Impact of daylight saving time shifts on data quality of a pharmacokinetic study

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Twice a year, most areas of North America and Europe observe a time shift. In spring, a positive shift occurs when clocks are reset from 02:00 to 03:00 hours, generally on a Sunday morning. In late autumn, a negative shift occurs when clocks are reset from 03:00 to 02:00 hours, generally on a Sunday morning. These time shifts can have an impact on the data quality if they are not considered appropriately. Especially for pharmacokinetic studies, this can lead to issues and wrong results in the calculation of time-dependent variables like area under the curve (AUC) or terminal half-life ($t_{1/2}$). It also affects recording of safety data like adverse events or serial ECGs. This paper describes possible pitfalls in the study set-up and possible impact on data quality and analysis. It also shows traceable data handling options in case a solution in the data collection cannot be achieved.

Keywords: Daylight saving time, Data quality, Data handling, Pharmacokinetic studies

Introduction

Starting in the early twentieth century, many countries introduced daylight saving times (DSTs) in order to save energy. Time shifts of any kind cause people who have to deal with date and time data a lot of problems. If time shifts occur in different time zones as described in van Bemmelen,[1] this can be handled in a straightforward manner technically. In his paper, van Bemmelen proposes the usage of informats to achieve comparability of central and local timestamps for different time zones. As van Bemmelen also indicated, the handling of DST is more advanced though. van Bemmelen gives an example for a DST correction which is not applicable when the timepart is close to midnight. The handling of DST switches is also not covered by SAS® standard solutions. SAS software does not offer an out of the box solution to implement DST. The SAS function `intck` respects leap years, but it does not respect DST.

This paper will provide an example of how the switch to DST can impact the data collection and analysis of a pharmacokinetic trial. There are pitfalls which can be avoided by careful planning of the study. Training and awareness of site personnel is of critical importance to ensure the data reliability. With data manipulations, the traceability and proper documentation is one key factor for later data usability in pooling activities or agency submissions. A traceable data handling workflow is proposed in the case of issues observed during the data collection.

Data Collection in Pharmacokinetic Studies

In general, the semi-annual switch to DST does not create significant issues in a clinical drug development program. In ordinary Phase 2+ studies, patients show up at the study site for their scheduled visits. In most cases, only dates are collected for efficacy or safety data. In a pharmacokinetic study in Phase 1, the situation is different though, especially if the sampling times cross a change in DST.

Phase 1 studies require a more detailed data collection over a short period of time to gather a comprehensive pharmacokinetic and safety profile. For this detailed information for the plasma, urine, sputem, and serum concentrations, as well as data for vital signs, ECG and adverse events are measured over a short period of time. In this context, the collection of both date and time is essential.

Often Phase 1 studies are conducted in healthy volunteers who are hospitalized over the weekend. The cohorts of healthy subjects are often dosed early Saturday to decrease the impact on the private life of the volunteers during the week. After dosing, data are collected over an interval of time that often continues into Sunday and beyond. So by nature of the trial design, Phase 1 studies are more affected by time shifts when the study is conducted on the weekend when the time change occurs.

In general, the data handling in a pharmacokinetic study is similar to studies which assess the efficacy of

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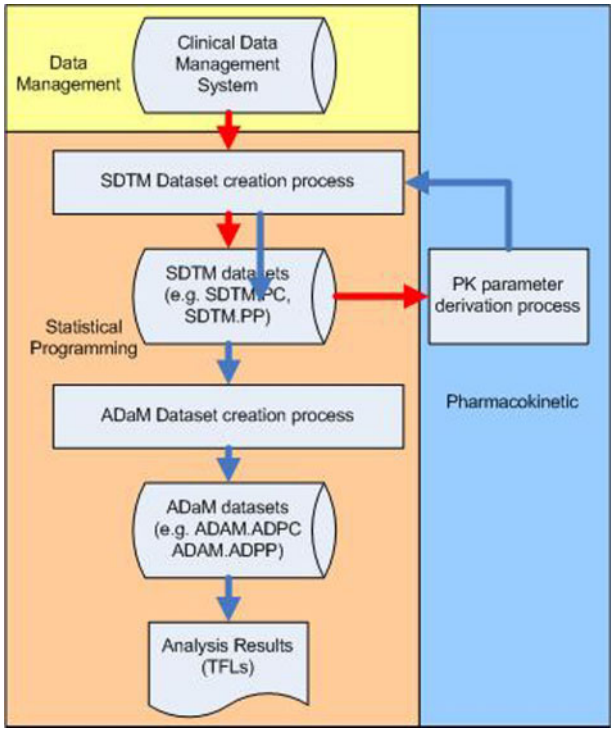

Figure 1 Data workflow in a pharmacokinetic study

a drug. The handover to the pharmacokineticist for the evaluation of the pharmacokinetic parameters is more complex though. This data workflow for a pharmacokinetic study is visualized in Fig. 1.

Data are entered in a clinical data management system and cleaned before the database lock. Usually, a data review meeting is held before the database lock in order to check for deviations to the study protocol. In a pharmacokinetic study, time deviations are often observed. After the database lock, the raw data can be remapped to SDTM datasets. Plasma concentrations will be stored in the SDTM domain PC. A tool like Knowledgebase Server from Pharsight® (PKS™) could then be used by the pharmacokineticist to derive the pharmacokinetic parameters like area under the curve (AUC) and $t_{1/2}$ based on the SDTM.PC data. The derived pharmacokinetic variables will be stored in the SDTM dataset PP. The SDTM data are then used to create the corresponding ADaM domains (e.g. ADPC and ADPP) for the statistical analysis and reporting.

Impact of Time Switch on a Pharmacokinetic Study

As described above, the assessment of time is important in a pharmacokinetic study. The conduct of a pharmacokinetic study during a switch to DST can impact the data assessment and can have an effect on the data quality.

If the study team does not take a switch to DST into account, the following describes a worst case scenario.

The pharmacokinetic blood sampling is scheduled for a study drug administration time of 08:00 hours local standard time (LST) in the morning. There is a switch to DST during the following night. The 24-hour post-dose measurement is then at 09:00 hours (DST). Consequently, the 36-hour measurement should be carried out at 21:00 hours (DST) and the 48-hour measurement at 09:00 hours (DST) the following day. It could be even worse if for some subjects the LST is still recorded (i.e. 08:00 and 20:00 hours).

In the worst case, the entered data would be checked as usual. No special checks would check if times like 02:23 hours appear. Times between 02:00 and 03:00 hours should not exist. But if the order of the measurements is still correct, most of the data checks would not fire for data inconsistencies without special adjustment.

As a result, data are entered and will stay as they are in the clinical database. In the next step, a programmer who is not aware of the switch to DST will take these data and remap them to SDTM.PC. The reference date RFSTDTC will be the first dosing data 08:00 hours. The +24-hour sampling will have the actual time 09:00 hours. Consequently, checks for protocol deviations for the data review meeting will produce output like 'Scheduled +24-hour blood sampling was performed 1 hour too late'.

In the worst case scenario, it is not recognized during the data review meeting that switch to DST was not respected and the SDTM.PC dataset is sent to the pharmacokineticist. The pharmacokineticist takes the actual sampling time to derive the PK parameters. Consequently, he will calculate time-dependent pharmacokinetic parameters like AUC and $t_{1/2}$ with the underlying assumption that everything was 1 hour too late. So the pharmacokineticist will slightly overestimate these parameters. If the time shift is after t_{max}, the estimated slope will appear slightly slower as it actually was. Estimates can deviate from reality up to 10% for these parameters.

After the derivation of the pharmacokinetic parameters, the pharmacokineticist sends the derived data back to the statistical programmer. The programmer will create the SDTM.PP and use this dataset also for the creation of the ADaM dataset ADPP. In all the tables, figures, and listings, the underestimated plasma concentrations and pharmacokinetic parameters are then consequently used. The data are used for further modeling and simulation, and would lead to greater non-random variability in all analysis in the case of pooled data analysis.

The above explained scenario describes the worst case, but it clearly shows several pitfalls which can occur during a switch to DST. These pitfalls can be avoided by careful planning of the study team and further considerations in the data analysis.

Proposal for Data Handling in Studies Impacted by a Time Switch

The following proposal will help to avoid most of the abovementioned issues.

First of all, the study team should be aware that there is a switch to DST. Based on that knowledge, the trial manager can instruct the study site personnel to strictly follow these basic rules:

- all study events (including blood samples, safety measurements, and AE reporting) which occur before the switch to DST at 02:00 hours must be recorded in the actual time (i.e. LST);
- the study clock will be set from 02:00 to 03:00 hours and from that time point, all study events will be recorded in DST.

These rules will ensure that adverse events which started at 01:55 hours and last for 10 minutes will have an end time of 03:05 hours. Blood samples taken the next morning will have sampling times collected according to DST. If the site personnel are clearly instructed and trained, the awareness of potential issues will be increased, and LST and DST mixtures may be avoided.

Once all the data are collected and entered in a database, the data should be checked as usual in a cleaning process. But in these cases, the data cleaning plan should include a check if times between 02:00 and 03:00 hours occur. If that is the case, queries should be raised to the investigator to correct these time points. This will ensure that mixtures of LST and DST records after the switch to DST appear in the database.

The programmer remaps the raw data to SDTM data. Since SAS software does not offer an out-of-the-box solution to consider time shifts, the programmer needs to adapt their SDTM programs for this case. The programmer should subtract 1 hour from all times which occur after the shift to DST. This can be easily solved with code similar to the following snippet:

```
%macro dst_adj(date=, time= );
   *** define macro variable for date
of the Sunday where the DST switch
occurs ***;
   %let DST_date=27MAR2011;
   if &date. >= "&DST_date"d and &time.
>= "01:59:59"t then do;
     old_time=&time.;
     new_time=&time.-60*60;
     &time.=new_time;
     %put "Note: adjustment of time for
subject " usubjid= &date.= old_time=
new_time=;
   end;
   else do;
     old_time=&time.;
     new_time=&time.;
   end;
   run;
%mend;
```

This macro can be easily included in a data step as follows:

```
pcdt=input(substr(pcdtc,1,index(pcdtc,
'T')),yymmdd10.);
pctm=input(substr(pcdtc,index(pcdt-
c,'T')+1),time5.);
format pcdt date9. pctm time5. old_
time new_time time5.;
%dst_adj(date=pcdt, time=pctm);
```

An example of how this may be implemented seen for taking the data from our worst case example and applying the macro is presented in Fig. 2.

These data modifications should be carried out for all SDTM datasets where times are an element of the data domain and affected by time changes. In addition to pharmacokinetic SDTM domains, this would include any other SDTM domains that may host serial time sampling [e.g. AE (adverse events), VS (vital signs), EG (electrocardiograms), CM (concomitant medications), LB (laboratory investigations), or pharmacodynamic data domains]. Regardless of the domain, all these modifications needs to be documented in the corresponding SDTM Data Definition Table (DDT) to ensure traceability and transparency between the CRF raw data and the SDTM database.

After performing the data transformations, the statistical programmer sends the SDTM.PC dataset to the pharmacokineticist. Since the programmer already took care of the data handling of the time issues, the pharmacokineticist can perform the pharmacokinetic parameter derivation per usual practice. He can use the actual times to derive the PK parameters including time-dependent variables like AUC and $t_{1/2}$. After he derived the pharmacokinetic parameters, he sends the data back to the statistical programmer.

The statistical programmer will create the SDTM.PP and the ADaM datasets ADPC, ADPP, or other required ADPPxxxx analysis datasets depending on the analysis requirements of the study. The TFLs for the clinical study report appendix should exactly reflect the data recorded in the CRFs.

For other time-dependent derived variables (i.e. duration of an AE), the transformed times should be derived and recorded in the appropriate ADaM datasets required for the planned analyses. For reporting purposes, the statistical programmer will need to back-transform the adjusted times to reflect the actual CRF entries. A similar code snippet like above can be easily created for all the ADaM datasets. For traceability reasons, it is also important to document this in the ADaM DDTs. Text in the TFL footnotes or in the clinical study report also help to further explain what has been carried out.

This proposal leads to a traceable and transparent data flow. It ensures that all involved parties can

pc.sas7bdat

	Unique Subject Identifier (DOMAIN)	Unique Subject Identifier (usubjid)	Numeric Result or Finding in Std Units (PCSTRESN)	Standard Units (PCSTRESU)	Specimen Material Type (PCSPEC)	Date/Time of Specimen Collection (PCDTC)	Planned Time Point Name (PCTPT)	pctm (pctm)	pcdt (pcdt)	old_time (old_time)	new_time (new_time)
1	PC	001-1001	0	µg/mL	PLASMA	2011-03-26T08:15	predose	8:15	26MAR2011	8:15	8:15
2	PC	001-1001	1.1	µg/mL	PLASMA	2011-03-26T08:30	0.25H	8:30	26MAR2011	8:30	8:30
3	PC	001-1001	3.3	µg/mL	PLASMA	2011-03-26T08:45	0.50H	8:45	26MAR2011	8:45	8:45
4	PC	001-1001	4	µg/mL	PLASMA	2011-03-26T09:00	0.75H	9:00	26MAR2011	9:00	9:00
5	PC	001-1001	4.2	µg/mL	PLASMA	2011-03-26T09:15	1.00H	9:15	26MAR2011	9:15	9:15
6	PC	001-1001	2.5	µg/mL	PLASMA	2011-03-26T10:15	2.00H	10:15	26MAR2011	10:15	10:15
7	PC	001-1001	1	µg/mL	PLASMA	2011-03-26T12:15	4.00H	12:15	26MAR2011	12:15	12:15
8	PC	001-1001	0.5	µg/mL	PLASMA	2011-03-26T16:15	8.00H	16:15	26MAR2011	16:15	16:15
9	PC	001-1001	0.27	µg/mL	PLASMA	2011-03-26T20:15	12.00H	20:15	26MAR2011	20:15	20:15
10	PC	001-1001	0.22	µg/mL	PLASMA	2011-03-27T02:15	18.00H	2:15	27MAR2011	3:15	2:15
11	PC	001-1001	0.18	µg/mL	PLASMA	2011-03-27T08:15	24.00H	8:15	27MAR2011	9:15	8:15
12	PC	001-1001	0.1	µg/mL	PLASMA	2011-03-27T20:15	36.00H	20:15	27MAR2011	21:15	20:15
13	PC	001-1001	0.05	µg/mL	PLASMA	2011-03-27T08:15	48.00H	8:15	27MAR2011	9:15	8:15
14	PC	001-1001	0	µg/mL	PLASMA	2011-03-27T20:15	60.00H	20:15	27MAR2011	21:15	20:15

Figure 2 SDTM.PC with temporary data presenting the LST and DST

continue to use the SDTM data for other purposes. The pharmacokinetic parameters are adequately estimated and can be used for further modeling and simulation purposes, and the SDTM database does not contain date and time information which could be misinterpreted as protocol deviations at a later point of time.

Enhancements

The above proposal fits for a shift from LST to DST. If a switch from DST to LST is observed, the whole scenario gets more complex. In a pretty unlikely scenario (e.g. an AE starts shortly before the time switch and ends 60 minutes after the switch), some times might occur more than once in the database. This scenario requires even more advanced planning. It could be solved with similar principles as described in this paper.

The manual setting of a macro variable *DST_date* could of course be automated. The switch from LST to DST usually follows some rules. Unfortunately, these rules change over time and even worse over location. Public domain databases like 'tz database'[2] store and maintain historical data and DST rules which could be accessed for automation. Based on the fact that a shift in time only occurs twice a year, it is questionable that this kind of automation is worth the effort.

Conclusion

In the twentieth century, people in North America and Europe adjusted to time switches. Resetting the clock for 1 hour is not a big deal for most of the people and everybody got used to it. What is not a big deal in the real world can cause issues when it comes to data collection and data analysis.

It was shown that a switch to DST can lead to multiple issues in the following data preparation and analyses. While a switch to DST does not have an effect on ordinary Phase 2+ studies, it might have an effect on pharmacokinetic studies. The best method to avoid all these issues is to avoid dosing in pharmacokinetic studies at a weekend where a switch to DST occurs. If that is not possible, a traceable data workflow proposal must be created. The essence of the proposal is to transform times after the switch to DST occurred with an addition of 1 hour. This has to happen in the SDTM remapping process to ensure further usage of other parties. For reporting purposes, these times should be back-transformed to exactly match the entries on the CRF.

References

1 van Bemmelen J. Timezone correction of dates. Basel: PhUSE; 2009.
2 Available from: http://www.twinsun.com/tz/tz-link.htm [cited 2011 Jul 15].