

Compare Pharmacokinetic Data Submission Processes in CDISC Environment

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ABSTRACT

Pharmacokinetic (PK) analysis is an essential part of early clinical research studies. In early clinical research, the turnaround time of PK analysis is one of the key factors. Shorten turnaround time of PK analysis can reduce the overall drug development time. FDA recommends generating Study Data Tabulation Model (SDTM) PC and PP and Analysis Data Model (ADaM) ADPC and ADPP domains, respectively, as part of PK analysis. There are different processes that can be followed for PK Analysis apart from the process mentioned in PhUSE White paper titled “Analyses and Displays Associated to Non-Compartmental Pharmacokinetics – with a focus on clinical trials”. This paper introduces different PK analysis processes and compares it with PhUSE and other alternative processes.

INTRODUCTION

Pharmacokinetics describes how the body absorbs, distributes, metabolizes and excretes a drug. Pharmacokinetic (PK) analysis plays a big role in early clinical research studies. It shows how the body affects the drug. As suggested by FDA, Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) from Clinical Data Interchange Standards Consortium (CDISC) are being used in clinical researches, including PK analysis in early phases of clinical trial studies. Using an efficient and accurate process to create SDTM and ADaM data can shorten the turnaround time of PK analysis, reduce the risk of potential errors in Tables, Listings, and Figures (TLFs), and have a clear traceability. Even though PhUSE has a recommended process for PK analysis, there is no standard process for PK analysis in the industry. Different companies use different processes for PK analysis. This paper highlights all the processes and lists the advantages and disadvantages of each process.

PK ANALYSIS PROCESSES

PHUSE PROCESS

In 2014, a white paper was created by the FDA/PhUSE to develop standard scripts for PK analysis. In the white paper, it proposed a process from clinical data sets and bioanalytical data sets to SDTM and ADaM. The PhUSE proposed PK analysis process is following the steps below:

1. SDTM PC is created first using standard SDTM structure data, clinical data sets, and Bio Analytical data.
2. Using the SDTM PC data set and ADaM Subject Level Analysis Dataset (ADSL), ADaM ADPC is generated.
3. ADaM ADPC is then used for NCA analysis to generate PK parameters using third party software like Phoenix Winnonlin® or SAS®. An interim derived data set is created including all the calculated PK parameters. This derived dataset is then used to create PP domain.
4. SDTM PP and ADSL are then used to create ADaM ADPP.

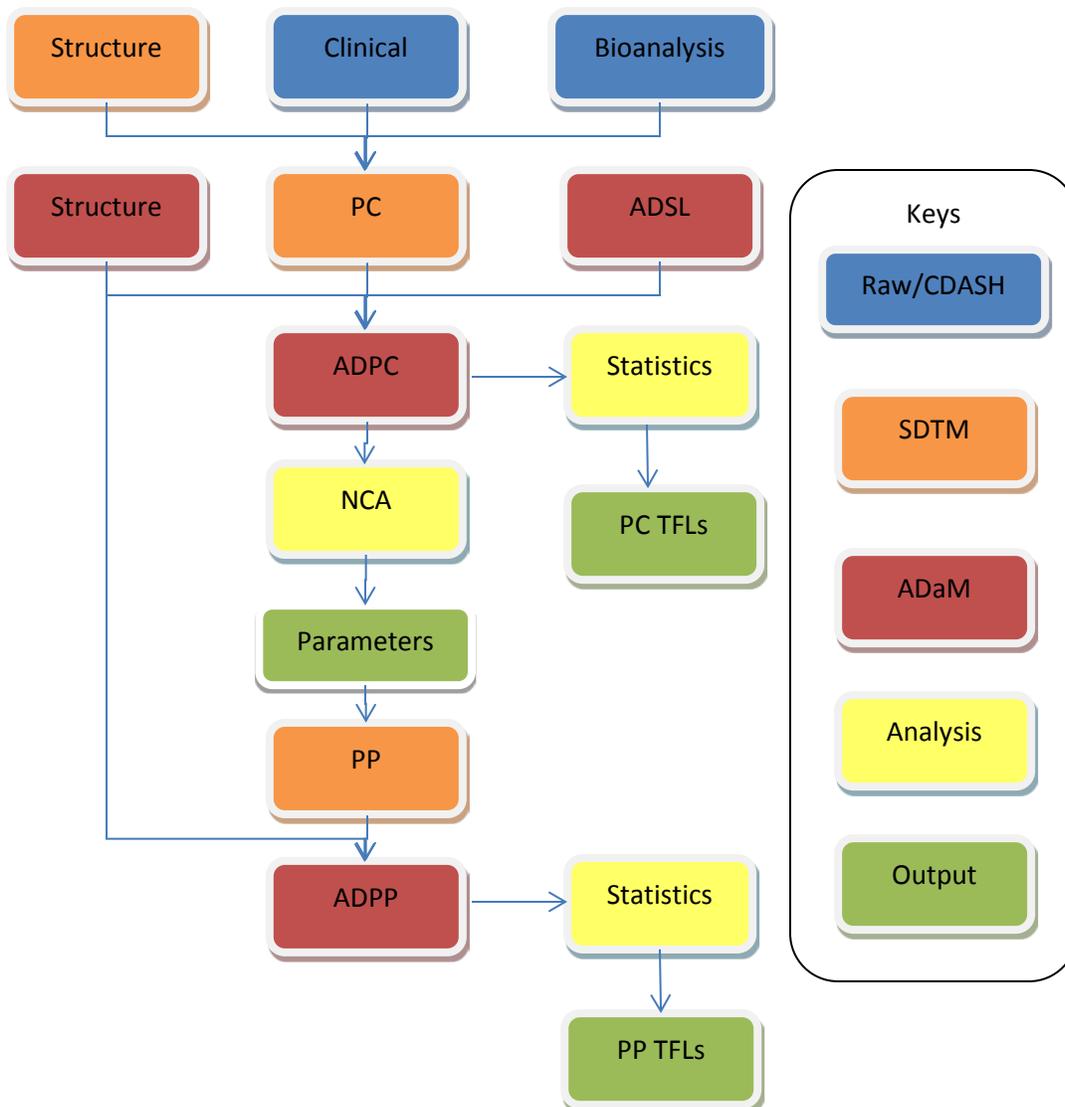


Figure 1. PK analysis process from PhUSE¹

PhUSE process develops PK concentration data sets PC and ADPC first. Then it does the Non-Compartmental analysis (NCA) based on ADPC. Finally, it creates PK parameters data sets PP and ADPP. This process provides a clear data flow from raw data to analysis data, which provides an obvious traceability. In this process, since PC/ADPC and PP/ADPP are created in the order, none of the data sets can be created simultaneously. It takes more time to create all the data sets. Since the turnaround time is important to early clinical studies, other processes may be considered.

OTHER PROCESSES

Besides, the PhUSE process, there are alternative approaches of PK analysis process.

PROCESS 1

Process 1 uses SAS[®] to calculate PK parameters. It (Figure 2) follows the steps below:

1. Based on protocol, SAP, clinical data, bioanalytical data, and SDTM structure, create SDTM PC.
2. According to ADaM structure and PC, create ADaM ADPC data set.
3. Create PK parameters data based on ADPC.
4. Based on SDTM structure and parameters data, create SDTM PP. Then create ADPP based on ADSL and ADaM structure.

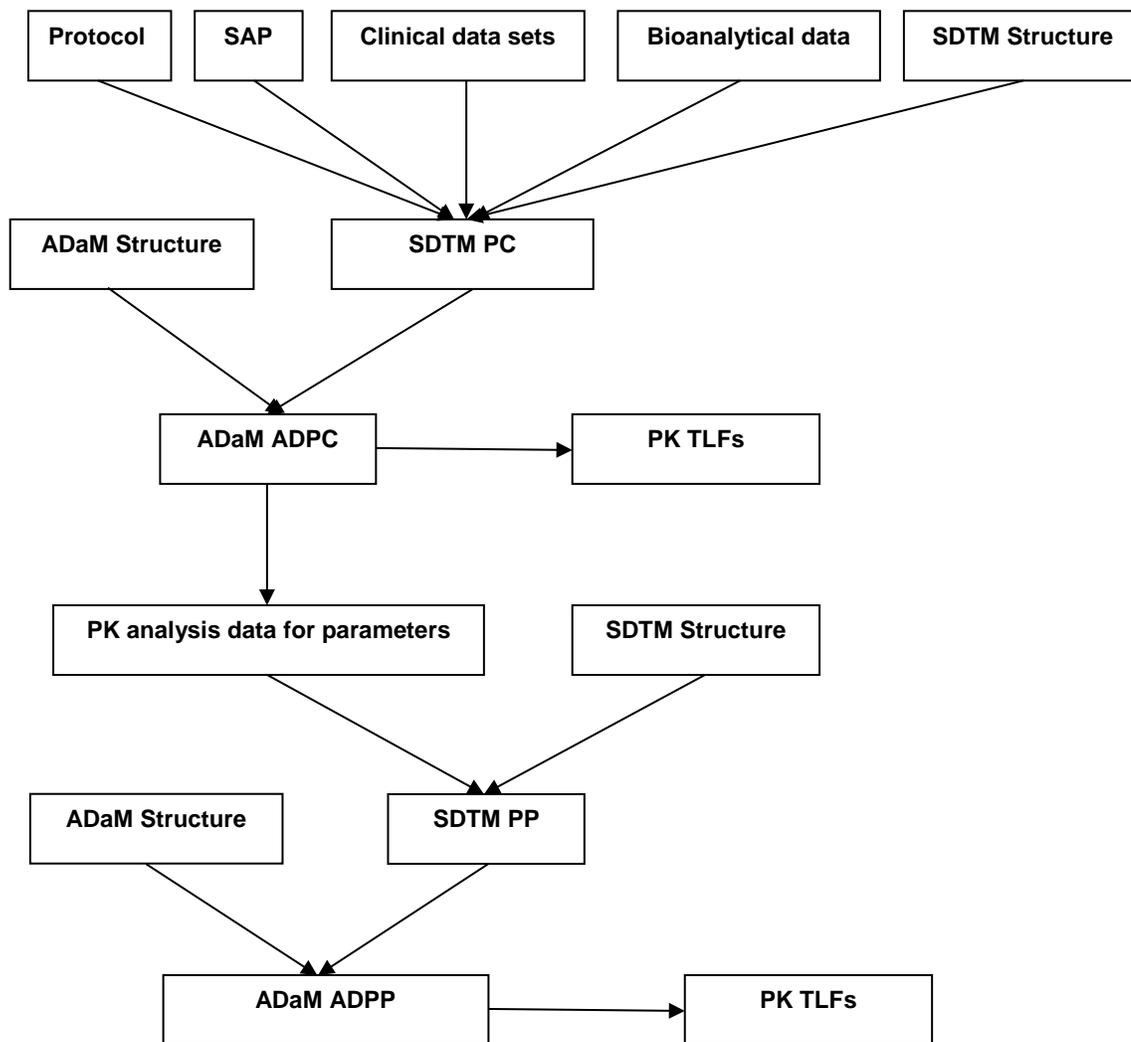


Figure 2 Implementation of CDISC ADaM in the Pharmacokinetics Department²

Process 1 creates PC and ADPC first. Then it calculates PK parameters based on ADPC. At last, it generates PP and ADPP. Compared to the PhUSE process, this process calculates PK parameters in SAS[®]. Based on the specifications, programmers can create SDTM PC/PP and ADaM ADPC/ADPP and TLFs. As parameters are generated programmatically using SAS[®], it can reduce some overall time for review and validation. But this process is not increasing the overall efficiency and is not reducing the overall timeline of PK analysis.

PROCESS 2

Process 2 is different from the first two processes. It follows the steps below (Figure 3):

1. Based on protocol, SAP, clinical data, bioanalytical data, create PK merge file.
2. PK merge file is then used to create PK Parameters in Winnonlin® and also used to create SDTM PC
3. According to ADaM structure and PC, create ADaM ADPC data set. At the same time, SDTM PP can be created based on PK parameters from Winnonlin® and Urine parameters from SAS®.
4. Create ADPP based on SDTM PP and ADaM structure.

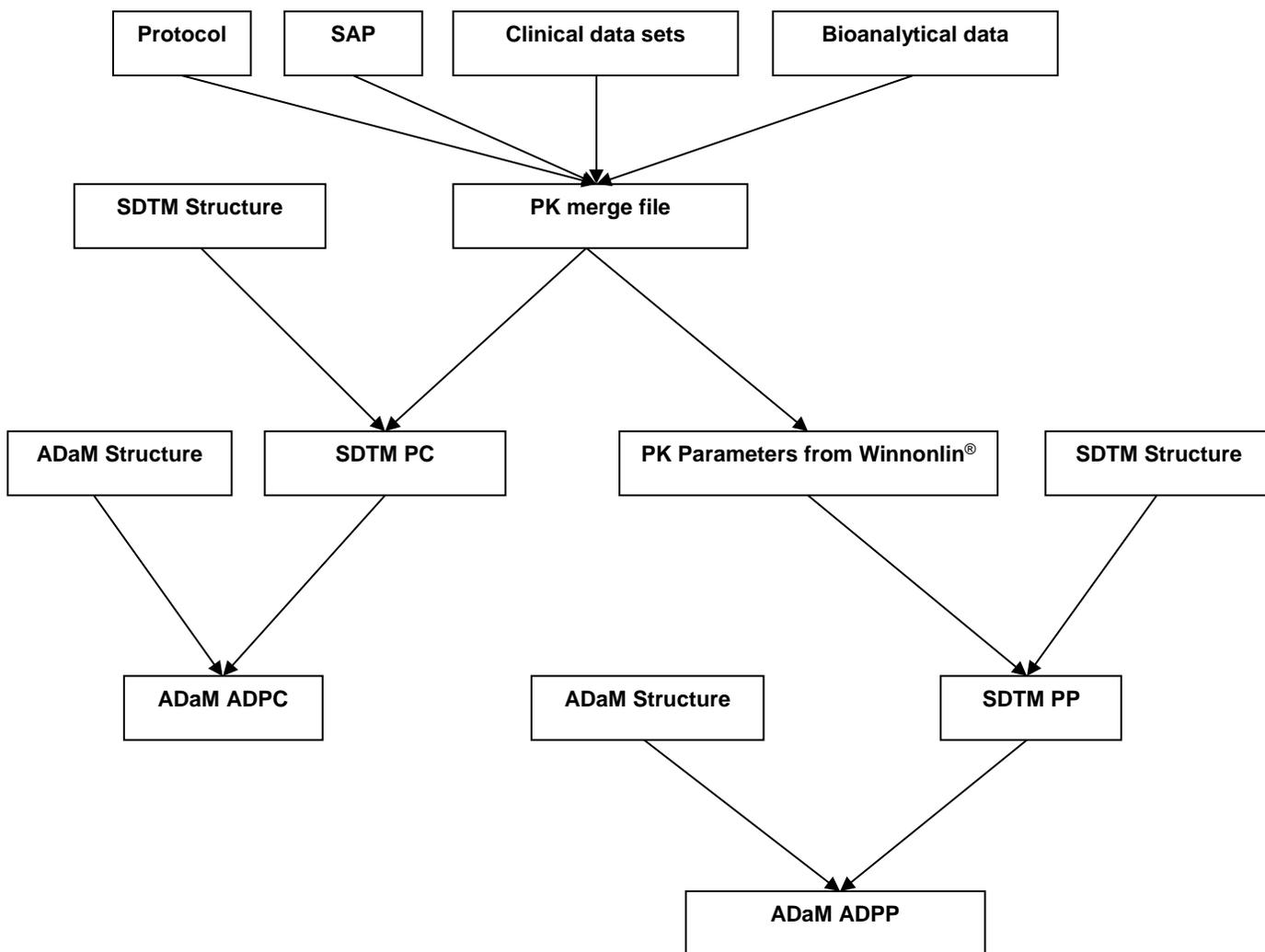


Figure 3 Pharmacokinetic Data Submission in the CDISC Environment³

In process 2, after creating the PK merge file which includes all CRF data and bioanalytical data, concentration (PC and ADPC) and parameters (PP and ADPP) data sets are created simultaneously. It can save some time by using this process which is helpful since turnaround time of PK analysis is the key for the early phase studies.

PROCESS 3

In process 3, work on SDTM PC and PK merge file can be done simultaneously. This process is more efficient in regards to overall timeline for PK analysis.

1. STDM PC and PK merge file are created simultaneously using Clinical data and Bioanalytical data.
2. ADPC programming is then continued while PK parameters are being generated using Winnonlin®/SAS® and then those parameters are used to create SDTM PP then ADaM ADPP.

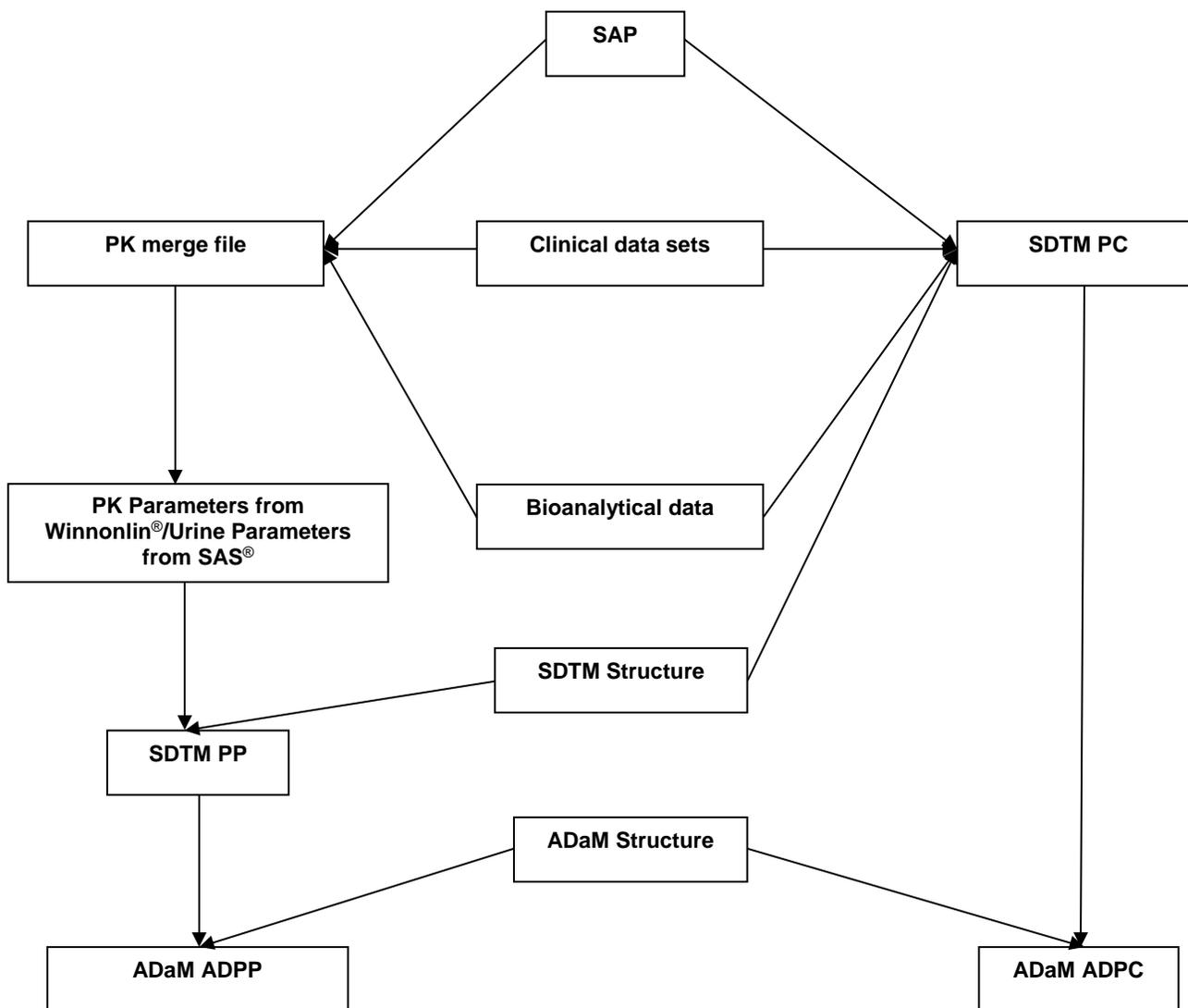


Figure 4 Process 3

As the generation of PK merge file/PP/ADPP and PC/ADPC are done separately, this process is more efficient and easier for traceability. Based on resourcing needs, two separate team of programmers can work simultaneously on concentration and parameter related datasets and TLFs and shorter timelines can be achieved.

COMPARISON OF THE PROCESSES

Since the turnaround time is critical in PK analysis, the efficiency of the process makes the team more productive. The process from PhUSE and the Process 1 use ADPC to calculate PK parameters. In these two processes, PP or ADPP cannot be created until ADPC is ready. For the Process 2, PK merge file is used to generate SDTM PC and PK parameters. After these two data have been created, additional

resources can be added and ADPC, PP, ADPP can be created simultaneously. Instead of creating PP based on ADPC, this step saves time. As the tasks for PK merge file, PC are separate, more resources can be involved in the beginning. PK concentration and PK parameters related SDTM and ADaM data sets can be worked on independently. In this case, ADPC and ADPP can be created much earlier for TLFs compared to other processes, which is a significant advantage for efficiency and management of resources.

Moreover, traceability is important in the clinical research. By looking at figure 1, figure 2, figure 3 and figure 4, we can easily tell that all these four processes have clear traceability back to the resource data.

	Pros	Cons
PhUSE	<ul style="list-style-type: none"> Less work involved as no separate PK merge file needs to be created Clear process flow 	<ul style="list-style-type: none"> Can increase overall timelines Updates to ADPC may require regeneration of PK parameters in Winnonlin® for traceability
Process 1	<ul style="list-style-type: none"> Less work involved as no separate PK merge file needs to be created Less time in generation and validation of PK parameters as parameters are generated programatically 	<ul style="list-style-type: none"> PK parameters are calculated in SAS® which is not validated software for PK parameters calculation like Winnonlin®, time-consuming Parameters need to be reviewed by a Pharmacokineticist Updates to ADPC may require regeneration of PK parameters in Winnonlin® for traceability
Process 2	<ul style="list-style-type: none"> Better traceability as PK merge file separate than PC/ADPC 	<ul style="list-style-type: none"> Increased work due to separate PK merge file May need additional resources
Process 3	<ul style="list-style-type: none"> Better traceability as PK merge file separate than PC/ADPC Achieve shorter timelines by having separate team work on concentration and parameter analysis. 	<ul style="list-style-type: none"> Increased work due to separate PK merge file May need additional resources

Table 1. Pros and Cons of these four processes

CONCLUSION

In summary, PK analysis data creation process can be done with or without PK scientists involved. When PK scientists are involved in the process, PK scientists calculate PK parameters in Winnonlin® and programmers will create a Winnonlin® input file, SDTM data sets and ADaM data sets. When PK scientists are not involved, programmers will calculate PK parameters and create SDTM data sets and ADaM data sets all in SAS®. This process can be carried out in two situations. The first situation is creating all the PK concentration and PK parameters data sets one by one. The second situation is creating PK concentration data sets and PK parameters data sets separately. Each process has its own pros and cons and any process can be chosen based on the requirements.

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