DISL

# Studies

Each line represents a unique PK assessment. PK assessment can be either a (scanned/tabulated) PK profile or one (or more) reported PK parameters or both.

Typical examples:

* A DDI study measuring PK profiles and PK parameters (e.g. AUC, Cmax) of a victim before and after administration of a perpetrator would be 2 lines, one for control (placebo) phase, one for treatment (with perpetrator) phase. If there are additional measurements for the perpetrator’s PK (e.g. PK profile or PK parameters), add a third line.
* A pediatric PK study measures PK in 40 children and reports 40 clearance parameters would be 40 lines.
* A multiple dose study measures PK profiles on day 1 and on day 7 would be 2 lines.
* A study where there is an IV loading dose via a 30 min infusion with the administration of a tablet 2 hours later would be one or two lines depending on the reported output. If there is only the report of a unique PK profile, one line would be enough. If there are specifically reports of PK parameters regarding the first and second administration (e.g. 2 Cmax values), 2 lines would be appropriate.
* If there is a study measuring total and unbound PK profiles and/or PK-Parameters, it would be 2 lines for this particular study part

The term “dataset” refers to the specific current line.

|  |  |  |
| --- | --- | --- |
| **ID** | | Integer. Specify a unique identifier for this data. This identifier should be used in all other subsheets. |
| **Study** | | String. <First author> plus <year>, e.g. Lamberg 1998. If inconclusive, follow the logic <Author> <Year>, <Author> <Year>**b**, <Author> <Year>**c**, etc. |
| **Reference** | | Reference to source. Ideally a link. PMID preferred. |
| **Grouping** | | String. Specify a unique grouping name for this particular dataset within the corresponding study. This could relate to phases, study arms, patient groups, individuals, etc.  Examples: “Control (Perpetrator Placebo)”, “with Perpetrator (Verapamil)”, “Individual 2”, “Day 7”,” Moderate Renal Impairment” |
| **Analyte** | | String. Specify the compound which was administered and analyzed in this dataset. |
| **PK properties** | **Compartment** | String. Specify compartment/location from which the data sample was taken, e.g. plasma, urine, etc. |
| **Data type** | String. Specify either “**Aggregated**” for all kind of aggregated data (e.g. mean, median, ranges, etc.), or “**Individual**” (i.e. for individual data), or “**Typical**” (this is a special case found in older articles where concentration-time-profiles of typical representative individuals are plotted |
| **Source** | String. Specify the source of the data in the corresponding original paper, e.g. Figure 2, Table 3, etc. |
| **Comment PK** | String. Specify in free text any particularities. |
| **DOSING REGIMEN** | **Dose** | Numeric. Specify the nominal dose given in the original source. |
| **Dose free API** | Numeric. Specify the dose of the free API (if deviating from “Dose”). Examples include: 5 mg BuSpar contain 5 mg buspirone hydrochloride and, thus, 9.14 mg buspirone. |
| **Dose Unit** | Specify unit of “Dose” / “Dose free API”, e.g. mg |
| **Route** | String. Specify route of administration, e.g. PO, IV, SC etc. In case there were multiple administrations with different routes **before** the data were measured, follow the logic <Route 1>-<Route 2>-<Route 3>…,  e.g. PO-IV-PO |
| **Times of Administration** | Specify time or multiple times of administrations before the data were measured. Choose a meaningful reference time point as zero, e.g. the time point of the first administered dose.  Example DDI study:  For the control (placebo) phase with a single dose administration of the victim, a meaningful reference point would be the administration of the victim itself; thus, just “0” needs to be entered.  For the treatment phase (with perpetrator), however, a meaningful reference point would be the first administration of the perpetrator. If this happened 72 hours before victim administration, “72” needs to be entered.  In case of multiple administrations, please follow the logic <time 1>-<time 2>-<time 3>-…,  e.g. “0-8-24-32”  In case of multiple administrations with a fixed interdose interval (tau), abbreviations are allowed by the triple (**S**tart time, **T**au, Number of **R**epetitions).  A study with the schedule 0-24-48-72-96 could be abbreviated with “S0-T24-R5”.  Multiple entries (with different formats or multiple S#-T#-R# entries) should be comma separated.  A study with the schedule 0-36-48-60-72-84-96-108 could be abbreviated with “0, S36-T12-R7”. |
| **Times Unit** | Specify unit for “Times of Administration”, e.g. h |
| **Comment Regimen** | String. Specify in free text any particularities. |
| **Details on administration / formulation** | **Administered form** | String. Specify (if available) the administered form (e.g. the specific salt), e.g. erythromycin stearate, erythromycin ethylsuccinate ester, erythromycin base, etc. |
| **Formulation type** | String. Specify (if available) the administered formulation, e.g. oral solution, IR tablet, enteric coated pellets, etc. Product names are also possible, e.g. BuSpar® Dividose® tablet |
| **Infusion duration [min]** | Specify infusion duration in minutes in case of iv administration. Specify 0 for bolus doses. In case of multiple infusions specified in “DOSING REGIMEN”, follow the logic <duration 1>-<duration 2>-<duration 3>…, e.g. 30-30-60-60 |
| **Water volume ingested for drug intake [mL]** | Specify water volume ingested for drug intake in mL (if available), e.g. 250 |
| **Comment on administration/formulation** | String. Specify in free text any particularities. |
| **Food** | **Fasted/Fed state** | Specify if administration was under fasting or fed conditions (if available). In case of mixed pattern, follow the logic <condition 1>-<condition 2>-<condition 3>, e.g. fasted-fed-fasted |
| **Duration of fasting before drug administration [h]** | Specify duration of fasting before drug administration in hours (if available) |
| **Duration of fasting after drug administration [h]** | Specify duration of fasting after drug administration in hours (if available) |
| **Comment on food intake** | String. Specify in free text any particularities. |
|  | **Species** | String. Define Species, e.g. Human |
| **Total** | **N** | Numeric. Specify total number of individuals underlying the dataset. |
| **Gender** | **N female** | Numeric. Specify total number of females (as a subgroup of “N”) underlying the dataset. |
| **Age** | **Avg** | Specify any average measure for age (in case of aggregated data) or individual age (in case of individual data) (if available) |
| **AvgUnit** | Specify unit for average measure of age, e.g. days, years etc. |
| **AvgType** | Specify type of average measure for age, e.g. “Arith. mean”, “Geom. mean”, “Median”, etc. (in case of aggregated data) or “Individual” (in case of individual data) |
| **Var** | Specify any variability measure for age (in case of aggregated data) (if available) |
| **VarUnit** | Specify unit for variability measure of age, e.g. days, years etc. |
| **VarType** | Specify type of variability measure for age, e.g. “Arith. SD”, “Geom. SD”, “Arith. CV”, “Geom. CV”, “Range” etc. (only in case of aggregated data) |
| **Min** | Specify minimum of age (in case of aggregated data) (if available) |
| **Max** | Specify maximum of age (in case of aggregated data) (if available) |
| **Weight** | **Avg** | Specify any average measure for weight (in case of aggregated data) or individual age (in case of individual data) (if available) |
| **AvgUnit** | Specify unit for average measure of weight, e.g. kg |
| **AvgType** | Specify type of average measure for weight, e.g. “Arith. mean”, “Geom. mean”, “Median”, etc. (in case of aggregated data) or “Individual” (in case of individual data) |
| **Var** | Specify any variability measure for weight (in case of aggregated data) (if available) |
| **VarUnit** | Specify unit for variability measure of weight, e.g. kg |
| **VarType** | Specify type of variability measure for weight, e.g. “Arith. SD”, “Geom. SD”, “Arith. CV”, “Geom. CV”, “Range” etc. (only in case of aggregated data) |
| **Min** | Specify minimum of weight (in case of aggregated data) (if available) |
| **Max** | Specify maximum of weight (in case of aggregated data) (if available) |
| **Height** | **Avg** | Specify any average measure for height (in case of aggregated data) or individual age (in case of individual data) (if available) |
| **AvgUnit** | Specify unit for average measure of height, e.g. cm, meter etc. |
| **AvgType** | Specify type of average measure for height, e.g. “Arith. mean”, “Geom. mean”, “Median”, etc. (in case of aggregated data) or “Individual” (in case of individual data) |
| **Var** | Specify any variability measure for height (in case of aggregated data) (if available) |
| **VarUnit** | Specify unit for variability measure of height, e.g. cm, meter etc. |
| **VarType** | Specify type of variability measure for height, e.g. “Arith. SD”, “Geom. SD”, “Arith. CV”, “Geom. CV”, “Range” etc. (only in case of aggregated data) |
| **Min** | Specify minimum of height (in case of aggregated data) (if available) |
| **Max** | Specify maximum of height (in case of aggregated data) (if available) |
| **BMI** | **Avg** | Specify any average measure for BMI (in case of aggregated data) or individual age (in case of individual data) (if available) |
| **AvgUnit** | Specify unit for average measure of BMI, e.g. kg/m² |
| **AvgType** | Specify type of average measure for BMI, e.g. “Arith. mean”, “Geom. mean”, “Median”, etc. (in case of aggregated data) or “Individual” (in case of individual data) |
| **Var** | Specify any variability measure for BMI (in case of aggregated data) (if available) |
| **VarUnit** | Specify unit for variability measure of BMI, e.g. kg/m² |
| **VarType** | Specify type of variability measure for BMI, e.g. “Arith. SD”, “Geom. SD”, “Arith. CV”, “Geom. CV”, “Range” etc. (only in case of aggregated data) |
| **Min** | Specify minimum of BMI (in case of aggregated data) (if available) |
| **Max** | Specify maximum of BMI (in case of aggregated data) (if available) |
| **BSA** | **Avg** | Specify any average measure for BSA (in case of aggregated data) or individual age (in case of individual data) (if available) |
| **AvgUnit** | Specify unit for average measure of BSA, e.g. m² |
| **AvgType** | Specify type of average measure for BSA, e.g. “Arith. mean”, “Geom. mean”, “Median”, etc. (in case of aggregated data) or “Individual” (in case of individual data) |
| **Var** | Specify any variability measure for BSA (in case of aggregated data) (if available) |
| **VarUnit** | Specify unit for variability measure of BSA, e.g. m² |
| **VarType** | Specify type of variability measure for BSA, e.g. “Arith. SD”, “Geom. SD”, “Arith. CV”, “Geom. CV”, “Range” etc. (only in case of aggregated data) |
| **Min** | Specify minimum of BSA (in case of aggregated data) (if available) |
| **Max** | Specify maximum of BSA (in case of aggregated data) (if available) |
| **Ethnicity or country** | | String. Specify ethnicity or country of the study, e.g. Caucasians, Japanese, Finland, etc. |
| **Comment Population** | | String. Specify in free text any particularities. |

# PK-Parameter

PK parameter lists extracted PK-Parameter for the studies listed in the “*Studies*” sheet.

Each line represents a specific dataset (i.e. time interval) and relates to a “grouping” of a “study” listed in the “*Studies*” sheet. Thus, the term “dataset” refers to the specific current line.

|  |  |
| --- | --- |
| **ID** | Cross reference to “ID” in “*Studies*“ |
| **Study** | Cross reference to “Study” in “*Studies*“ |
| **Reference** | Cross reference to “Reference” in “*Studies*“ |
| **Grouping** | Cross reference to “Grouping” in “*Studies*“ |
| **Analyte** | Cross reference to “Analyte” in “*Studies*“ |
| **t0** | Specify the begin of the time interval for this dataset. Usually this is related to the time of the last administration specified in “Times of Administration” listed in in the “*Studies*” sheet. For example, in a single dose study (also in the control (placebo) grouping of a DDI phase) this is usually 0; however, considering PK- Parameters of a victim drug in a DDI study in the treatment (with Perpetrator) grouping, this would be the time of the victim administration relative to the first administration of the perpetrator, e.g. 79 |
| **tend** | Specify the end of the time interval for this dataset.  This could be inf (typically in single dose administration) or the specific value for tau (in multiple dose studies), e.g. 12, 24, or specific values for reported tend.  Please note that the value of “t0” needs to be added. |
| **t Unit** | Specify unit of “t0” and “tend”, e.g. h |
| **AUC Avg** | Specify any average measure for AUC (in case of aggregated data) or individual AUC (in case of individual data) (if available) for the current dataset.  In case of availability of multiple AUC values for the current dataset,  prefer AUC\_inf in case of single dose data, prefer AUC\_tau in case of multiple dose data (0 means time of last administration). Please see also below “AUC Type”, and above “t0” and “tend” for the time interval relevant for AUC determination. |
| **AUC AvgUnit** | Specify unit for average measure of AUC, e.g. µg\*h/L, etc. |
| **AUC AvgType** | Specify type of average measure for AUC, e.g. “Arith. mean”, “Geom. mean”, “Median”, etc. (in case of aggregated data) or “Individual” (in case of individual data) |
| **AUC Var** | Specify any variability measure for AUC (only in case of aggregated data) |
| **AUC VarUnit** | Specify unit for variability measure of AUC, e.g. µg\*h/L, %, etc. |
| **AUC VarType** | Specify type of variability measure for AUC, e.g. “Arith. SD”, “Geom. SD”, “Arith. CV”, “Geom. CV”, “Range”, “95% CI” etc. (only in case of aggregated data) |
| **AUC Type** | Specify details on the AUC type. That is “AUC\_inf”, “AUC\_tau” ,“AUC\_tend”, “AUC\_inf\_unbound”, “AUC\_tau\_unbound”, “AUC\_tend\_unbound” |
| **Cmax Avg** | Specify any average measure for Cmax (in case of aggregated data) or individual Cmax (in case of individual data) (if available) for the current dataset. |
| **Cmax AvgUnit** | Specify unit for average measure of Cmax, e.g. µg/L, etc. |
| **Cmax AvgType** | Specify type of average measure for Cmax, e.g. “Arith. mean”, “Geom. mean”, “Median”, etc. (in case of aggregated data) or “Individual” (in case of individual data) |
| **Cmax Var** | Specify any variability measure for Cmax (only in case of aggregated data) |
| **Cmax VarUnit** | Specify unit for variability measure of Cmax, e.g. µg/L, %, etc. |
| **Cmax VarType** | Specify type of variability measure for Cmax, e.g. “Arith. SD”, “Geom. SD”, “Arith. CV”, “Geom. CV”, “Range”, “95% CI” etc. (only in case of aggregated data) |
| **Cmax Type** | Specify type of Cmax measurement, i.e. “Cmax” or “Cmax\_unbound” |
| **CL Avg** | Specify any average measure for Clearance (in case of aggregated data) or individual Clearance (in case of individual data) (if available) for the relevant dataset. |
| **CL AvgUnit** | Specify unit for average measure of CL, e.g. L/h, etc. |
| **CL AvgType** | Specify type of average measure for CL, e.g. “Arith. mean”, “Geom. mean”, “Median”, etc. (in case of aggregated data) or “Individual” (in case of individual data) |
| **CL Var** | Specify any variability measure for CL (only in case of aggregated data) |
| **CL VarUnit** | Specify unit for variability measure of CL, e.g. L/h, %, etc. |
| **CL VarType** | Specify type of variability measure for CL, e.g. “Arith. SD”, “Geom. SD”, “Arith. CV”, “Geom. CV”, “Range”, “95% CI” etc. (only in case of aggregated data) |
| **CL Type** | Specify type of clearance measurement, i.e. “CLiv”, “CL/F”, “CLiv\_unbound”, “CL/F\_unbound”  CLiv specifies systemic clearance (usually after IV administration), CL/F specifies apparent total clearance (usually after PO administration) |
| **Comment** | String. Specify in free text any particularities. |

# PK-Profiles

PK parameter lists extracted PK-Parameter for the studies listed in the “*Studies*” sheet.

|  |  |
| --- | --- |
| **ID** | Cross reference to “ID” in “*Studies*“ |
| **Study** | Cross reference to “Study” in “*Studies*“ |
| **Reference** | Cross reference to “Reference” in “*Studies*“ |
| **Grouping** | Cross reference to “Grouping” in “*Studies*“ |
| **Analyte** | Cross reference to “Analyte” in “*Studies*“ |
| **Compartment** | Cross reference to “Compartment” in “*Studies*“ |
| **Time** | Specify time point of data point in relation to the “Times of Administration” listed in in the “Studies” sheet. Thus, this is NOT necessarily time after dose but rather time after first administration (including potentially other compounds administered in the respective grouping, e.g. in DDI studies in the treatment (with Perpetrator) grouping. E.g. Some concentration time profiles have time units starting from 0h, but not stating that this is time e.g. after 1 hour infusion. Hence time 0h should be 1h and all following times should be shifted with 1h. |
| **Time Unit** | Specify unit for “Time”. |
| **Avg** | Specify any average measure (in case of aggregated data) or individual (in case of individual data) (if available)  If the value is below the lower limit of quantification (LLOQ), write as <<LLOQ>, e.g. <0.5 |
| **AvgUnit** | Specify unit for average measure, e.g. µg/L, %, etc. |
| **AvgType** | Specify type of average measure for Cmax, e.g. “Arith. mean”, “Geom. mean”, “Median”, etc. (in case of aggregated data) or “Individual” (in case of individual data) |
| **Var** | Specify any variability measure (in case of aggregated data) |
| **VarUnit** | Specify unit for variability measure, e.g. µg/L, %, etc. |
| **VarType** | Specify type of variability measure for CL, e.g. “Arith. SD”, “Geom. SD”, “Arith. CV”, “Geom. CV”, “Range”, “95% CI” etc. (only in case of aggregated data) |
| **LLOQ** | Specify (if available) the lower limit of quantification. |
| **Comment** | String. Specify in free text any particularities. E.g. that there is a deviating n for a specific measurement. |

# DDI

This sheet is exclusively meant for reports of DDI studies and lists respective AUC and Cmax ratios.

The term “dataset” refers to the specific current line.

|  |  |
| --- | --- |
| **ID** | Cross reference to “ID” in “*Studies*“. Usually multiple lDs from the respective study are available (minimum usually 2, 1 for the control (Placebo) phase and 1 for the Treatment (with Perpetrator) phase. Prefer to pick here the ID for the respective victim drug in the with Perpetrator grouping |
| **Study ID** | Cross reference to “Study” in “*Studies*“ |
| **Reference** | Cross reference to “Reference” in “*Studies*“ |
| **Grouping** | Cross reference to “Grouping” in “*Studies*“ |
| **Substrate** | Specify the respective victim drug of which changes in the PK are assessed in this dataset |
| **Perpetrator** | Specify the respective perpetrator |
| **Route Substrate** | Specify route of administration of the victim **before** the respective dataset here, e.g. PO (Usually cross reference to “Route of Administration” in “*Studies*“) |
| **Route Perpetrator** | Specify route of administration of the perpetrator in the respective dataset here, e.g. PO |
| **Compartment** | Specify compartment/location from which the data sample of the victim was taken, e.g. plasma, whole blood etc. (Usually Cross reference to “Compartment” in “*Studies*“) |
| **AUCR Avg** | Specify any average measure for AUCR (in case of aggregated data) or individual AUC (in case of individual data) (if available) for the current dataset.  In case AUCR is not reported, assess AUCR via either (i) the ratio of the average measure for AUC during the with Perpetrator phase and the average measure for AUC during the with Control (Placebo) phase or (ii) the ratio of the average measure for CL during the with Control (Placebo) phase and the average measure for CL during the with Perpetrator phase.  The entered value should be comparable to the simulated ratio. Caution should be exercised in case the AUCR is reported in a dose normalized fashion but the doses of the victim actually differed in control phase and treatment phase (with perpetrator). Then the value might need to be un-dose-normalized. See also “**R Dose correction factor**” below. |
| **AUCR AvgType** | Specify type of average measure for AUC, e.g. “Arith. mean”, “Geom. mean”, “Median”, etc. (in case of aggregated data) or “Individual” (in case of individual data)  In case of estimating AUCR by dividing two Avg values of AUCs or CLs specify this as “**Approx. Avg**” |
| **AUCR Var** | Specify any variability measure for AUCR (only in case of aggregated data) |
| **AUCR VarType** | Specify type of variability measure for AUCR, e.g. “Arith. SD”, “Geom. SD”, “Arith. CV”, “Geom. CV”, “Range”, “95% CI” etc. (only in case of aggregated data) |
| **CmaxR Avg** | Specify any average measure for CmaxR (in case of aggregated data) or individual AUC (in case of individual data) (if available) for the current dataset.  In case AUCR is not reported, assess CmaxR via the ratio of the average measure for Cmaxduring the with Perpetrator phase and the average measure for Cmaxduring the with Control (Placebo) phase.  The entered value should be comparable to the simulated ratio. Caution should be exercised in case the AUCR is reported in a dose normalized fashion but the doses of the victim actually differed in control phase and treatment phase (with perpetrator). Then the value might need to be un-dose-normalized. See also “R Dose correction factor” below. |
| **CmaxR AvgType** | Specify type of average measure for AUC, e.g. “Arith. mean”, “Geom. mean”, “Median”, etc. (in case of aggregated data) or “Individual” (in case of individual data)  In case of estimating CmaxR by dividing two Avg values of Cmax specify this as “**Approx**. CmaxR” |
| **CmaxR Var** | Specify any variability measure for CmaxR (only in case of aggregated data) |
| **CmaxR VarType** | Specify type of variability measure for CmaxR, e.g. “Arith. SD”, “Geom. SD”, “Arith. CV”, “Geom. CV”, “Range”, “95% CI” etc. (only in case of aggregated data) |
| **t\_placebo\_0** | Specify the begin of the victim dosing time for the control (placebo) phase. Usually this is related to the time of the administration specified in “Times of Administration” listed in in the “*Studies*” sheet in the respective control (placebo) grouping; would usually be 0. |
| **t\_placebo\_end** | Specify the end of the victim sampling time interval for the control (placebo) phase.  This could be inf (typically in single dose administration) or the specific values for reported tend, e.g. 24  Please note that the value of “t\_placebo\_0” needs to be added (in the example here 0+24=24). |
| **t\_treatment\_0** | Specify the victim dosing time for the treatment (with Perpetrator) phase. Usually this is related to the time of the administration (specified in “Times of Administration” listed in in the “*Studies*” sheet in the respective treatment (with Perpetrator) grouping, e.g. 79 |
| **t\_treatment\_end** | Specify the end of the victim sampling time interval for the treatment phase (with Perpetrator) phase.  This could be inf (typically in single dose administration) or the specific values for reported tend, e.g. 103  Please note that the value of “t\_treatment\_0” needs to be added (in the example here 79+24=103). |
| **t Unit** | Specify unit for the times above. |
| **R Dose correction factor** | This factor is for information only and provides the factor between the dose-normalized and the direct (un-dose-normalized) AUCR /CmaxR.  In case the victim was administered with the same dose in control and treatment (with perpetrator) phase, this factor is 1.  In other cases, this factor is “dose of victim in treatment phase (with perpetrator)” divided by “dose of victim in control phase (without perpetrator)”. In such cases a reported *dose-normalized* AUCR or CmaxR should be multiplied by this value (see above **AUCR Avg** and **AUCR Avg**). |
| **Comment** | String. Specify in free text any particularities. |
| **DOSING REGIMEN PERPETRATOR** | See above for specification (follow rules as in “Studies” sheet). |