multiple rows per timepoint in ADPC/ADPD to account for the different substitution methods. These rules will often involve the use of the LLOQ values, so it is important to check that the SAP contains these specifics. It is recommended to include the LLOQ values in the data transfer specification as these should be provided by the vendor (i.e., bioanalytical laboratory). It is worth noting that PK concentrations are often plotted on a semi-log scale, therefore substituting BLQ values with zeros can cause issues.
- *Is it clear in the SAP which parameters the programmer will be producing and how?*
    - The SAP should detail all the parameters to be produced for each analyte but it is important to discuss which ones if any will be calculated by the programmer. For example urine PK parameters are usually represented by the amount of drug excreted per time interval and cumulatively, which can be simply calculated by multiplying the concentration by the urine volume for each interval and summing these as required. This can be done in SAS by the programmer. However most blood/plasma/serum parameters such as tmax, Cmax and AUC are calculated using WinNonlin and would be produced by the pharmacokineticist. Depending on the approach taken different structures may be required for ADPC/ADPP (for example urine excretion of drug may be included in ADPC if this is calculated by the programmer).
      tmax=time of maximum concentration
      Cmax=maximum concentration
      AUC=area under the curve
    - The SAP should specify how missing or incomplete urine samples should be handled, e.g. if calculating the amount excreted from 0 hours through to 24 hours post dose and one of the intervals, say 3-6 hours post dose is missing.
    - Ensure that any calculation formulae detail which units the concentrations/time should be in and that this corresponds with the data received. If not, conversion factors will need to be supplied to get the concentrations into the desired units.
    - If there are a lot of parameters to be derived it would be advantageous to split these across two datasets if PK and PD analysis are separate; ADPC containing the pharmacokinetic data and ADPD containing the

pharmacodynamic data. This will help manage the size of the ADaM datasets as well as allowing variables to be grouped logically.

- *Is imputation for missing timepoints required?*
    - It should be confirmed whether any imputation is expected for missing data and if so this should be detailed in the SAP.
- Are the definitions for the PK population and/or the PD population clear in the SAP?
    - Any potential exclusions of data from the PK/PD analysis should be detailed in the SAP, this could be required for protocol deviations, e.g. due to errors in dosing which could give unreliable results or a subject terminating the study early which could leave insufficient data. The pharmacokineticist may identify further data that should be excluded from analysis, a process should be in place to ensure the programmers exclude such data from the PK/PD analysis.
- For calculations of actual sampling times is it clear if the start date/time or end date/time of a drug infusion should be used? Are the timepoints in the data relative the start date/time or end date/time of an infusion?
- Does the SAP specify the decimal precision to display the calculated PK/PD parameters to for use in analysis?
- Baseline adjustment may be required for endogenous compounds. This may involve, for example, subtracting the baseline concentration from the post baseline concentration at each timepoint to account for the pre-existing concentrations, is this clearly stated in the SAP?

COMMON PITFALLS

As programmers we are used to producing ADaM datasets to CDISC standards using the ADaM implementation guide together with the TFL shells to know what we need to include in our ADaM datasets. When it comes to PK and PD parameters that are produced by the pharmacokineticist using software such as WinNonlin there are further requirements of the ADaM datasets ADPC/ADPD that a programmer producing these datasets for the first time may not be aware of;

- It is required for use in WinNonlin software that pre-dose timepoints aren't negative, the programmer will need to change pre-dose timepoints such as -0.25 hours to 0 in ADPC/ADPD.
- Are there any timepoints that come through in the raw data that serve as both a post dose timepoint for one day but also a pre-dose timepoint for the next day? If so, this timepoint may need to be split into two records, one for the post dose timepoint and one for the pre-dose timepoint. e.g., the 24 hour post dose time point may also be the pre-dose time point on Day 2; thus if it is required to plot trough concentrations over time, as well as calculate PK parameters to 24 hours post-dose both time points should be represented in the ADPC dataset, see diagram below.

Raw data

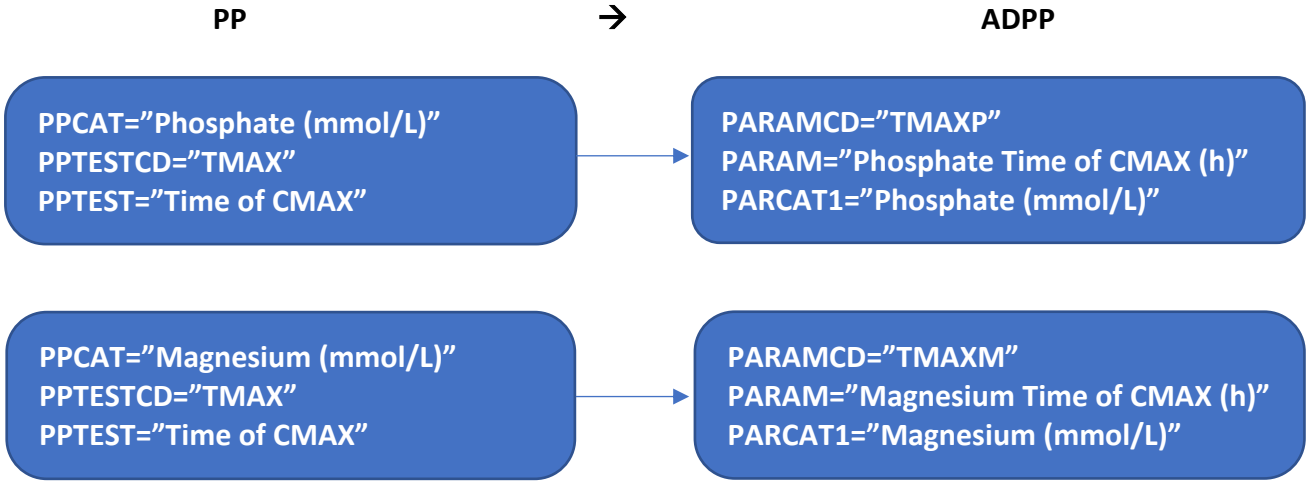
Day	Timepoint	Timepoint reference	Concentration
DAY 1	20 HRS POST-DOSE	DOSE 1	xx
DAY 1	22 HRS POST-DOSE	DOSE 1	xx
DAY 1	24 HRS POST-DOSE	DOSE 1	xx
DAY 2	1 HR POST-DOSE	DOSE 2	xx

Note how the 24 hours post-dose timepoint from day 1 in the raw data is mapped as both the 24 hours post-dose timepoint for day 1 and the pre-dose timepoint for day 2 for analysis.

Mapping for analysis

Day	Timepoint	Analysis Timepoint	Analysis Timepoint reference	Concentration
DAY 1	20 HRS POST-DOSE	20 hrs post-dose	Dose 1	xx
DAY 1	22 HRS POST-DOSE	22 hours post-dose	Dose 1	xx
DAY 1	24 HRS POST-DOSE	24 hours post-dose	Dose 1	xx
DAY 2		Pre-dose	Dose 2	xx
DAY 2	1 HR POST-DOSE	1 hour post-dose	Dose 2	xx

- If there are urine samples, check how the client would like the volumes included in the dataset, e.g. as a separate record or as an additional variable, there is no right or wrong method, but they may have a preference.
- Check whether adjustments for daylight savings need to be taken into account when working out actual sampling times relative to dose timing. If the clocks go forward or back during a PK profile then it is important to make any necessary adjustments in the calculation of the actual sampling time post dose.
- There are additional requirements for ADPC/ADPD for use in producing the parameters that go into PP;
    - As rules for handling BLQ values for use in tables, figures, listings and parameters can differ additional records per timepoint may be required in ADPC/ADPD for producing the parameters with rules applied in AVAL.
    - ARELTM/U (Analysis Relative Time/Unit) variables are required, ARELTM is the time of sample collection minus the time of dose administration, pre-dose timepoints should be set to 0 for this.
    - DOSEA/U (Actual Treatment Dose/Unit) variables are required, These contain the dose/unit of dose the subject was taking in relation to that specific record in ADaM.
- Parameters are usually received back as a CSV file from the pharmacokineticist, it is worth requesting a test transfer to show the structure of this file so that SDTM.PP can be programmed up front. Parameters that are stored in SDTM.PP usually have the parameter name in PPCAT, with the parameter tests in PPTESTCD, be careful when creating ADPP to ensure CDISC compliance and that the parameter value is associated with at most one PARCAT1 value and that PARAMCD to PARAM is a one-to-one mapping. The Pinnacle 21 validator would pick up on this but worth noting to ensure correct programming up front. Please see example below for CDISC compliant mapping of two PP records to two ADPP records; note how PARAMCD can't be a direct copy of PPTESTCD in this case due to numerous concentration parameters.



DATA ISSUES TO LOOK OUT FOR

- When post dose timepoints go over 24 hours it seems to be a common occurrence for the date to remain the same whilst the time goes to the start of the calendar day, see example below. This makes the post dose timepoint appear first chronologically and can make programming problematic. It's good to get this reported back to data management and get these types of issues resolved as soon as possible.

Date/time	Timepoint
2019-07-05T21:00	20 HRS POST-DOSE
2019-07-05T23:00	22 HRS POST-DOSE
2019-07-05T01:00	24 HRS POST-DOSE

The 24 hours post dose timepoint goes into the next calendar day but the date still remains the 5th when it should be the 6th.

- Check that concentrations have the correct units in the data transfers from the vendors. It has been known for concentrations to be transferred in different units than specified in the DTS.
- Scheduled timepoints may be missing from the data. This may be reported correctly, however it is best to query missing timepoints and to also know what to do when deriving parameters that use multiple timepoints and there is a timepoint missing, e.g. a 0-24 hours timepoint that is derived using 0-3 hours through to 18-24 hours.

TIMELINES

- *Have you allowed an adequate buffer in your timelines?*
    - It is always important to ensure enough time is allowed for any unforeseen issues when planning timelines but this becomes even more crucial when working with PK/PD data. TFLs produced from ADPP are often created for the first time in the run up to a deliverable as a result of parameters produced from ADPC/ADPD not being available in advance. One of the reasons for this is PK/PD data being unblinding. Due to this, the required TFLs will need to be programmed from scratch and these TFLs won't have been reviewed previously, so enough time is needed for both the programming, senior review and addressing of any senior review comments. It is possible to use dummy data to allow the upfront programming of the datasets and TFLs however dummy data can be problematic and it may be difficult to obtain good quality PK/PD dummy data which can cause re-work further down the line.
    - A further point to note when sending TFLs for senior review is any comments that require updates to ADPC/ADPD will require the parameters produced from these to be recalculated. This can be time consuming and cause additional effort and this needs to be considered when creating timelines.

CONCLUSION

Dealing with a study with a large focus on PK/PD analysis for the first time as a programmer can be confusing, there are additional steps in the creation of SDTM and ADaM that we are not used to seeing and terms that we may not be familiar with. With a little bit of prior knowledge and awareness of the PK process for SDTM and ADaM programming this need not be such a daunting task.

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CONTACT INFORMATION

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