

Dosing In NONMEM® Data Sets an Enigma

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ABSTRACT

Dosing data plays an integral part in Non-Linear Mixed Effects Modelling(NONMEM®) or Modeling and Simulation(M&S) data sets. Representing accurate dosing information and history in these data sets leads to an efficient and robust Pharmacokinetic/Pharmacodynamic(PK/PD) analysis. Dosing source data collected for a Phase II/Phase III QD (once daily dose) or BID (twice daily dose) study (e.g.: Oncology) can often be complex and would require complicated transformations before it is included in a NONMEM® data set. The transformations may involve expansion of dosing history, multiple imputations, dose time imputations etc. There are various methods that could be used to program the Dosing module in a NONMEM® data set building exercise. Choosing the best approach for a study will depend on a range of factors like – it results in a compact NONMEM® data set, do you want a simple and direct approach, is incomplete dosing source data collected for the study and various other factors. There is often confusion in the minds of scientific programmers and pharmacometricians on which path to take. In this paper, we try to solve this puzzle by illustrating some common methods with detailed examples. We also look at the advantages and disadvantages of each method towards the end of the paper.

INTRODUCTION

A typical NONMEM® data set structure consists of Dosing records and PK observations stacked together. Various covariates are then merged on to the resulting structure as unique variables to complete the data set. Dosing records represent information like dosing date and time, dose amount and formulation. PK observations constitute details like the actual PK date and time of collection, nominal time and plasma concentration from a validated assay. Covariates can include data from demographics, labs, vitals and concomitant medications.

The Dosing records are a vital cog in these data sets and play a key role in PK/PD Analysis. In a simple Phase I or an early Phase II study the dosing data collected is straight forward and their inclusion into a NONMEM® data set is uncomplicated. But, when we have Phase III studies where repeat dosing is involved and the subject doses at home on a daily basis, incorporating such a dosing history into a NONMEM® data set can be arduous. In the next few sections we will try to make this task a little simpler by looking at various techniques of adding such dosing histories to these data sets. To clearly interpret the concepts in this paper it is assumed that the reader has basic knowledge of the SDTM domains and the NONMEM® data set structure.

METHOD 1 – EXPAND AND INCLUDE EVERY SINGLE DOSE

In this method we will discuss one of the commonly used approaches of adding dosing data into a NONMEM® data set. This will involve expanding a dosing history to every single dose and then including each of these dosing records in the resulting data set.

In this example we will consider a study which has a QD Dosing regimen. To illustrate this example let us first look at the sample source data and then a sample output which is a result of this technique.

USUBJID	EXTRT	EXDOSE	EXDOSU	EXDOSFRQ	EXSTDTC	EXENDTC	EXSTDY	EXENDY	
101	AS3150	1.25 mg		QD	6/15/2015	7/12/2015	1	28	--Row 1
101	AS3150	2.5 mg		QD	7/13/2015	8/11/2015	29	58	--Row 2
101	AS3150	5 mg		QD	8/12/2015	9/7/2015	59	85	--Row 3

EX Domain

USUBJID	ECSEQ	ECTRT	ECDOSE	ECDOSU	VISIT	ECSTDTC	ECSTDY
101	2	AS3150	1.25 mg		Day 1	2015-06-15T09:00	1
101	3	AS3150	1.25 mg		Day 2	2015-06-16T09:10	2
101	4	AS3150	1.25 mg		Week 1	2015-06-21T07:30	7
101	6	AS3150	1.25 mg		Week 1	2015-06-22T10:45	8
101	7	AS3150	1.25 mg		Week 2	2015-06-27T07:30	13
101	8	AS3150	1.25 mg		Week 2	2015-06-28T07:30	14
101	10	AS3150	1.25 mg		Week 2	2015-06-29T10:30	15
101	11	AS3150	1.25 mg		Week 3	2015-07-05T08:00	21
101	13	AS3150	1.25 mg		Week 3	2015-07-06T10:30	22
101	14	AS3150	1.25 mg		Week 4	2015-07-11T08:00	27
101	15	AS3150	1.25 mg		Week 4	2015-07-12T08:00	28

EC Domain

Table 1. SDTM EX and EC Domains for Subject 101

Table 1 above shows the source Dosing data for subject 101 collected in the SDTM domains EX and EC. In the EX domain all the doses the subject took is represented using start(EXSTDTC) and stop(EXENDTC) dates. We will concentrate on row 1 where the subject took a 1.25 mg dose everyday starting from 15JUN2015 to 12JUL2015. In the EC domain all the single day doses (total of 11) that were taken at the clinic between 15JUN2015 to 12JUL2015 with the actual date/time of dosing are represented. The remaining doses between this period were taken at home and will not have the actual time of dosing recorded.

Table 2 below illustrates the process of generating the output NONMEM® data set dosing module. First, we expand the Row 1 from the EX domain to account for all the doses from 15JUN2015 to 12JUL2015. There is a new Dosing record created for each of the days between this period. But TIME will be initially missing for all the records. We will merge in the 11 dose records from EC domain which have dose times available in variable ECSTDTC to this expanded data set. But there will be a few more records with no time of collection that remain after the actual times are merged in. These missing times can be imputed by using the Last Observation Carried Forward(LOCF) method as shown in the last step of the process. Another option that is often used to impute missing times is to set the time to a constant value like 8 am for QD dosing. The Event Identification (EVID) flag is set to 1 for all the Dose records and variables Additional Doses(ADDL), Inter-dose Interval(II) and Steady State(SS) are all set to 0 to indicate that every dose is included. The inclusion of II, SS and ADDL is optional for this method.

IDORIG	DOSEMG	DATE	TIME	AMT	EVID	ADDL	II	SS
101	1.25	6/15/2015		1250	1	0	0	0
101	1.25	6/16/2015		1250	1	0	0	0
101	1.25	6/17/2015		1250	1	0	0	0
101	1.25	6/18/2015		1250	1	0	0	0
101	1.25	6/19/2015		1250	1	0	0	0
101	1.25	6/20/2015		1250	1	0	0	0
101	1.25	6/21/2015		1250	1	0	0	0
101	1.25	6/22/2015		1250	1	0	0	0
101	1.25	6/23/2015		1250	1	0	0	0
101	1.25	6/24/2015		1250	1	0	0	0
101	1.25	6/25/2015		1250	1	0	0	0
101	1.25	6/26/2015		1250	1	0	0	0
101	1.25	6/27/2015		1250	1	0	0	0
101	1.25	6/28/2015		1250	1	0	0	0
101	1.25	6/29/2015		1250	1	0	0	0
101	1.25	6/30/2015		1250	1	0	0	0
101	1.25	7/1/2015		1250	1	0	0	0
101	1.25	7/2/2015		1250	1	0	0	0
101	1.25	7/3/2015		1250	1	0	0	0
101	1.25	7/4/2015		1250	1	0	0	0
101	1.25	7/5/2015		1250	1	0	0	0
101	1.25	7/6/2015		1250	1	0	0	0
101	1.25	7/7/2015		1250	1	0	0	0
101	1.25	7/8/2015		1250	1	0	0	0
101	1.25	7/9/2015		1250	1	0	0	0
101	1.25	7/10/2015		1250	1	0	0	0
101	1.25	7/11/2015		1250	1	0	0	0
101	1.25	7/12/2015		1250	1	0	0	0



IDORIG	DOSEMG	DATE	TIME	AMT	EVID	ADDL	II	SS
101	1.25	6/15/2015	9:00	1250	1	0	0	0
101	1.25	6/16/2015	9:10	1250	1	0	0	0
101	1.25	6/17/2015		1250	1	0	0	0
101	1.25	6/18/2015		1250	1	0	0	0
101	1.25	6/19/2015		1250	1	0	0	0
101	1.25	6/20/2015		1250	1	0	0	0
101	1.25	6/21/2015	7:30	1250	1	0	0	0
101	1.25	6/22/2015	10:45	1250	1	0	0	0
101	1.25	6/23/2015		1250	1	0	0	0
101	1.25	6/24/2015		1250	1	0	0	0
101	1.25	6/25/2015		1250	1	0	0	0
101	1.25	6/26/2015		1250	1	0	0	0
101	1.25	6/27/2015	7:30	1250	1	0	0	0
101	1.25	6/28/2015	7:30	1250	1	0	0	0
101	1.25	6/29/2015	10:30	1250	1	0	0	0
101	1.25	6/30/2015		1250	1	0	0	0
101	1.25	7/1/2015		1250	1	0	0	0
101	1.25	7/2/2015		1250	1	0	0	0
101	1.25	7/3/2015		1250	1	0	0	0
101	1.25	7/4/2015		1250	1	0	0	0
101	1.25	7/5/2015	8:00	1250	1	0	0	0
101	1.25	7/6/2015	10:30	1250	1	0	0	0
101	1.25	7/7/2015		1250	1	0	0	0
101	1.25	7/8/2015		1250	1	0	0	0
101	1.25	7/9/2015		1250	1	0	0	0
101	1.25	7/10/2015		1250	1	0	0	0
101	1.25	7/11/2015	8:00	1250	1	0	0	0
101	1.25	7/12/2015	8:00	1250	1	0	0	0



IDORIG	DOSEMG	DATE	TIME	AMT	EVID	ADDL	II	SS
101	1.25	6/15/2015	9:00	1250	1	0	0	0
101	1.25	6/16/2015	9:10	1250	1	0	0	0
101	1.25	6/17/2015	9:10	1250	1	0	0	0
101	1.25	6/18/2015	9:10	1250	1	0	0	0
101	1.25	6/19/2015	9:10	1250	1	0	0	0
101	1.25	6/20/2015	9:10	1250	1	0	0	0
101	1.25	6/21/2015	7:30	1250	1	0	0	0
101	1.25	6/22/2015	10:45	1250	1	0	0	0
101	1.25	6/23/2015	10:45	1250	1	0	0	0
101	1.25	6/24/2015	10:45	1250	1	0	0	0
101	1.25	6/25/2015	10:45	1250	1	0	0	0
101	1.25	6/26/2015	10:45	1250	1	0	0	0
101	1.25	6/27/2015	7:30	1250	1	0	0	0
101	1.25	6/28/2015	7:30	1250	1	0	0	0
101	1.25	6/29/2015	10:30	1250	1	0	0	0
101	1.25	6/30/2015	10:30	1250	1	0	0	0
101	1.25	7/1/2015	10:30	1250	1	0	0	0
101	1.25	7/2/2015	10:30	1250	1	0	0	0
101	1.25	7/3/2015	10:30	1250	1	0	0	0
101	1.25	7/4/2015	10:30	1250	1	0	0	0
101	1.25	7/5/2015	8:00	1250	1	0	0	0
101	1.25	7/6/2015	10:30	1250	1	0	0	0
101	1.25	7/7/2015	10:30	1250	1	0	0	0
101	1.25	7/8/2015	10:30	1250	1	0	0	0
101	1.25	7/9/2015	10:30	1250	1	0	0	0
101	1.25	7/10/2015	10:30	1250	1	0	0	0
101	1.25	7/11/2015	8:00	1250	1	0	0	0
101	1.25	7/12/2015	8:00	1250	1	0	0	0

Table 2. Process of Output Data Set Generation for Method 1

This method generates a comprehensive Dosing module that consists of a record for every dose the subject took.

METHOD 2 – USING ADDL IN CONJUNCTION WITH II

In this method we will discuss using variables Additional Doses(ADDL) and Inter-Dose Interval(II) in tandem to create a collapsed Dosing module in a NONMEM® data set. This method is more complex than the initial technique and involves establishing and following certain rules of inclusion. The rules of dosing record inclusion are listed below:

1. The dose records in the source data set which have the actual date/time of dosing populated, will be included.
2. The first dose taken by the subject will be included.
3. The dose record on the day of PK and the dose record prior to the day of PK will be included if it is a QD Dosing regimen.
4. The dose records in the source data set where change of dose (dose reduction/dose increase) occurs for the subject, will be included.
5. If there is a dose interruption that occurs for a subject, then the very next dose record where the dose amount is greater than 0, will be included.
6. Dose record where the time difference is not exactly 24 hours (QD doses) between two consecutive daily doses, will be included.

ADDL is defined as the total number of additional continuous doses without interruption that have been collapsed into a single dose record and will have an associated II. II is defined as the Inter-dose interval flag which will indicate the dosing regimen with values 24 for QD and 12 for BID.

In this example we will consider a study which has a QD Dosing regimen. To illustrate this example let us first look at the sample source data and then a sample output which is a result of this technique.

USUBJID	EXSTDTC	EXENDTC	ASTDY	AENDY	EXTRT	EXDOSTOT	EXDOSFRQ	DOSINT	
3	12/22/2014	12/24/2014	1	3	AS101	300	QD		--Row 1
3	12/25/2014	12/26/2014	4	5	AS101	0	NOT APPLICABLE	Y	--Row 2
3	12/27/2014	12/30/2014	6	9	AS101	300	QD		--Row 3
3	12/31/2014	1/1/2015	10	11	AS101	0	NOT APPLICABLE	Y	--Row 4
3	1/2/2015	1/7/2015	12	17	AS101	200	QD		--Row 5
3	1/8/2015	2/9/2015	18	50	AS101	300	QD		--Row 6
3	2/10/2015	2/12/2015	51	53	AS101	0	NOT APPLICABLE	Y	--Row 7
3	2/13/2015	2/15/2015	54	56	AS101	200	QD		--Row 8
3	2/16/2015	6/9/2015	57	170	AS101	300	QD		--Row 9

EX Domain

USUBJID	AVISIT	EXSTDTC	ADT	ATM	ATPTN
3	CYCLE 1 DAY 1	22DEC14:12:45	22-Dec-14	12:45	0
3	CYCLE 1 DAY 1	22DEC14:12:45	22-Dec-14	13:15	0.5
3	CYCLE 1 DAY 1	22DEC14:12:45	22-Dec-14	14:45	1.5
3	CYCLE 1 DAY 1	22DEC14:12:45	22-Dec-14	17:15	4.8
3	CYCLE 2 DAY 1	19JAN15:10:05	19-Jan-15	10:05	0
3	CYCLE 3 DAY 1	16FEB15:10:40	16-Feb-15	10:30	0

PC Domain

Table 3. SDTM EX and PC Domains for Subject 003

Table 3 above shows the source Dosing and PK data for subject 003 collected in the SDTM domains EX and PC. In the EX domain all the doses the subject took is represented using start(EXSTDTM) and stop(EXENDTC) dates. Row 2,4 and 7 indicate dose interruptions within those periods. Row 5 and 8 indicate dose reduction within those periods. The PC domain above for subject 003 has rich sampling collected on Cycle 1 Day 1 and two trough samples, one on Cycle 2 Day 1 and the other on Cycle 3 Day 1. EXSTDTM represents the actual dose date/time associated with these PK samples.

In the next few steps we will see how to apply the rules of inclusion and then derive ADDL and II to build the dosing module for subject 003. The first step in the process will be to expand each row in the EX domain to single day doses as done in method 1 and merge in the actual dose date/time(EXSTDTM) from the PC domain to this expanded data set. Next, we will apply the rules step by step to build the output data set.

USUBJID	DATE	TIME	DV	VISIT	AMT	ANALYTE	EVID	NTIME	ADDL	II
3	12/22/2014	12:45	.	CYCLE 1 DAY 1	.	AS101	2	0	.	.
3	12/22/2014	12:45	.	Dose	300	AS101	1	0	.	.
3	12/22/2014	13:15	2640	CYCLE 1 DAY 1	.	AS101	0	0.5	.	.
3	12/22/2014	14:45	2320	CYCLE 1 DAY 1	.	AS101	0	1.5	.	.
3	12/22/2014	17:15	1340	CYCLE 1 DAY 1	.	AS101	0	6	.	.
3	1/19/2015	10:05	1.94	CYCLE 2 DAY 1	.	AS101	0	0	.	.
3	1/19/2015	10:05	.	Dose	300	AS101	1	0	.	.
3	2/16/2015	10:30	2.09	CYCLE 3 DAY 1	.	AS101	0	0	.	.
3	2/16/2015	10:40	.	Dose	300	AS101	1	0	.	.

Table 4. Step 2 in Output Data Set Generation for Method 2

Table 4 above shows the Step two in this data set generation. We have included all the six PK observations from the PC domain. From the expanded dose data set we bring in these three marked dose records which satisfy rule #1 where all the three dose records which have actual time of dosing from EXSTDTM are included. Row 1 also satisfies rule #2 where the first dose for the subject is included.

USUBJID	DATE	TIME	DV	VISIT	AMT	ANALYTE	EVID	NTIME	ADDL	II
3	12/22/2014	12:45	.	CYCLE 1 DAY 1	.	AS101	2	0	.	.
3	12/22/2014	12:45	.	Dose	300	AS101	1	0	.	.
3	12/22/2014	13:15	2640	CYCLE 1 DAY 1	.	AS101	0	0.5	.	.
3	12/22/2014	14:45	2320	CYCLE 1 DAY 1	.	AS101	0	1.5	.	.
3	12/22/2014	17:15	1340	CYCLE 1 DAY 1	.	AS101	0	6	.	.
3	1/18/2015	.	.	Dose	300	AS101	1	0	.	.
3	1/19/2015	10:05	1.94	CYCLE 2 DAY 1	.	AS101	0	0	.	.
3	1/19/2015	10:05	.	Dose	300	AS101	1	0	.	.
3	2/15/2015	.	.	Dose	200	AS101	1	0	.	.
3	2/16/2015	10:30	2.09	CYCLE 3 DAY 1	.	AS101	0	0	.	.
3	2/16/2015	10:40	.	Dose	300	AS101	1	0	.	.

Table 5. Step 3 in Output Data Set Generation for Method 2

Table 5 above illustrates step three. We bring in two more additional dose records rows 2 and 4 from the expanded dose data set. Rows 1,2,3,4 and 5 satisfy rule #3 where the dose record on the day of PK and the dose record on the prior day of PK need to be included. Note that dose records on Rows 2 and 4 do not have TIME populated because no dosing time is collected in the source for the same.

USUBJID	DATE	TIME	DV	VISIT	AMT	ANALYTE	EVID	NTIME	ADDL	II	
3	12/22/2014	12:45	.	CYCLE 1 DAY 1	.	AS101	2	0	.	.	
3	12/22/2014	12:45	.	Dose	300	AS101	1	0	.	.	--Row 1
3	12/22/2014	13:15	2640	CYCLE 1 DAY 1	.	AS101	0	0.5	.	.	
3	12/22/2014	14:45	2320	CYCLE 1 DAY 1	.	AS101	0	1.5	.	.	
3	12/22/2014	17:15	1340	CYCLE 1 DAY 1	.	AS101	0	6	.	.	
3	1/8/2015	.	.	Dose	300	AS101	1	0	.	.	--Row 2
3	1/18/2015	.	.	Dose	300	AS101	1	0	.	.	--Row 3
3	1/19/2015	10:05	1.94	CYCLE 2 DAY 1	.	AS101	0	0	.	.	
3	1/19/2015	10:05	.	Dose	300	AS101	1	0	.	.	--Row 4
3	2/15/2015	.	.	Dose	200	AS101	1	0	.	.	--Row 5
3	2/16/2015	10:30	2.09	CYCLE 3 DAY 1	.	AS101	0	0	.	.	
3	2/16/2015	10:40	.	Dose	300	AS101	1	0	.	.	--Row 6

Table 6. Step 4 in Output Data Set Generation for Method 2

Table 6 above illustrates step four of the process. The dose record indicated by Row 2 is added from the expanded dose data set. This dose record satisfies rule #4 where change of dose occurs on this day from 200mg to 300mg. Note that TIME will be missing for this record.

USUBJID	DATE	TIME	DV	VISIT	AMT	ANALYTE	EVID	NTIME	ADDL	II	
3	12/22/2014	12:45	.	CYCLE 1 DAY 1	.	AS101	2	0	.	.	
3	12/22/2014	12:45	.	Dose	300	AS101	1	0	.	.	--Row 1
3	12/22/2014	13:15	2640	CYCLE 1 DAY 1	.	AS101	0	0.5	.	.	
3	12/22/2014	14:45	2320	CYCLE 1 DAY 1	.	AS101	0	1.5	.	.	
3	12/22/2014	17:15	1340	CYCLE 1 DAY 1	.	AS101	0	6	.	.	
3	12/27/2014	.	.	Dose	300	AS101	1	0	.	.	--Row 2
3	1/2/2015	.	.	Dose	200	AS101	1	0	.	.	--Row 3
3	1/8/2015	.	.	Dose	300	AS101	1	0	.	.	--Row 4
3	1/18/2015	.	.	Dose	300	AS101	1	0	.	.	--Row 5
3	1/19/2015	10:05	1.94	CYCLE 2 DAY 1	.	AS101	0	0	.	.	
3	1/19/2015	10:05	.	Dose	300	AS101	1	0	.	.	--Row 6
3	2/13/2015	.	.	Dose	200	AS101	1	0	.	.	--Row 7
3	2/15/2015	.	.	Dose	200	AS101	1	0	.	.	--Row 8
3	2/16/2015	10:30	2.09	CYCLE 3 DAY 1	.	AS101	0	0	.	.	
3	2/16/2015	10:40	.	Dose	300	AS101	1	0	.	.	--Row 9

Table 7. Step 5 in Output Data Set Generation for Method 2

Table 7 above illustrates step five. The dose records on Rows 2,3 and 7 are included which satisfy rule #5 where each of these doses are the very first day after dose interruption where dose amount (AMT) is greater than 0. Note TIME will be missing for these dose records.

Rule #6 does not apply to this example and it is more common in BID dosing studies. We will skip this rule for this example. We still have dose time missing for some of the included dose records. In the next step we will look at a method to impute these missing times.

USUBJID	DATE	TIME	DV	VISIT	AMT	ANALYTE	EVID	NTIME	ADDL	II	
3	12/22/2014	12:45	.	Dose	300	AS101	1	0	.	.	--Row 1
3	12/27/2014		.	Dose	300	AS101	1	0	.	.	--Row 2
3	1/2/2015		.	Dose	200	AS101	1	0	.	.	--Row 3
3	1/8/2015		.	Dose	300	AS101	1	0	.	.	--Row 4
3	1/18/2015	10:05	.	Dose	300	AS101	1	0	.	.	--Row 5
3	1/19/2015	10:05	.	Dose	300	AS101	1	0	.	.	--Row 6
3	2/13/2015		.	Dose	200	AS101	1	0	.	.	--Row 7
3	2/15/2015	10:40	.	Dose	200	AS101	1	0	.	.	--Row 8
3	2/16/2015	10:40	.	Dose	300	AS101	1	0	.	.	--Row 9



USUBJID	DATE	TIME	DV	VISIT	AMT	ANALYTE	EVID	NTIME	ADDL	II	
3	12/22/2014	12:45	.	Dose	300	AS101	1	0	.	.	--Row 1
3	12/27/2014	12:45	.	Dose	300	AS101	1	0	.	.	--Row 2
3	1/2/2015	12:45	.	Dose	200	AS101	1	0	.	.	--Row 3
3	1/8/2015	12:45	.	Dose	300	AS101	1	0	.	.	--Row 4
3	1/18/2015	10:05	.	Dose	300	AS101	1	0	.	.	--Row 5
3	1/19/2015	10:05	.	Dose	300	AS101	1	0	.	.	--Row 6
3	2/13/2015	10:05	.	Dose	200	AS101	1	0	.	.	--Row 7
3	2/15/2015	10:40	.	Dose	200	AS101	1	0	.	.	--Row 8
3	2/16/2015	10:40	.	Dose	300	AS101	1	0	.	.	--Row 9

Table 8. Step 6 in Output Data Set Generation for Method 2

In Table 8 above we impute the dose time for dose records which have the time missing (tables show only the dose records). Rows 1,6 and 9 represent the dose records with the actual time already populated on the day of PK collection. In the initial step the dose time is carried backward to the previous day from the actual time (PK day) available. Rows 5 and 8 get populated by this method. The remaining missing times are populated using the LOCF (Last Observation Carried Forward) approach to carry forward the last available time. Rows 2,3,4 and 7 are populated using this LOCF approach.

USUBJID	DATE	TIME	DV	VISIT	AMT	ANALYTE	EVID	NTIME	ADDL	II
3	12/22/2014	12:45	.	CYCLE 1 DAY 1	.	AS101	2	0	.	.
3	12/22/2014	12:45	.	Dose	300	AS101	1	0	2	24
3	12/22/2014	13:15	2640	CYCLE 1 DAY 1	.	AS101	0	0.5	.	.
3	12/22/2014	14:45	2320	CYCLE 1 DAY 1	.	AS101	0	1.5	.	.
3	12/22/2014	17:15	1340	CYCLE 1 DAY 1	.	AS101	0	6	.	.
3	12/27/2014	12:45	.	Dose	300	AS101	1	0	3	24
3	1/2/2015	12:45	.	Dose	200	AS101	1	0	5	24
3	1/8/2015	12:45	.	Dose	300	AS101	1	0	9	24
3	1/18/2015	10:05	.	Dose	300	AS101	1	0	0	0
3	1/19/2015	10:05	1.94	CYCLE 2 DAY 1	.	AS101	0	0	.	.
3	1/19/2015	10:05	.	Dose	300	AS101	1	0	21	24
3	2/13/2015	10:05	.	Dose	200	AS101	1	0	1	24
3	2/15/2015	10:40	.	Dose	200	AS101	1	0	0	0
3	2/16/2015	10:30	2.09	CYCLE 3 DAY 1	.	AS101	0	0	.	.
3	2/16/2015	10:40	.	Dose	300	AS101	1	0	113	24

NONMEM dataset with compact doses.

Expanded view of the ADDL

addl	date	time	USUBJID	EXDOSTOT	EXDOSFRQ	ii
2	12/22/2014	12:45	3	300 QD		24
	12/23/2014	12:45	3	300 QD		
	12/24/2014	12:45	3	300 QD		
	12/25/2014	12:45	3	0 QD		
	12/26/2014	12:45	3	0 QD		
3	12/27/2014	12:45	3	300 QD		24
	12/28/2014	12:45	3	300 QD		
	12/29/2014	12:45	3	300 QD		
	12/30/2014	12:45	3	300 QD		
	12/31/2014	12:45	3	0 QD		
	1/1/2015	12:45	3	0 QD		
5	1/2/2015	12:45	3	200 QD		24
	1/3/2015	12:45	3	200 QD		
	1/4/2015	12:45	3	200 QD		
	1/5/2015	12:45	3	200 QD		
	1/6/2015	12:45	3	200 QD		
	1/7/2015	12:45	3	200 QD		
9	1/8/2015	12:45	3	300 QD		24
	1/9/2015	12:45	3	300 QD		
	1/10/2015	12:45	3	300 QD		
	1/11/2015	12:45	3	300 QD		
	1/12/2015	12:45	3	300 QD		
	1/13/2015	12:45	3	300 QD		
	1/14/2015	12:45	3	300 QD		
	1/15/2015	12:45	3	300 QD		
	1/16/2015	12:45	3	300 QD		
	1/17/2015	12:45	3	300 QD		

Table 9. Step 7 in Output Data Set Generation for Method 2

The Table 9 above represents the final NONMEM® dosing module for subject 003 with all dose time populated. The ADDL is now calculated and II is populated for all the dosing records. Since this is a QD dosing study II will be set to a constant 24 for all dose records where ADDL>0 and set to 0 where ADDL=0. The EVID flag is set to 1 for all dose records. The expanded dose data with every single dose between the first day of dosing to 17JAN2015 is shown in the second table above. This expanded dose data is an illustration of how the ADDL is counted for the first four dose records in the output data set. For e.g.: the first dose record on 22DEC2014 is included in the output data set. There are four additional dose records after 22DEC2014 and before the next included dose record on 27DEC2014. But between these four additional doses, the doses on 25DEC2014 and 26DEC2014 are interrupted, therefore the ADDL for the first dose is 2. Similarly, the 27DEC2014 is the next dose included in the output data set. There are five additional doses after 27DEC2014 and before 02JAN2015 which is the next included dose. But between these five additional doses, the doses on 31DEC2014 and 01JAN2015 are interrupted, therefore the ADDL for the 27DEC2014 dose record is 3. Similarly, ADDL is calculated for the remaining dose records included in the output data set.

This method generates a compact Dosing module which represents the entire dosing history.

METHOD 3 – USING SS, II AND EVID

In this method we will discuss using variables Steady State(SS), Inter-Dose Interval(II) and Event Identification Flag (EVID) in tandem to create a compact Dosing module in a NONMEM® data set. When the rate of drug input into the body is equal to the rate of drug elimination from the body, steady state (SS) has been achieved. When the steady state will be reached for a particular drug should be defined by the pharmacometrician.

In this example we will consider a study which has a BID Dosing regimen. To illustrate this example let us first look at the sample source data and then a sample output which is a result of this technique.

USUBJID	EXDOSE	EXDOSU	EXSTDTC	EXENDTC	EXSTDY	EXENDY	EXTPT
3	300 mg		6/29/2012	7/10/2012	1	12	AM DOSE
3	300 mg		6/29/2012	7/10/2012	1	12	PM DOSE
3	300 mg		7/11/2012	7/11/2012	13	13	AM DOSE
3	0 mg		7/11/2012	7/11/2012	13	13	PM DOSE
3	0 mg		7/12/2012	7/12/2012	14	14	AM DOSE
3	0 mg		7/12/2012	7/12/2012	14	14	PM DOSE
3	0 mg		7/13/2012	7/13/2012	15	15	AM DOSE
3	100 mg		7/13/2012	7/13/2012	15	15	PM DOSE
3	100 mg		7/14/2012	7/31/2012	16	33	AM DOSE
3	100 mg		7/14/2012	7/31/2012	16	33	PM DOSE

EX Domain

RDOMAIN	USUBJID	IDVARVAL	QNAM	QLABEL	QVAL
PC	3	6/29/2012	DOSCURRE	DOSE DATE AND TIME	2012-06-29T11:30:00
PC	3	7/9/2012	DOSCURRE	DOSE DATE AND TIME	2012-07-09T10:20:00
PC	3	7/9/2012	DOSPRIOR	DATE AND TIME OF PRIOR DOSE	2012-07-08T21:00:00
PC	3	7/20/2012	DOSPRIOR	DATE AND TIME OF PRIOR DOSE	2012-07-19T21:00:00

SUPPPC Domain

Table 10. SDTM EX and SUPPPC Domains for Subject 003

Table 10 above shows the source Dosing and Dosing date/time data for subject 003 collected in the SDTM domains EX and SUPPPC. In the EX domain all the doses the subject took is represented using start(EXSTDTC) and stop(EXENDTC) dates. There are a few dose interruptions. In the SUPPPC domain for each of the PK observations collected on dates in IDVARVAL the reference dose date/time associated with these PK observations is collected in variable QVAL.

USUBJID	DOSE	FREQ	VIST	NOMT	ACTD	EVID	AMT	SS	II	DV	DATETIME	
3	300	2	C1D1	0	1	2	2012-06-29T11:30:00	
3	300	2	Dose	.	1	1	300	0	0	.	2012-06-29T11:30:00	--Row 1
3	300	2	C1D1	0.5	1	0	.	.	.	476	2012-06-29T12:04:00	
3	300	2	C1D1	1	1	0	.	.	.	2220	2012-06-29T12:34:00	
3	300	2	C1D1	2	1	0	.	.	.	3020	2012-06-29T13:21:00	
3	300	2	C1D1	4	1	0	.	.	.	468	2012-06-29T15:40:00	
3	300	2	C1D1	6	1	0	.	.	.	240	2012-06-29T17:20:00	
3	300	2	Dose	.	10	4	300	1	12	.	2012-07-08T21:00:00	--Row 2
3	300	2	C1D10	0	11	0	.	.	.	138	2012-07-09T08:35:00	
3	300	2	Dose	.	11	1	300	1	12	.	2012-07-09T10:20:00	--Row 3
3	300	2	C1D10	0.5	11	0	.	.	.	426	2012-07-09T10:50:00	
3	300	2	C1D10	1	11	0	.	.	.	1320	2012-07-09T11:20:00	
3	300	2	C1D10	2	11	0	.	.	.	1950	2012-07-09T12:20:00	
3	300	2	C1D10	4	11	0	.	.	.	891	2012-07-09T14:35:00	
3	300	2	C1D10	6	11	0	.	.	.	388	2012-07-09T16:20:00	
3	100	2	Dose	.	21	4	100	1	12	.	2012-07-19T21:00:00	--Row 4
3	100	2	C2D1	0	22	0	.	.	.	72.7	2012-07-20T08:50:00	

Table 11. Process of Output Data Set Generation for Method 3

Table 11 above illustrates the process of generating the output NONMEM® data set dosing module for this method. The marked records are the dose records and the rest are PK observations for this subject. The PK observations on Visit C1D1 are rich samples. There a couple of trough samples, one during Visit C1D10 (Nominal Time-NOMT=0) and the other during visit C2D1 (Nominal Time-NOMT=0). There are also rich PK samples collected during C1D10.

In this method the only dose records that will be included in the output data set are the reference doses with the actual date/time of collection represented in QVAL of the SUPPPC domain. For subject 003 we have four such reference doses which are all included in the data set above. For this example, we will assume that the steady state was reached from Visit C1D8. Therefore, the doses on visits prior to C1D8 will have SS=0 in this case Row 1. All other doses on or after C1D8 will have SS set to 1 as shown by Rows 2,3 and 4. Inter-dose interval (II) is set to a constant 12 for all dose records except when SS=0 as this is a BID dosing regimen. II is 0 when SS is 0. EVID flag in this method will vary between dose records unlike the first 2 methods where it was set to a constant 1. For doses associated with rich PK samples EVID=1 as in Rows 1 and 3. For trough samples EVID will be set to 4 as in Rows 2 and 4. EVID=4 instructs NONMEM® to reset the dosing compartment.

There are some drawbacks with this method. A few of these issues are listed below:

1. In the example above what happens if some of the reference dose times are missing in QVAL from the SUPPPC domain? There should be some discussions with pharmacometricians on techniques to impute such missing time before reference doses are included in the output data set.
2. What happens when the reference dose dates for trough PK samples are not identified in the SDTM source data sets? It will be a complex exercise to first identify these reference doses before including them in the output data set.

3. Consider a study which has the entire dosing history collected in the source data and you still decide to use this method where you are accounting only for the reference doses in the output data set. This will involve making a lot of assumptions regarding how the subjects were dosed for the entire duration of the study.
4. This method would be a better fit for a study which has incomplete dosing history collected in the source data.
5. Steady State assumption is compound driven and not applicable to every molecule.

ADVANTAGES AND DISADVANTAGES

METHOD 1	METHOD 2	METHOD 3
Simple method to program and code.	More complex method which involves ADDL computations and rules of inclusion for dose records.	Can be simple or complex depending on how reference doses are collected in the source data sets.
Faster implementation time.	Longer implementation time.	Faster or longer implementation time depending on how reference doses are collected in the source data sets.
Size of the output NONMEM® data set will be huge as every single day dose are included.	Compact NONMEM® data set.	Very compact NONMEM® data set.
Represents the entire dosing history with few or no assumptions.	Represents the entire dosing history with few or no assumptions.	Does not represent the entire dosing history and will involve many assumptions surrounding dose intake.
Performing QC on a data set built using this method will be straight forward.	Use of graphical QC techniques might be apt.	Use of graphical QC techniques might be apt.

CONCLUSION

In addition to the methods discussed in this paper, we could also have studies where a combination of two or more of these techniques could be the best approach. As you can see from the methods discussed above, there are multiple options available to program the dosing module of a NONMEM® data set. But selecting the appropriate approach for your study should be done in consultation with the pharmacometricians who are the primary stakeholders of these data sets.

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