PK Submit™ User's Guide

Applies to:
PK Submit™ 1.1

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Contents

PK Submit

PK Submit is a Phoenix Plugin designed to automatically generate the CDISC domains and supporting documentation relevant to non-compartmental analysis (NCA) used in electronic submissions to regulatory agencies as part of an Investigational New Drug (IND) or New Drug Application (NDA).

PK Submit supports the generation of CDISC domains in either the SDTM (Study Data Tabulation Model) or the SEND (Standard for Exchange of Nonclinical Data) format.

CDISC SDTM is a unified way of transmitting information in drug studies with precise column names and a common file format. The CDISC STDM implementation in PK Submit is compliant with the standards in the *SDTM Implementation Guide: Human Clinical Trials version 3.2*.

CDISC SEND is an implementation of SDTM for nonclinical studies and specifies a consistent format for presenting and exchanging nonclinical data. The CDISC SEND implementation in PK Submit is compliant with the standards in the *SEND Implementation Guide: Nonclinical Studies Version 3.0/3.1*.

The CDISC ADaM implementation in PK Submit is compliant with the standards in the *Analysis Data Model Implementation Guide Version 1.1*.

For further information, please visit the Clinical Data Interchange Standards Consortium Web site at www.cdisc.org.

Using typical study data files as a starting point, PK Submit will do the following:

- Produce Phoenix worksheets
- Create Phoenix workflow NCA objects
- Produce the requested domain and file output.
- Validate the data according to CDISC Standards and FDA validation rules and generate a validation report.

Note: When updating the PK Submit Phoenix Plugin, be sure to uninstall the previous version of the Plugin before installing the newer version.

This section contains the following topics:

See also: “PK Submit Examples”

Create PC Domain

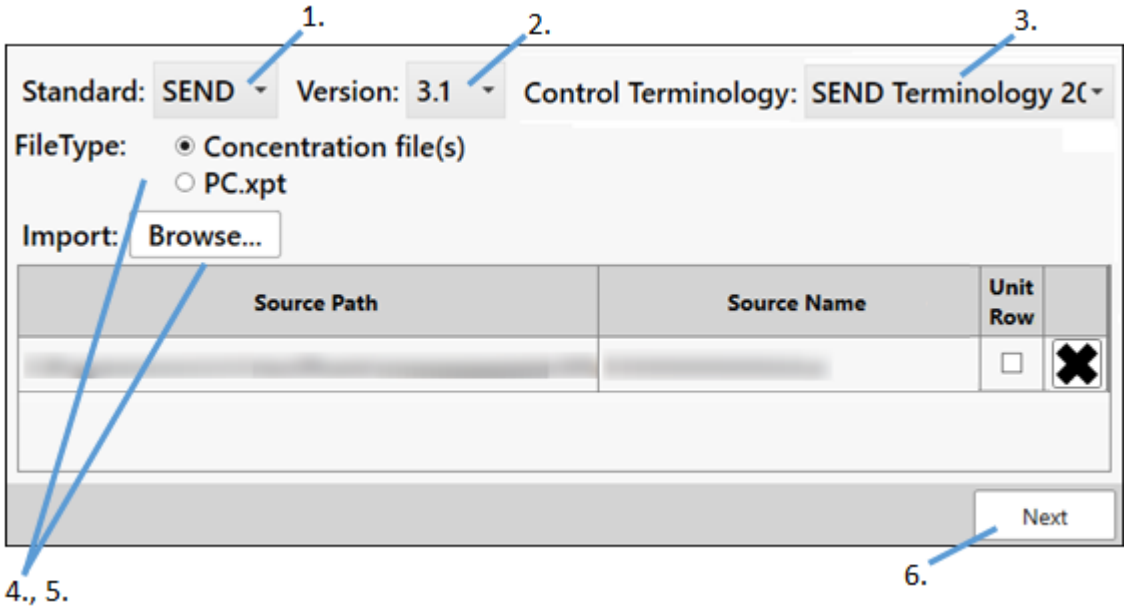
Select **PK Submit > PC > Create PC Domain** from the main menu.

This wizard allows you to import various input data files (concentration and dosing), perform data exclusions and add comments to data records, as well as configure an NCA.

The PC domain is created from a Master PC worksheet which is created and modified throughout the steps in this wizard. This worksheet contains concentration data from bioanalytical data sets, all PC domain variables, and additional variables needed for the NCA. At the end of this process, PK Submit will use this worksheet to create other worksheets/files in the Data folder:

Creating the PC Domain using the wizard involves the following tasks:

Select the concentration data files



1. In the first page of the wizard, specify the CDISC standard output type from the **STANDARD** pull-down menu.
2. Choose the CDISC version from the **Version** pull-down menu.
3. From the **Control Terminology** menu, select the terminology mapping list to use.

   Up to five terminology lists can be imported via the Phoenix *Preferences* dialog and appear in this list. See "Preferences" for more information.
4. Select the **Concentration file(s)** radio button and use the **Browse** button to select Excel or `.csv` files external to Phoenix or, if a project is open in Phoenix, use the **From Selected Phoenix Project** button to select worksheets from the project.

   Multiple concentration files can be selected as PC data sources.

   Check the **Unit Row** box to indicate that the file contains a row for the units (available for concentration files).

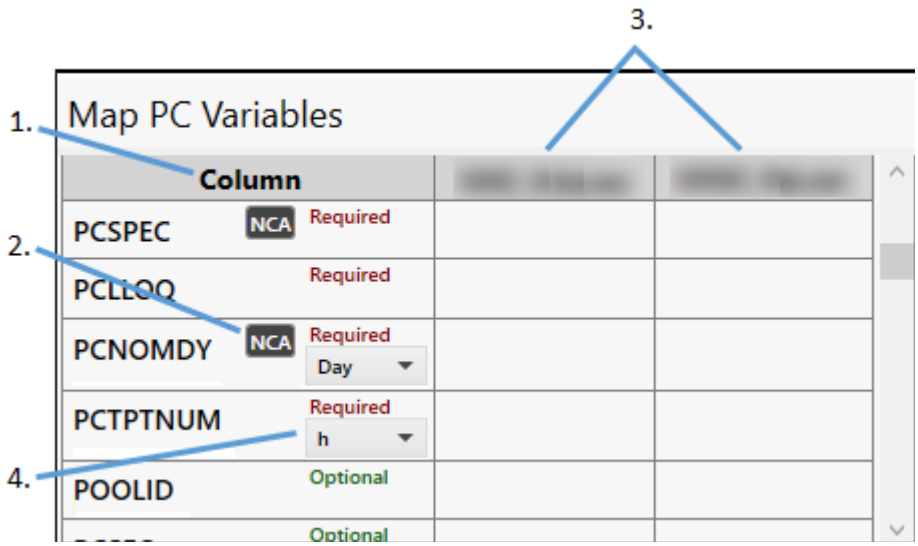
   Click the X at the end of the row to remove the corresponding concentration file from the table.
5. Select the **PC.xpt** radio button and use the **Browse** button to select an `.xpt` file external to Phoenix or, if a project is open in Phoenix, use the **Load PC From Phoenix Project** button to load the PC data from the Data folder.

   Only one `PC.xpt` file can be selected as the PC data source.

Note: When importing from the external system, you must have write permission to the directory where the files being imported are located or an error will be displayed.

6. Click **Next**.

Map the PC variables



The next page of the wizard provides the ability to map source data columns to PC domain variables and other columns useful for the NCA for each source file selected in the previous page of the wizard. Previously stored mappings are automatically populated from the SQLite database associated with each user profile.

1. The first column in the top table lists the Standard PC domain variable names that can be mapped plus other essential variables. The variable names depend on whether SEND or SDTM was specified on the first page of the wizard.
2. An **NCA** button in a source data column cell indicates this variable is or can be designated as an NCA Sort variable.

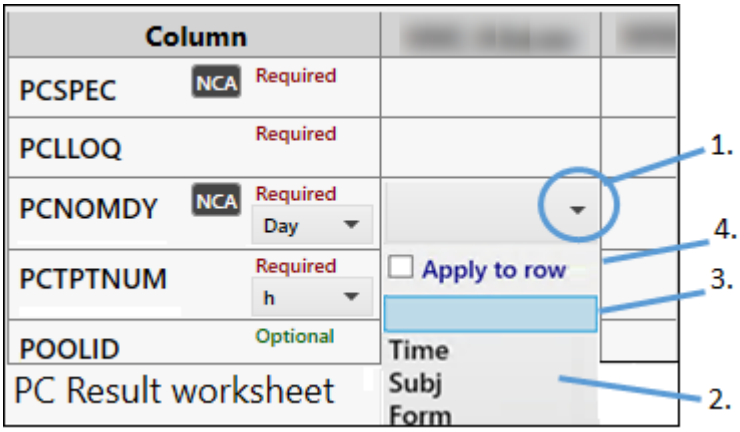
   Click NCA to toggle between a selected Sort variable and NCA, an unselected, but potential, Sort variable. If the button does not switch to unselected, it means the Sort variable is required and cannot be unselected (e.g., USUBJID, PCTEST, PCSPEC). Sometimes there are multiple variables that can be Sort variables, but they are mutually exclusive (e.g., VISITDY or PCDY can be used, but not both). In such cases, when one variable is selected as the Sort variable, the **NCA** button for the other variables changes to unselected.
3. The remaining columns in the Map PC Variables table list the source data column name for each data source selected in the previous page of the wizard, one column per selected data source. If the source data file does not have the mapping for the PC domain variable, the cell is empty. If the empty cell is a required field, it will be highlighted in red.
4. For variable or data source columns that have units, use the dropdown menu to select the unit.

The PC Result worksheet panel at the bottom of the page presents the contents of the Master PC worksheet based on the source data columns and the specified mappings. All required and expected SEND/SDTM columns (whether mapped or not) are displayed. Optional columns will be displayed only if they are mapped.

See also:

Manually map variable to data column
Manually map data column to variable
Add data column as a new variable
Add ADSL and DM variables
Add expression-based columns
Data conversion

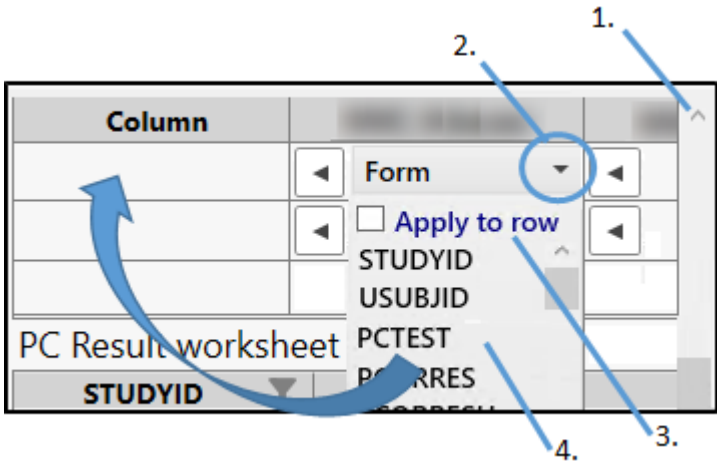
Manually map variable to data column



1. Click on the cell to be mapped.
2. Select a source data column from the list.
3. To unmap a source data column, click on the cell and select the blank area from the list.
4. When multiple source data files are present, check the **Apply to row** box to apply the selected source data column to all cells in the row.

Note: PK Submit stores all manual mappings in the SQLite database. These mappings are applied automatically when using PK Submit in subsequent sessions. SQLite database mappings are stored for each user profile.

Manually map data column to variable



Any source data columns that are not mapped to a variable are listed at the bottom of the mapping table. (They are not included in the PC Result Worksheet table at the bottom of the page, however.)

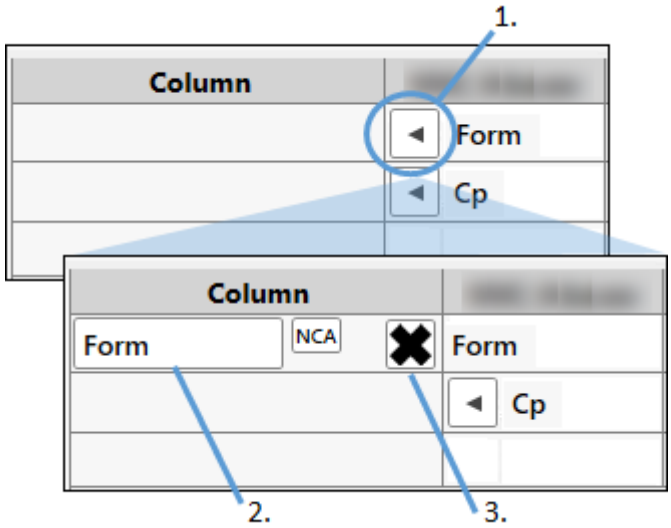
1. Scroll toward the bottom of the mapping table to find the unmapped columns

2. Click the down arrow in the cell of the desired unmapped data column to view a list of unmapped variables.
3. When multiple source data files are present, click the **Apply to row** box to apply the mapping to all cells in the row.
4. Select the variable to be mapped from the list.

The source data column cell will move to the row for the selected variable.

Note: If the study data has the urine volume and unit, you must map the urine volume to the column URINE_VOLUME and the urine volume unit to URINE_VOLUME_UNIT and PCEVLINT.

Add data column as a new variable



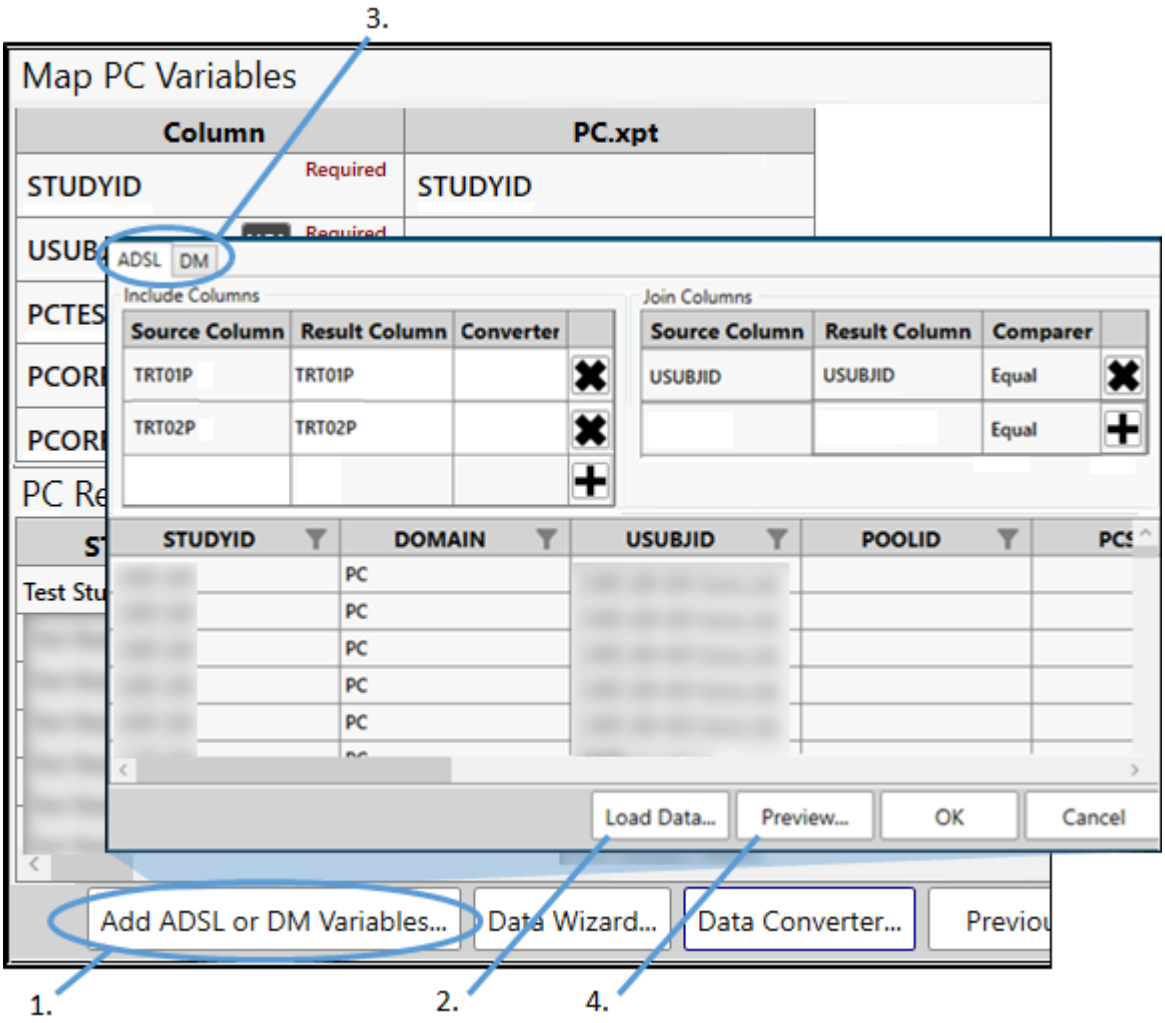
1. Click the **Left Arrow** button next to the unmapped source data column name (unmapped data are listed at the bottom of the table) to create a new PC domain variable.

   The unmapped column name will move into the “Column” column and move up so that it is listed at the bottom of the mapped columns (you may have to scroll up to see it).
2. Enter a new name, if desired.
3. Use the X button to delete the variable and return the source data column to an unmapped state.

Add ADSL and DM variables

Data for ADSL and DM variables can be merged into the Master PC worksheet.

1. At the bottom of the *Map PC Variables* page, click the **Add ADSL or DM Variables** button.



2. Use the **Load Data** button to select an ADSL and/or DM file external to Phoenix.

   If a project is open in Phoenix, use the **Load Data From Phoenix Project** button to load the data from the Data folder.

3. Use the **ADSL** and **DM** tabs at the top to switch between the two domains.

4. Click the **Preview** button at the bottom to show the merged data in the Master PC Worksheet at the bottom of the dialog.

   Newly added columns of data will appended to the Worksheet table, so you may have to scroll to the last column(s) to see the data.

The following instructions are applicable in both tabs.

To add data columns

Use the "Include Columns" table to add columns from the ADSL or DM variable source file to Master PC worksheet.

1. Click in the **Source Column** cell and select the name of the source data column to add.

2. If needed, click in the **Result Column** cell and edit the name that will appear in the Master PC worksheet as the column header.

Click + to confirm the addition of the row to the “Include Column” table.

Click X to remove the associated row from the table.

To define join columns

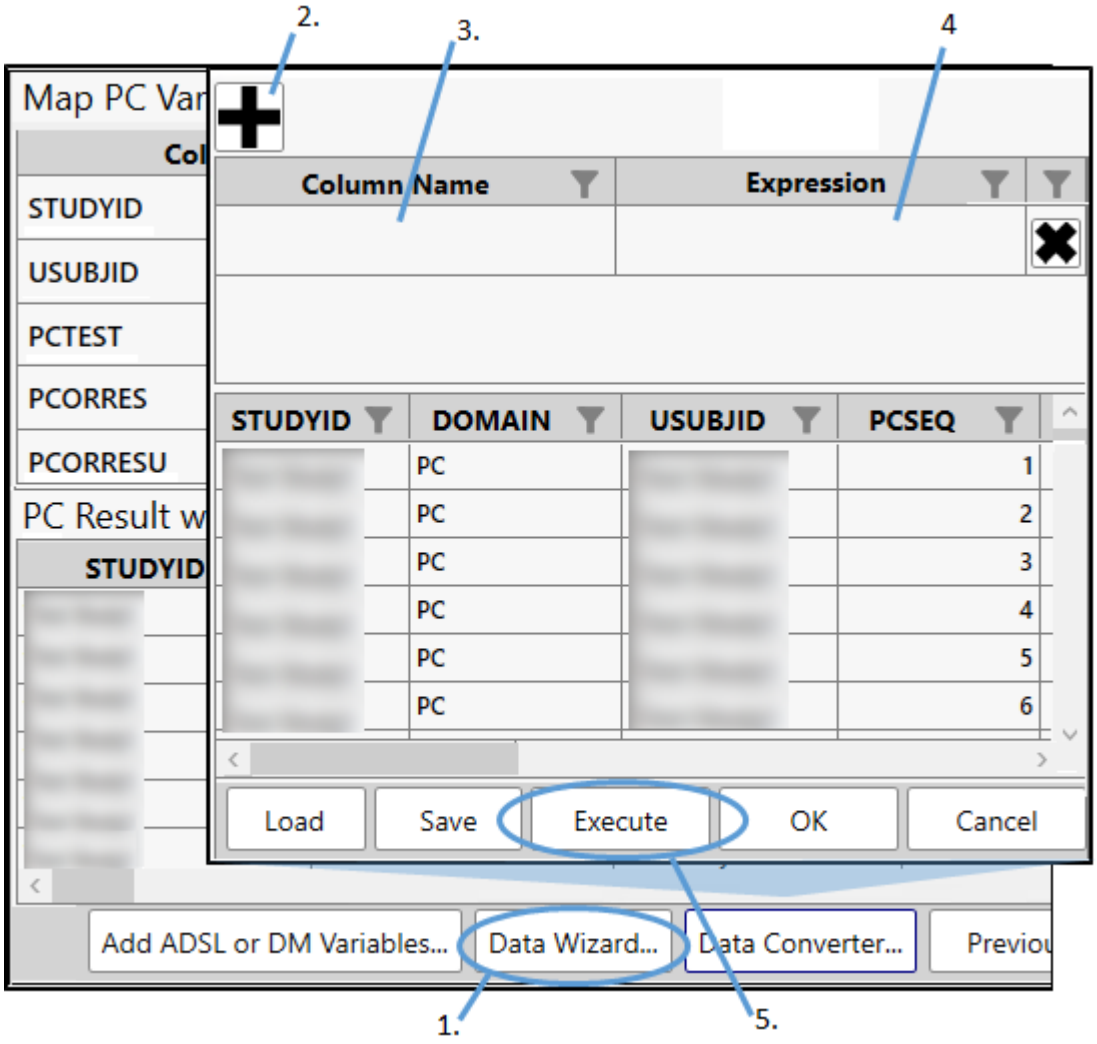
Columns that are identified in the “Join Columns” table are used to connect the data being added with the appropriate subject by matching the values with those in the Master PC worksheet’s column with the same header.

1. Click in the **Source Column** cell and select the name of the source data column that contains the subject identifier information.
2. If needed, click in the **Result Column** cell and edit the name that will appear in the Master PC worksheet as the column header.

Click + to confirm the addition of the row to the “Join Column” table.

Click X to remove the associated row from the table.

Add expression-based columns



1. Click the **Data Wizard** button at the bottom of the *PC Mapping* page.
2. In the dialog, click + to add a row in the top table for defining an equation.
3. In the **Column Name** cell, enter the header for the new column.
4. In the **Expression** cell, type an expression using column headers and operators.
   Formulas include:
   LEN(expression)
   ISNULL(expression, replacementvalue)
   IIF(expr, truepart, falsepart)
   TRIM(expression)
   SUBSTRING(expression, start, length)
   Wildcard Characters ("ItemName LIKE '*product*'", "ItemName LIKE '*product'", "ItemName LIKE 'product*'")

   Operators include:
   <, <=, =, <>, =, IN, LIKE
   + (append)
   - (subtraction)

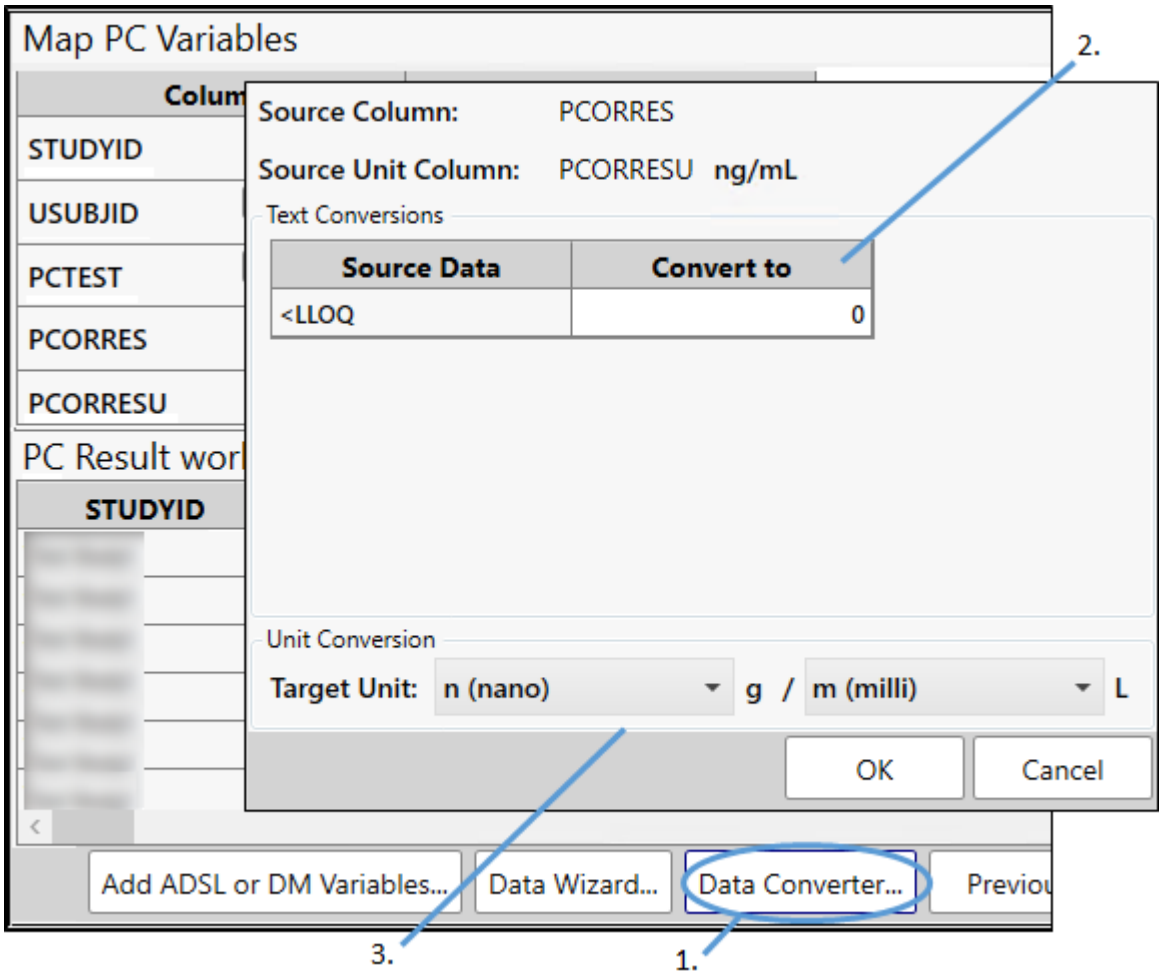
* (multiplication)
/ (division)
% (modulus)

5. Click **Execute** to apply the expression and add the results as a new, appended column in the Master PC Worksheet.

Click X to remove the associated row from the table (the appended column is also removed from the Worksheet.

Expressions can be saved as to a file (`.expr`) using the **Save** button and then reused later using the **Load** button.

Data conversion



1. Click the **Data Wizard** button at the bottom of the *PC Mapping* page.

Any text value detected in the data mapped to PCORRES is listed in the Data Converter tool.

2. Enter the numeric value with which to replace the text in the Source Data column.
In the image above, a zero (“0”) will replace any instance of “<LLOQ” in the PCORRES source data column. PK Submit stores the numeric values in a PCCALCN column in the Master PC worksheet, which is then combined with PCORRES to form a PKConc analysis variable.
3. Use the two pull-down menus to define the target concentration unit (e.g., ng/mL).
These units are stored in the PCCALCNU column. PK Submit compares the units with those in

PCORRESU and multiplies the values in PCORRES by the necessary factor to obtain the target units.

4. Click **OK**.

Special note about LLOQ

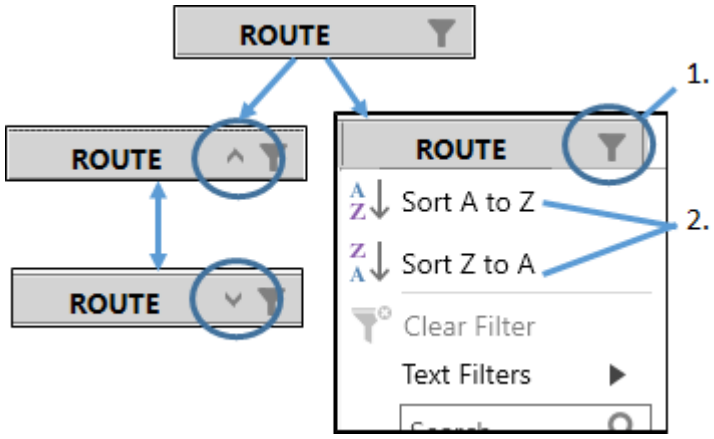
According to FDA recommendations, test results that fall below the LOQ need to have "BLQ" in PCSTRESC. Although PK Submit supports a number of different file type imports, the nomenclature used by scientists for reporting LLOQ values varies greatly. As a result, the process of identifying LLOQ values and inserting 'BLQ' into PCSTRESC cannot be automated. However, using the Data Wizard, it is possible for you to create expressions specific to your data that will generate the appropriate entries in the PCSTRESC.

For this example, a result that fell below the LOQ is indicated in PCORRES by "< 0.1" (where 0.1 is the LLOQ value). First, look for "<" in PCORRES and then place "BLQ" in the corresponding cell of a new column. Next, use the contents of the new column to replace the values in PCSTRESC.

1. Using the Data Wizard, click + and enter a name for the new column (e.g., PCSTRESCBQL).
2. Enter the expression:
   IIF(PCORRES LIKE '%<%','BLQ',PCORRES)
3. Click + to add a second column and enter PCSTRESC as the name.
4. For the expression, enter the name used for the first new column (e.g., PCSTRESCBQL).
5. Click **Execute**.

For your data, replace the "<" in step 2 with the value or part of the value used in PCSTRESC to indicate LLOQ.

Sort the PC result worksheet

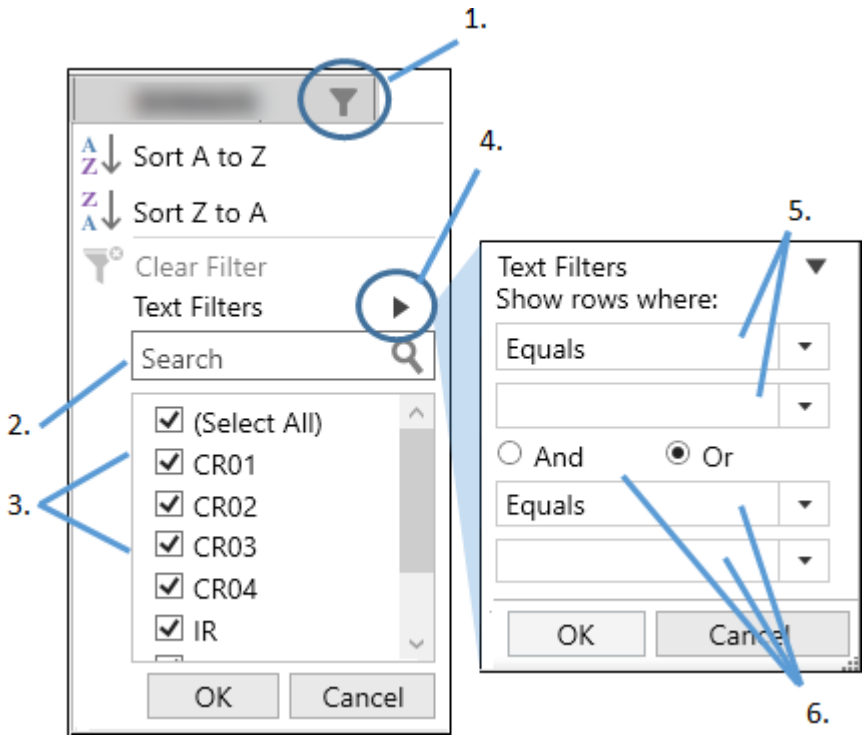


Sorting the columns in the results worksheet can be accomplished by simply clicking on the column header cell. Clicking the header multiple times will toggle between ascending and descending order. A sort direction indicator is shown in the header.

Alternatively:

1. Click  in the header.
2. In the popup, select **Sort A to Z** or **Sort Z to A**.

Filter the PC result worksheet



1. In the header of the column to be filtered, click  .
   The popup lists all values found in that column.
2. To search for values, begin typing the text in the Search field and the list in the popup will automatically be filtered as you type.
3. Use the check boxes in the list to control which rows are shown (checked boxes) or hidden (unchecked boxes) in the result worksheet. Use the **(Select All)** check box to check or uncheck all items in the list at the same time.
4. To define a filter criteria, click **Right Arrow** button next to **Text Filters**.
5. Use the dropdown menus to set the operators and value to set the criteria.
6. To include a second criteria, select the **And** or **Or** radio button and use the second set of drop-down menus to define the second criteria.

Click **Next** in the *PC Mapping* page to move to the *NCA Keys Selection* page.

PK Submit checks to make sure all of the required mapping is complete. If there are any issues, the mapping table will be highlighted with a red border. You cannot proceed until all of the mapping is completed correctly.

PK Submit will also check that the USUBJID values contain the STUDYID. If not, the system will ask to concatenate the STUDYID to the USUBJID as per CDISC standards.

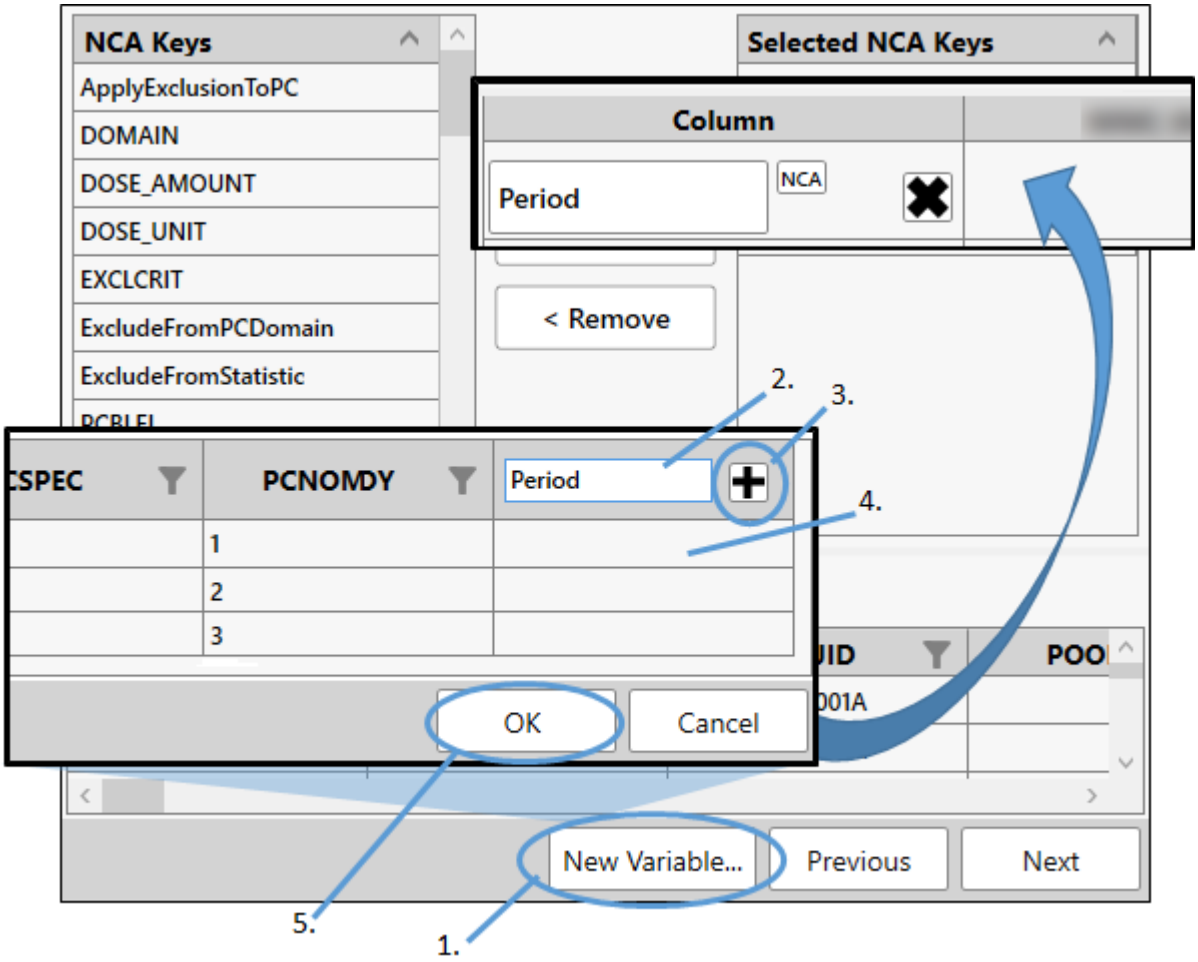
Identify NCA keys

Use the **Select >** and **< Remove** to identify the data columns to use as sort keys for the NCA.

Click **Next** in the *NCA Keys Selection* page to move to the *Dosing* page.

Add new variable

Typically, new variables are created only when needed NCA sort variables are not part of the PC domain and are not present in the source data. Using the **New Variable** button, new columns can be added and the associated data entered for each profile. The information is added to the PC Result worksheet.

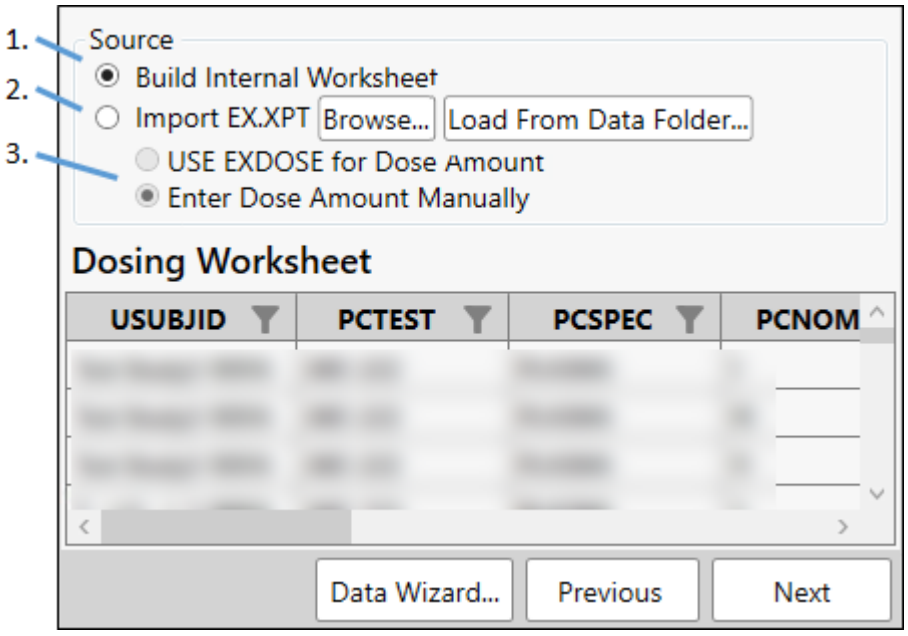


1. Click the **New Variable** button at the bottom of the *NCA Key Selection* page.
2. In the dialog, enter the name of the new variable in the last column's header field.
3. Click + next to the field. (The icon turns to an X and can be used to remove the newly added variable.)
4. Add the data for the variable to the cells in the column.
5. Click **OK** to add the variable to the mapping page.

The variable will be added as a new row and placed alphabetically in the list. It can be set as an NCA Sort variable using the NCA button. Use the X icon to remove it from the variable list.

Note: Variables added in this way are not saved to the SQLite database. They are study-specific.

Build or import dosing data



1. Select the **Build Internal Worksheet** radio button to populate the Dose Amount, Route, and Dose Unit columns using the data mapped into the DOSE_AMOUNT, Route, and DOSE_UNIT variables in the Master PC worksheet

Or

2. Select the **Import EX.XPT** radio button to populate the Route, Dose Date Time, Dose Amount, and Dose Unit columns with the data from the EX.XPT file, if the data from the file match the profile in the Dosing worksheet. Use the **Browse** button to select the file from the file system or use the **Load from Data Folder** button to select it from a Phoenix project's Data Folder.
3. If importing the data from EX.XPT file, select the **Use EXDOSE for Dose Amount** radio button to populate Dose Amount and Dose Unit columns using EX.EXDOSE and EX.EXDOSEU data in the file.

   Or

   Use the **Enter Dose Amount Manually** radio button to populate the Dose Amount and Dose Unit columns using data mapped into the DOSE_AMOUNT and DOSE_UNIT variables in the Master PC worksheet.

A popup will display the number of Dose records imported.

4. When applicable, enter the Dose Date Time, Infusion Duration, and TAU values manually into the Dosing worksheet.

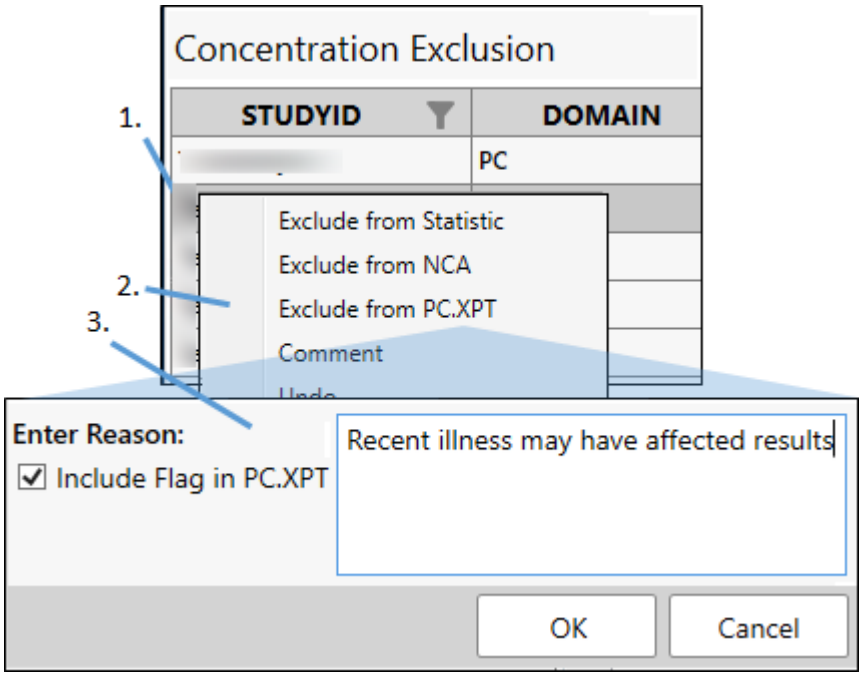
Click the **Data Wizard** button at the bottom of the *Dosing* page to add expression-based columns of data to the Dosing Worksheet. See "Add expression-based columns" for more information.

Click **Next** to move to the *Data Exclusion and Comments* page.

A popup will warn if the PCRFTDTC column is not populated. If ***all*** Dose_Date_Time (PCRFTDTC) are not populated, the popup will display the number of Dose_Date_Time rows not populated/populated.

Exclude data

Manually select data



1. To exclude a data record(s), select the corresponding row(s) in the first table on the page.
2. Right-click a selected row and select **Exclude from Statistic**, **Exclude from NCA**, or **Exclude from PC.XPT** from the menu.
3. In the popup dialog, enter the reason for exclusion and click **OK**.

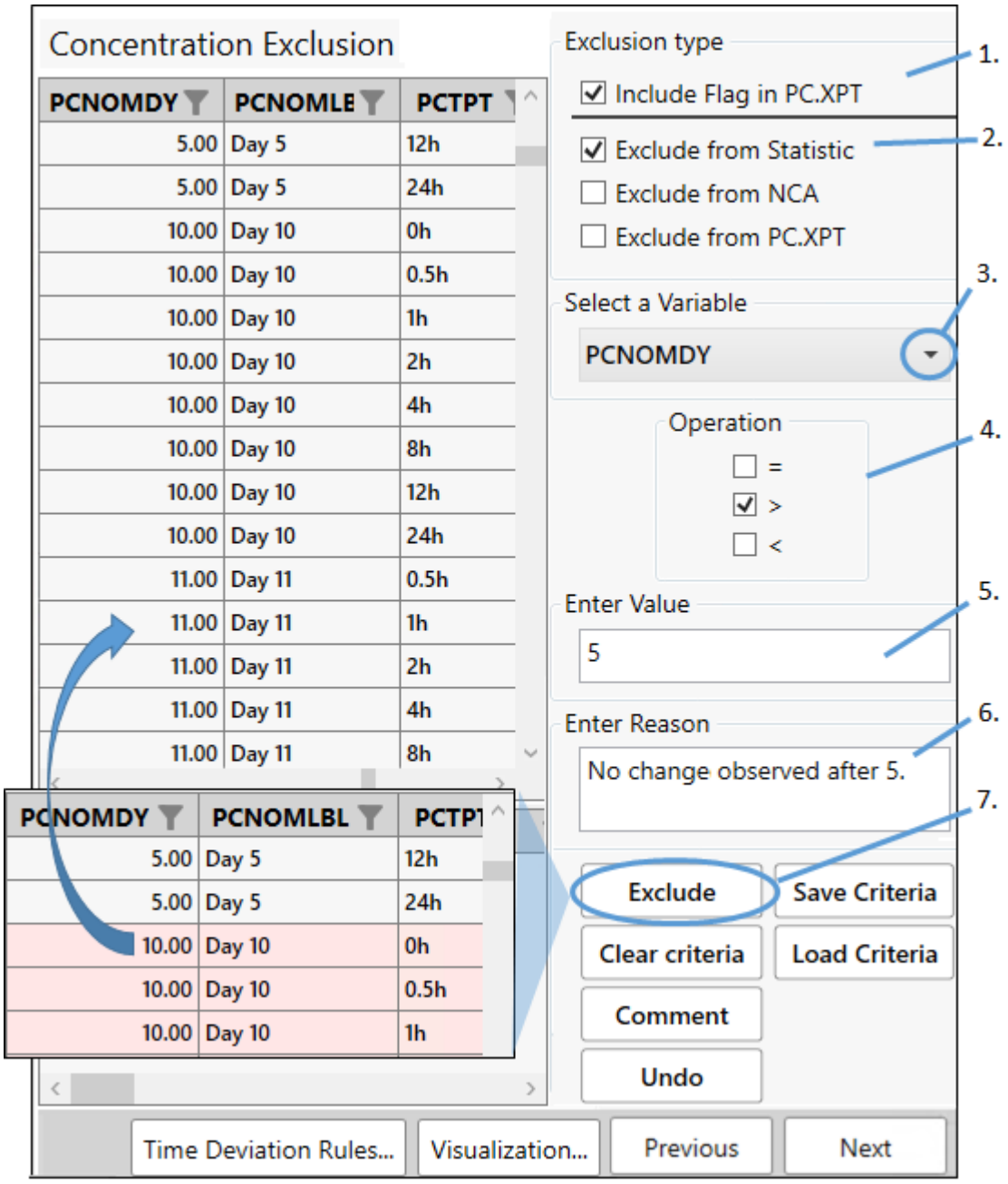
   For **Exclude from Statistic** or **Exclude from NCA**, when SEND is the standard, use the **Include Flag in PC.XPT** checkbox to indicate if a column for an exclusion flag should be included in the PC domain file.

   For **Exclude from PC.XPT**, if there are any comments in the CO domain for the selected records, they will need to be removed before the exclusion can be performed.

Note: Use the filter icons beside each column name to aid in the selection of records for manual exclusion.

Use criteria to select data

Filter criteria can also be used to identify the records to exclude.



1. When SEND is the standard, use the **Include Flag in PC.XPT** checkbox to indicate if a column for an exclusion flag should be included in the PC domain file.

   For SDTM, concentrations are recorded in the SUPPPC output domain.
2. Select where the exclusions are to be applied: **Exclude from Statistic**, **Exclude from NCA**, or **Exclude from PC.XPT**.
3. Select the variable on which to base the exclusions.
4. Check the box(es) for the operator(s) to use in the criteria. Use combinations of two operators, if needed (e.g., check **<** and **=** to indicate the value is “less than or equal to”).
5. Type the value in the **Enter Value** field.

Note: Only a single value is supported for the **Enter Value** field. If multiple values are entered (e.g., a comma-separated list), no exclusions will be applied.

6. Enter a reason for the exclusion.
7. Click **Exclude**.
   The rows that match the criteria will be shaded pink.
   For **Exclude from PC.XPT**, if there are any comments in the CO domain for the selected records, they will need to be removed before the exclusion can be performed.

To remove the previously applied exclusion, click the **Undo** button.

To remove the exclusion of a specific row, right-click the row and select **Undo**.

Click **Clear Criteria** to clear the fields and settings made on the page (any rows marked for exclusion will remain shaded).

Use the **Save Criteria** and **Load Criteria** buttons to re-use exclusion criteria with a different data set.

For SEND 3.x, the reason is stored in the Master PC worksheet column PCREASEX, and PCEXCLFL="Y" when the record is excluded from NCA or ExcludeFromPCDomain="Y" when excluding from PC.XPT. In addition, EXCLCRIT="Exclusion criteria" when filter criteria are used.

For SDTM 3.2, in the Master PC worksheet, ExcludeFromNCA="Y" when the record is excluded from NCA or ExcludeFromPCDomain="Y" when excluding from PC.XPT. In addition, EXCLCRIT="Exclusion criteria" when filter criteria are used. The reason is not recorded. However, a record is created in the CO domain for NCA exclusions.

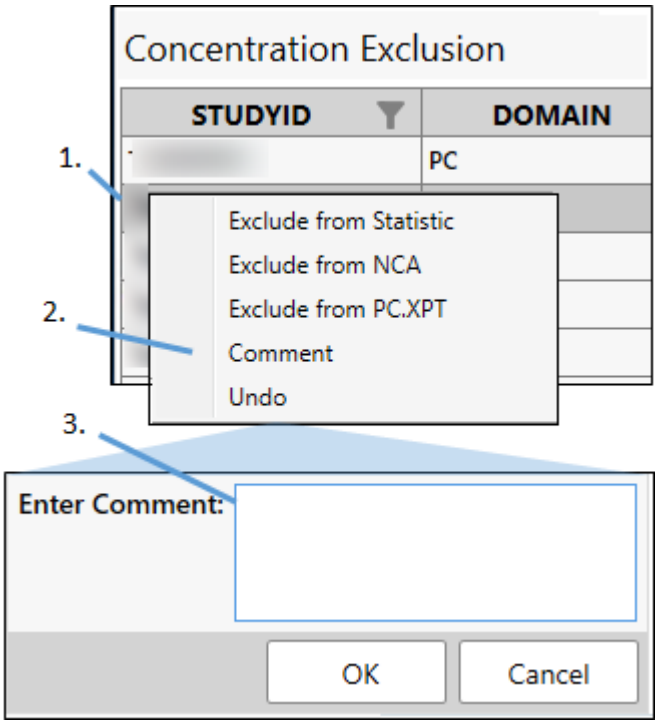
When **Exclude from NCA** is specified, the data records (where the column PCEXCLFL is set to "Y") will be excluded from NCA_PLASMA_Worksheet or NCA_URINE_Worksheet; but will still be presented in the PC.XPT.

When **Exclude from PC.XPT** is specified, the data records that are marked as excluded from PC.XPT will be removed when the file PC.XPT is created. The records that are excluded from the PC domain will be included in the NCA_PLASMA_Worksheet and NCA_URINE_Worksheet

Add comments

Manually select data
Use criteria to select data

Manually select data

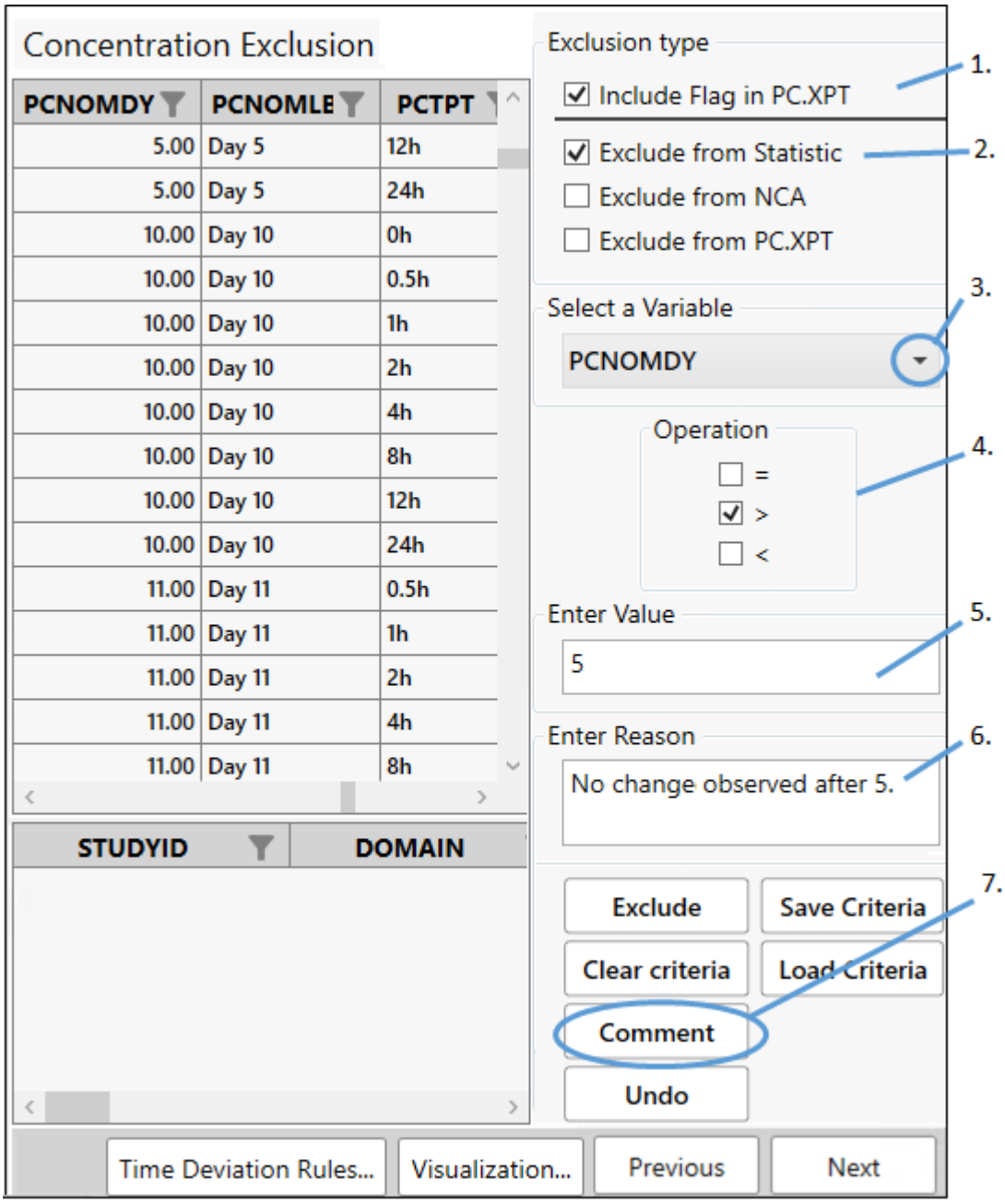


1. To add a comment to a data record(s), select the corresponding row(s) in the first table on the page.
2. Right-click a selected row and select **Add Comment** from the menu.
3. In the popup dialog, enter the comment and click **OK**.

The column COVAL in the CO domain stores the comment. If the comment is more than 200 characters, additional COVAL columns will be added and sequentially numbered (e.g., COVAL1, COVAL2).

Use criteria to select data

Filter criteria can also be used to identify the records on which to comment.



1. Use the checkbox to indicate if a column for an exclusion flag should be included in the PC.XPT file.
2. Select where the exclusions are to be applied: **Exclude from Statistic**, **Exclude from NCA**, or **Exclude from PC.XPT**.
3. Select the variable on which to base the criteria.
4. Check the box(es) for the operator(s) to use in the criteria. Use combinations of two operators, if needed (e.g., check **<** and **=** to indicate the value is "less than or equal to."
5. Type the value in the **Enter Value** field.

Note: Only a single value is supported for the **Enter Value** field. If multiple values are entered (e.g., a comma-separated list), no comments will be applied.

6. In the **Enter Reason or Comment** field, type the comment.
7. Click **Comment**.

The column COVAL in the CO domain stores the comment.

To remove all the applied comments, click the **Undo** button.

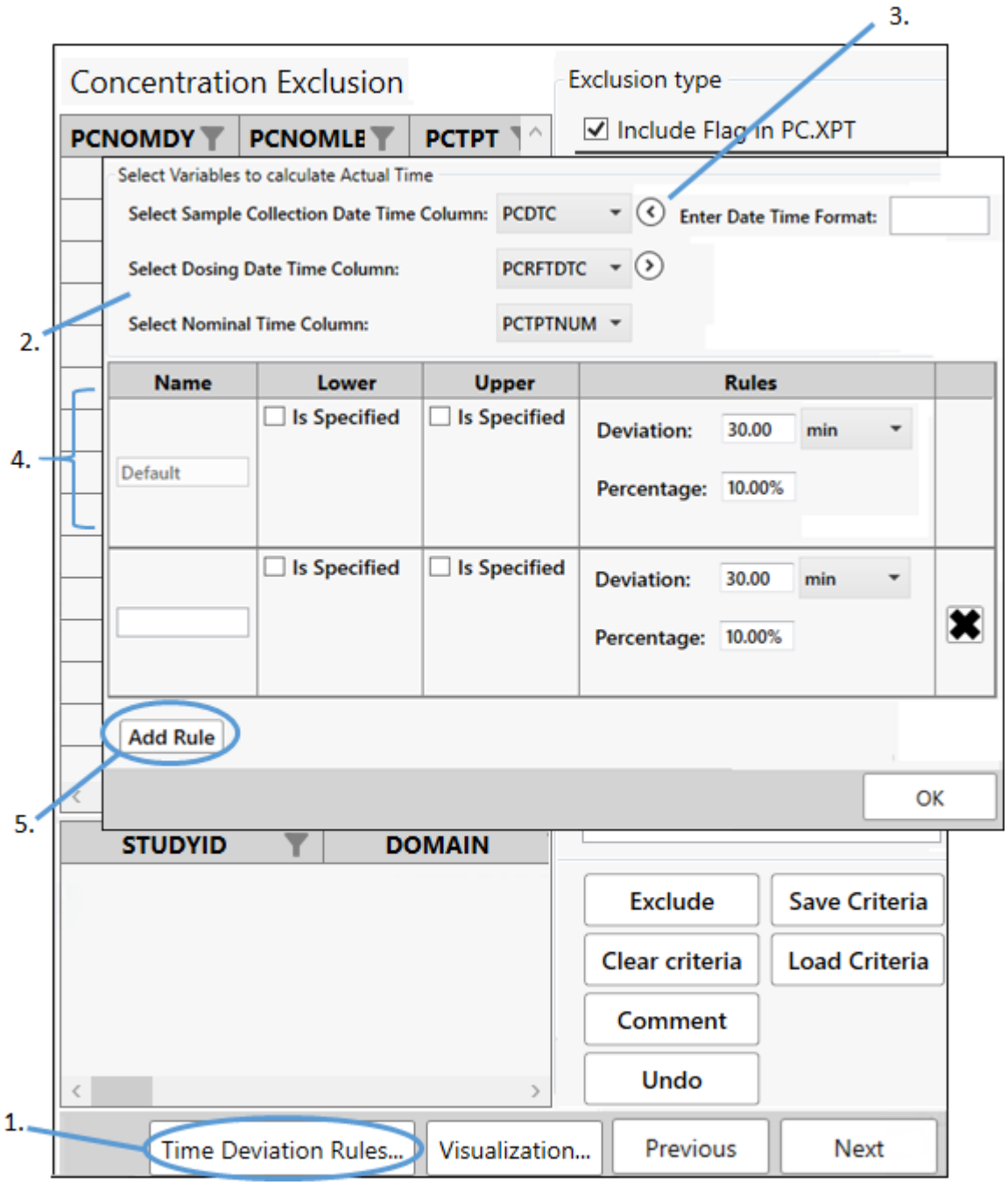
To remove a specific comment, right-click the row and select **Undo**.

Click **Clear Criteria** to clear the fields and settings made on the page.

Click **Next** to move to the *NCA Configuration* page.

Time deviation rules

By defining a time deviation rule, the user can identify sample data where the collection time deviated more than a specified tolerance of time. That tolerance can be set as a length of time or a percentage of time deviation. For example, in the following image, the default rule will flag any samples with a time deviation greater than or equal to 30 minutes or a percent time deviation greater than or equal to 10%. When a rule is broken, a flag is set in the DeviationRuleApplied column.



1. From the *Data Exclusions and Comments* page, click **Time Deviation Rules** at the bottom of the page.
2. Select the columns that contain the **Sample Collection Date Time**, **Dosing Date Time**, and **Nominal Time** data from the menus.
3. If needed, click the right arrow circle button and type the format of the data in the **Enter Date Time Format** field (e.g., MM/DD/YY HH:MM:SS).
4. For each deviation (row), specify the following:
   Name: Enter a name for referring to the deviation rule.
   Lower: Check the **Is Specified** box to display tools for setting a lower nominal time limit.
   Upper: Check the **Is Specified** box to display tools for setting a upper nominal time limit.

Rules: Enter an amount of time in the **Deviation** field and/or a percentage in the **Percentage** field with which to compare the sample time data.

5. Use the **Add Rule** button at the bottom to add another row to the table.

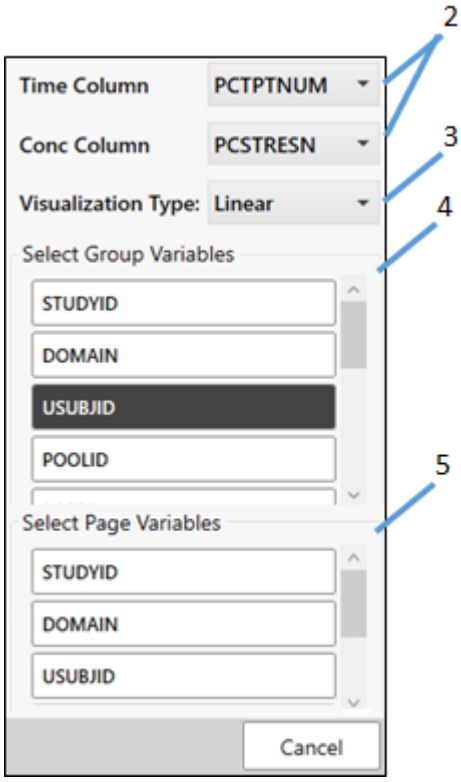
Time deviation is computed as:

- For amount of time deviation (reported in the Deviation PK column): Sample_Collection_DateTime – (Dosing_DateTime + Nominal_Time)
- For percentage of time deviation (reported in the Percent Deviation column): [(Amount_of_Time_Deviation)/Nominal_Time] * 100

Visualization

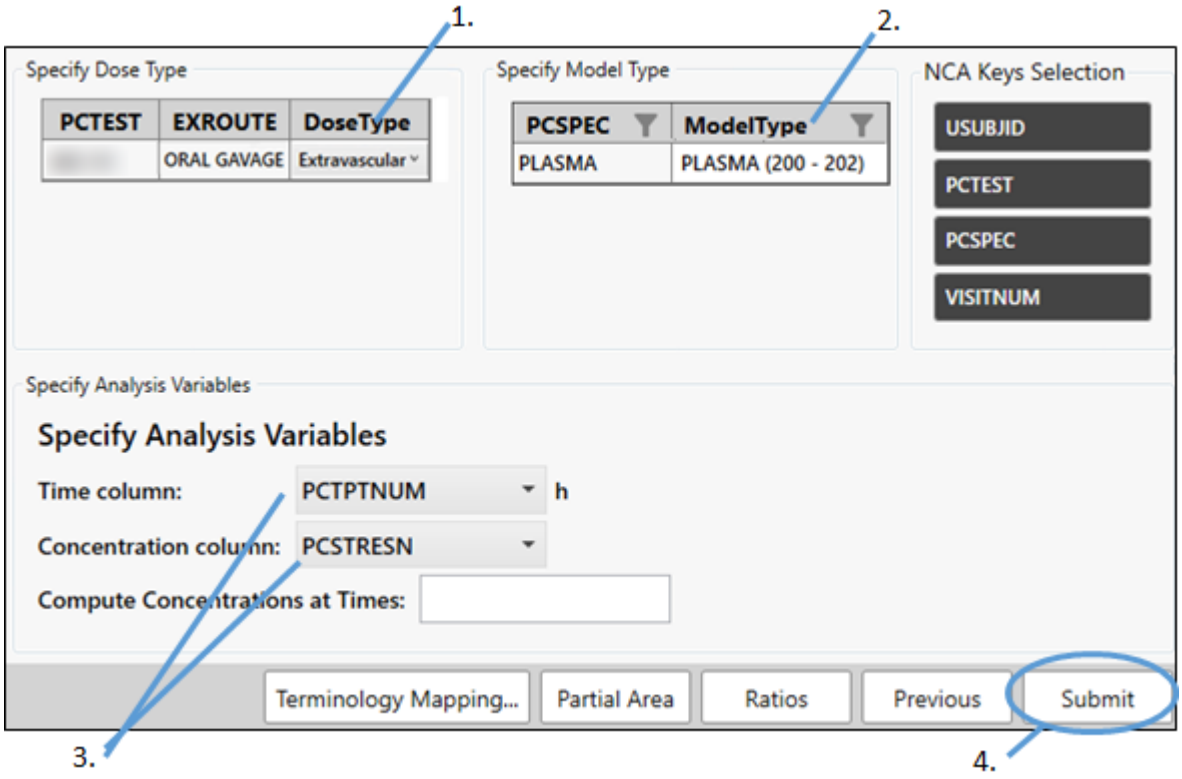
PK Submit allows users to take a quick look at the time vs concentration graphs of the data through a visualization tool. (Note that these graphs are provided for a visual overview of the data and cannot be saved.)

1. From the *Data Exclusions and Comments* page, click **Visualization** at the bottom of the page.
2. Use the **Time** and **Conc Column** menus to select a different column.



3. Switch between **Linear** and **Logarithmic** graphing scales using the **Visualization Type** menu.
4. Adjust how the data is grouped on the graphs by clicking different variable buttons in the **Select Group Variables** list.
5. Adjust how the graphs are grouped on a page by clicking different variable buttons in the **Select Page Variables** list.

Configure settings for NCA



1. Click in the **DoseType** cell and select one of the dose type from the menu (**Extravascular**, **IV Bolus**, **IV Infusion**) for each unique combination of analyte and route
2. Click in the **Model Type** cell and select the type from the menu (**PLASMA (200-202)** or **URINE (210-212)**) for each biological matrix.
3. From the **Time column** and **Concentration column** menus, select the variable to use.
4. For the SEND standard, check the **Sparse NCA** box to indicate that this is a sparse study when appropriate.
   Note that the **Sparse NCA** box appears only if the SEND standard is selected.
5. In the **Compute Concentrations at Times** field, enter a comma-separated list of times at which the corresponding concentration is to be calculated.
6. For the SEND standard, check the **Sparse NCA** box to indicate that this is a sparse study when appropriate.
   Note that the **Sparse NCA** box appears only if the SEND standard is selected.

The **Terminology Mapping** button can be used to set the mapping of the matrix to the CDISC code list. (See "Terminology mapping" for more details.)

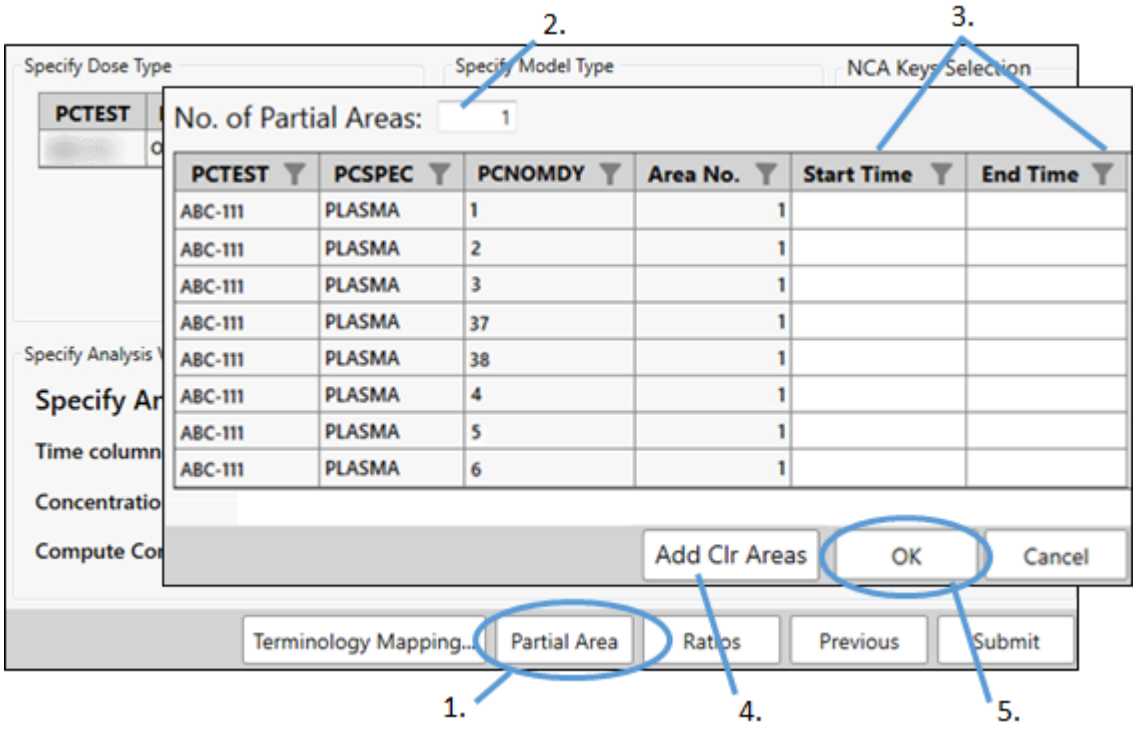
The **Partial Area** button can be used to set up partial areas. (See "Define partial areas" for more details.)

The **Ratios** button can be used to "Set up accumulation ratio calculations" and "Set up metabolite to parent ratio calculations".

7. When finished with the domain specifications, click the **Submit** button.

Define partial areas

1. Click the **Partial Area** button at the bottom of the *NCA Configuration* page.

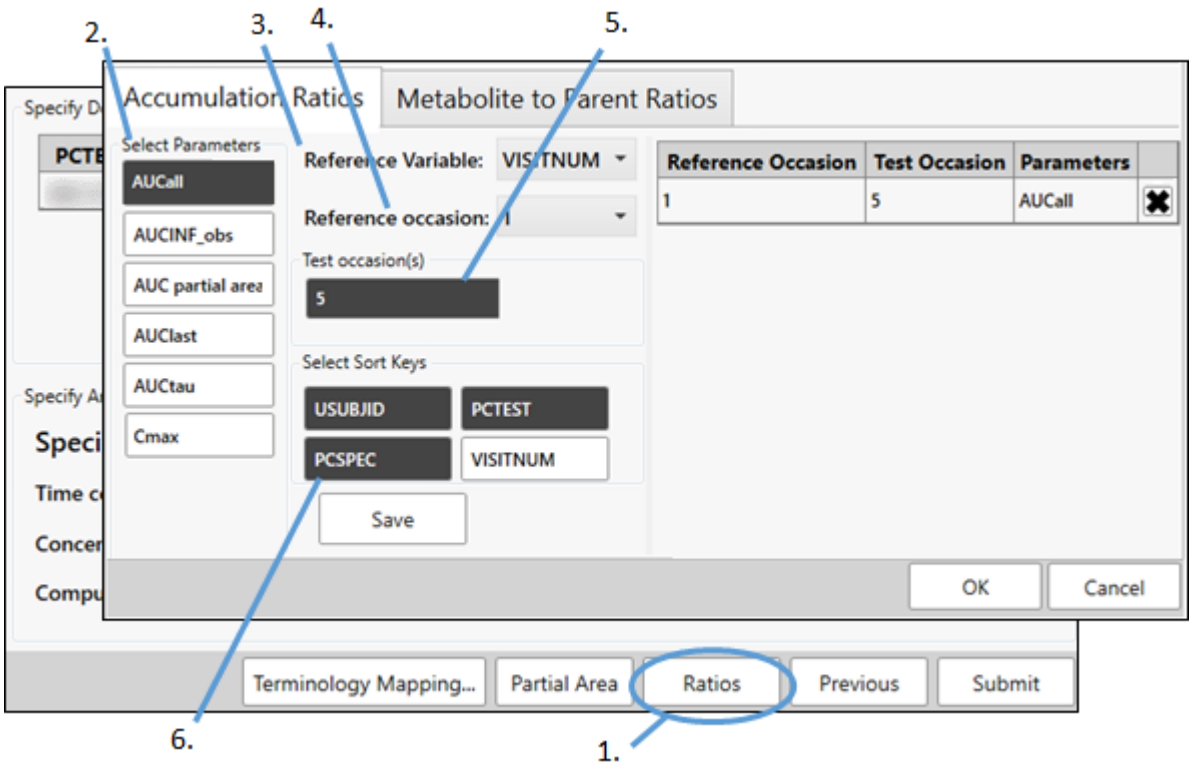


2. In the dialog, enter how many partial areas to use in the **No. of Partial Areas** field.
3. Enter the **Start Time** and **End Time** for each partial area (row) in the table.
4. Click **Add Clr Areas** to have the application find and fill in the **Start Time** of the first urine interval and the **End Time** of the last urine interval for each urine collection occasion.

   The Clr (renal clearance) parameter is then automatically calculated during the Finalize PD Data step of creating the PP domain and merged with the other NCA parameters for reporting.
5. Click **OK**.

Set up accumulation ratio calculations

1. Click the **Ratios** button at the bottom of the *NCA Configuration* page.
2. In the Accumulation Ratios tab of the dialog, select the PK parameters for the calculations by clicking one or more buttons on the left.



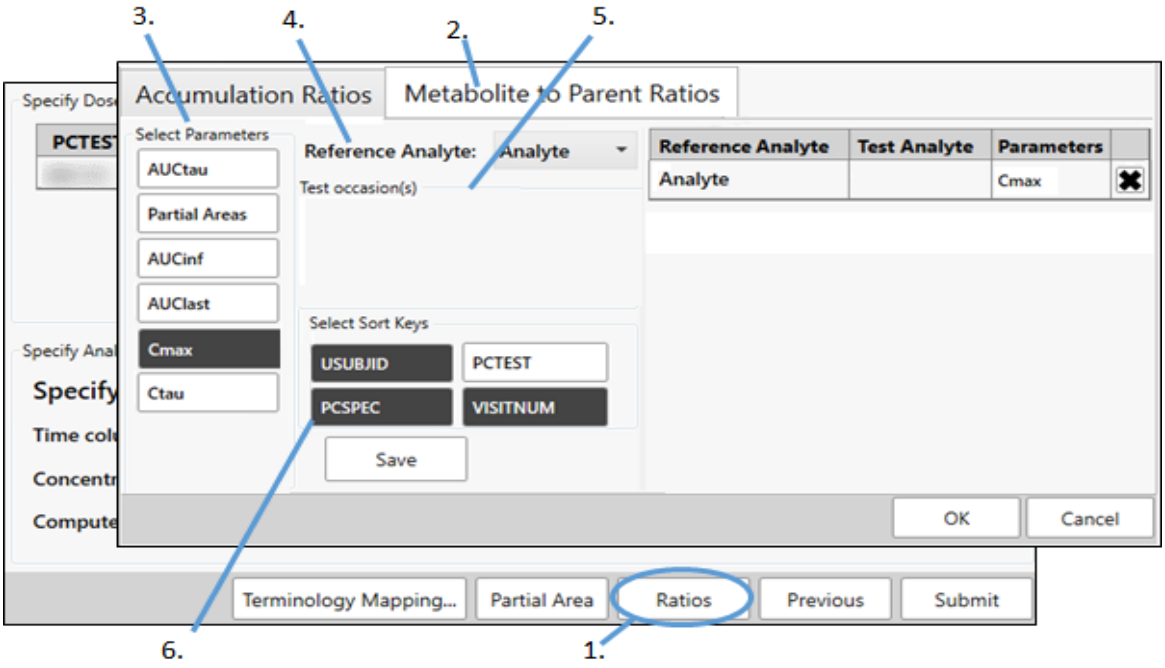
3. Select the variable to serve as the reference from the **Reference Variable** menu.
4. Select the occasion to serve as the reference from the **Reference occasion** menu.
5. Select the **Test occasion(s)** to use in the ratio calculation by clicking one or more of the occasion buttons (there is only one shown in the image above).
6. Under **Select Sort Keys**, toggle the sort keys being used by clicking the buttons multiple times. The Master PC Worksheet will update as you change these keys, so you can immediately see the effects of switching sort keys. Changing the sort keys here does not affect the NCA sort keys.

   Use the **Save** button to add the selections to the table on the right.

Accumulation ratios are reported as RAUCall, RAUCINF, RAUC(Start-End times), RAUClast, RAUC-tau, RCmax columns of data in the NCA Final PK Parameters worksheet.

Set up metabolite to parent ratio calculations

1. Click the **Ratios** button at the bottom of the *NCA Configuration* page.
2. Select the **Metabolite to Parent Ratios** tab.



3. Choose the PK parameters for the calculations by clicking one or more buttons on the left.
4. Select the analyte to serve as the reference from the **Reference Analyte** menu.
5. Select the **Test occasion(s)** to use in the ratio calculation by clicking one or more of the occasion buttons (there are none shown in the image above).
6. Under **Select Sort Keys**, toggle the sort keys being used by clicking the buttons multiple times. The Master PC Worksheet will update as you change these keys, so you can immediately see the effects of switching sort keys. Changing the sort keys here does not affect the NCA sort keys.

   Use the **Save** button to save the selections to the table on the right.

Accumulation ratios are reported as MPAUCall, MPAUCINF, MPAUC(Start-End times), MPAUClast, MPAUCtau, MPCmax columns of data in the NCA Final PK Parameters worksheet.

Validation of PC domain creation

Once **Submit** is clicked in the wizard, PK Submit performs numerous checks, including the following:

- STUDYID is unique for the PC domain.
- The following variables are “Y” or “null”: PCFAST, PCSPCUFL, PCBLFL, and PCEXCLFL.
- PCTEST is less than 40 characters.
- The combinations of PCTEST and PCTESTCD are unique. Every PCTEST value should only have one PCTESTCD.
- The contents of PCORRESU and PCSTRESU are defined in the PKUNIT code list.
- When PCBLFL=Y, PCSTRESC and PCSTRESU are populated.
- PCTPTNUM and PCTPT are the same.
- PCTPTNUM and PCELTM are the same.
- PCRFTDTC, PCDTC and PCENDTC are in a valid format.
- When PCENDTC is populated, PCENDY is populated as well.
- When PCRFTDTC is populated, PCTPTREF is populated as well.

- Proper order of columns and the type for each variable.
- The following variables are populated: STUDYID, DOMAIN, USUBJID, PCSEQ, PCTESTCD, PCTEST, PCORRES, PCORRESU, PCSTRESC, PCSTRESN, PCSTRESU, PCNAM (SDTM only), PCSPEC, PCBLFL (SEND only), PCLLOQ, VISITNUM (SDTM only), PCDTC, PCNOMDY (SEND only), PCRFTDTC (SEND only).
- Variables conform with their controlled terms in the code list.

A failure results in a displayed warning message and/or a message written to the Validation Report in the created Phoenix project Documents folder.

Output

When the PC domain is created, the wizard adds the Master PC Worksheet to the Data folder of the Phoenix project. A CDISC folder is also added to the Data folder that contains

PC (PC domain)

CO (CO domain)

SUPPPC (supplemental PC domain)

ADPC (validation report, SDTM standard only with ADaM data imported)

ADSL (ADSL domain, SDTM standard only with ADaM ADSL data imported)

DM (DM domain, SDTM standard only with ADaM DM data imported)

The following NCA worksheets are also added to the Data folder.

NCA_PLASMA_Worksheet: Excludes all samples when the PCEXCLFL="Y" and all records where the matrix (PCSPEC) belongs to the model type: URINE (210 –212).

NCA_URINE_Worksheet: Excludes all samples when the PCEXCLFL="Y" and all records where the matrix (PCSPEC) belongs to the model type: PLASMA (200 –202). The StartTime column is added and populated using the formula: StartTime = PCTPT – PCEVLINT.

NCA_DOSING_Worksheet

NCA_SORT_KEYS (list of sorting columns in the PC domain and corresponding column names in the dosing data)

The following are added to the Documents folder:

Study Configuration (list of all setting values for the study)

Validation Report (list of any issues identified during the domain creation process.

An NCA object for plasma and/or for urine are added to the workflow.

Add Exclusion and Comment

The **PK Submit > Exclusion and Comment** menu item opens the PC creation wizard to the Data Exclusion and Comments page where you can re-visit the study previously imported, specify data to exclude, add comments, and modify NCA parameter settings (refer to "Exclude data" and the sections that follow it). The PC domain is updated with the modified information when the **Submit** button is clicked.

Create PP Domain

This wizard allows you to select the final PK parameters to exclude, add comments, and generate the PP domain.

Select **PK Submit > Create PP Domain** from the main menu.

The required parameters worksheet will typically come directly from an NCA object, but may also be created through the Data Wizard or some other process in Phoenix.

If an NCA Final Parameter(s) worksheet is already part of the project, it will automatically be selected as the Parameter Worksheet.

Use the **Browse** button to select a different worksheet that contains the parameters in a stacked format using the *Select Object* dialog.

Click **OK**.

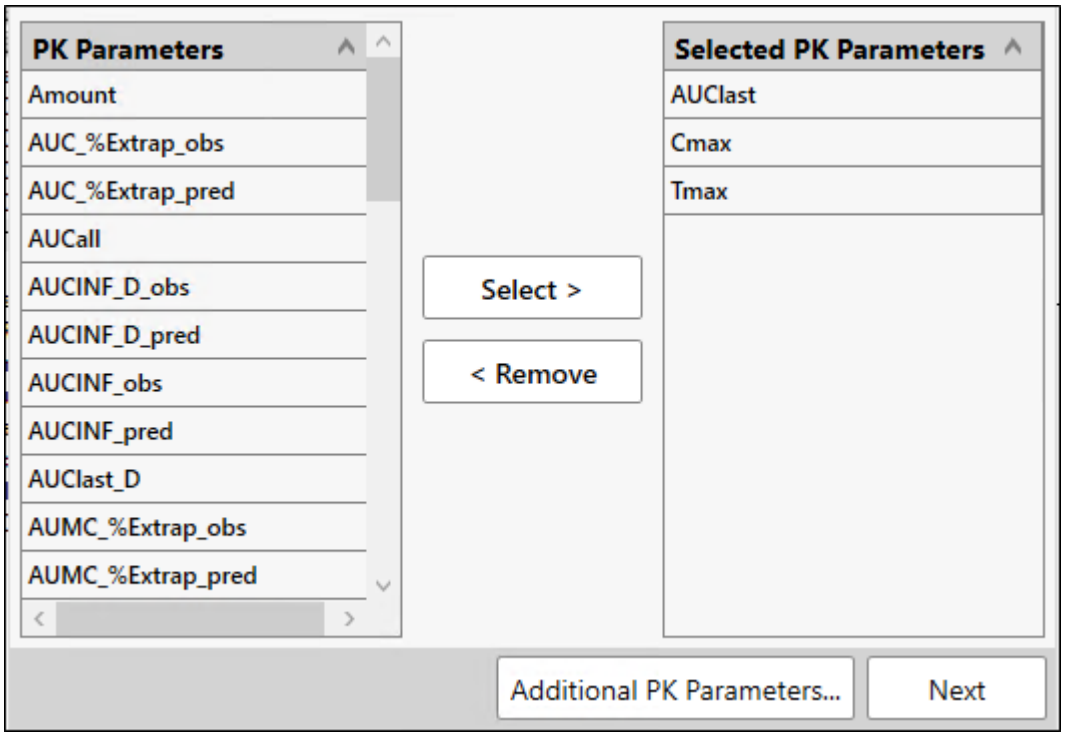
Note: If the final parameters worksheet is user-created, it is important that it includes all data contained in the NCA Final Parameters worksheet(s). New parameters merged with the NCA parameters must be stored in the “Parameter” column, and their corresponding values stored in the “Estimate” column. All other variables should also be populated to match the NCA results.

Creating the PP Domain using the wizard involves the following tasks:

Select PK parameters
Exclude parameters
Add comments
Validation of PP domain creation
Output

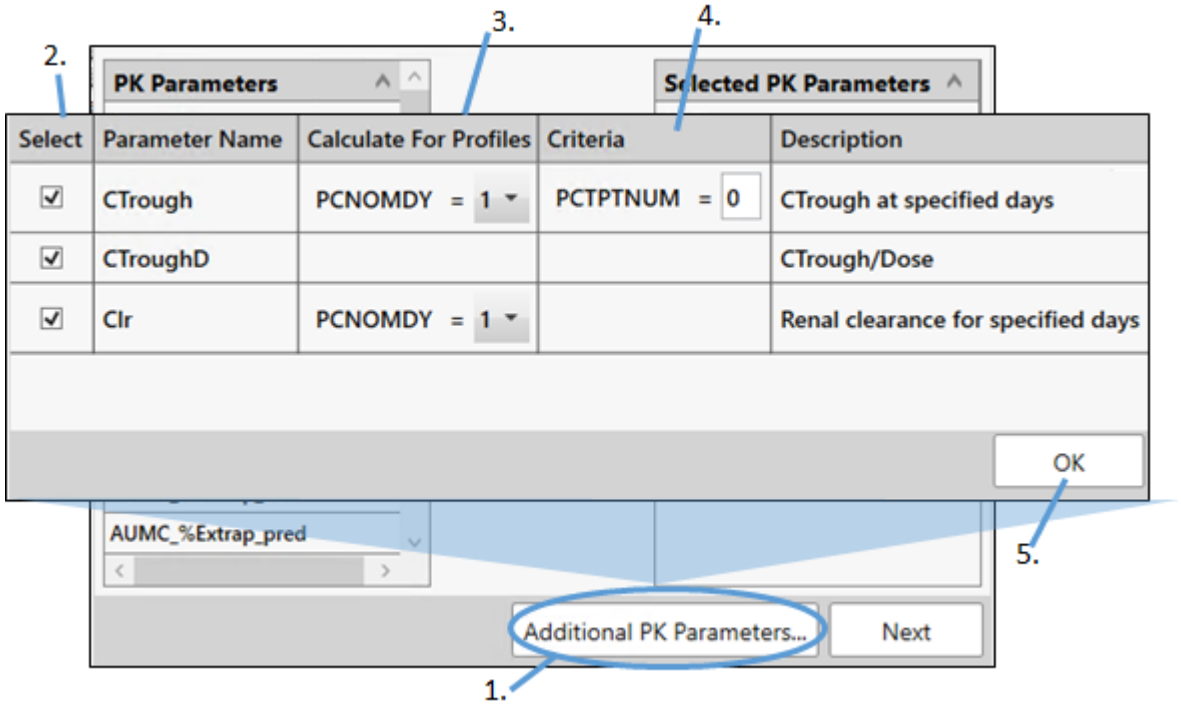
Select PK parameters

Select parameters from one list and use the **Select >** and **< Remove** buttons to move them between the two lists. Parameters in the list on the right will be included in the PP domain report.



To include other parameters:

1. Click **Additional PK Parameters** at the bottom of the page.



2. Check the **Select** checkbox(es) to include CTrough, CTroughD, and/or Clr parameter calculations in the PP domain report.

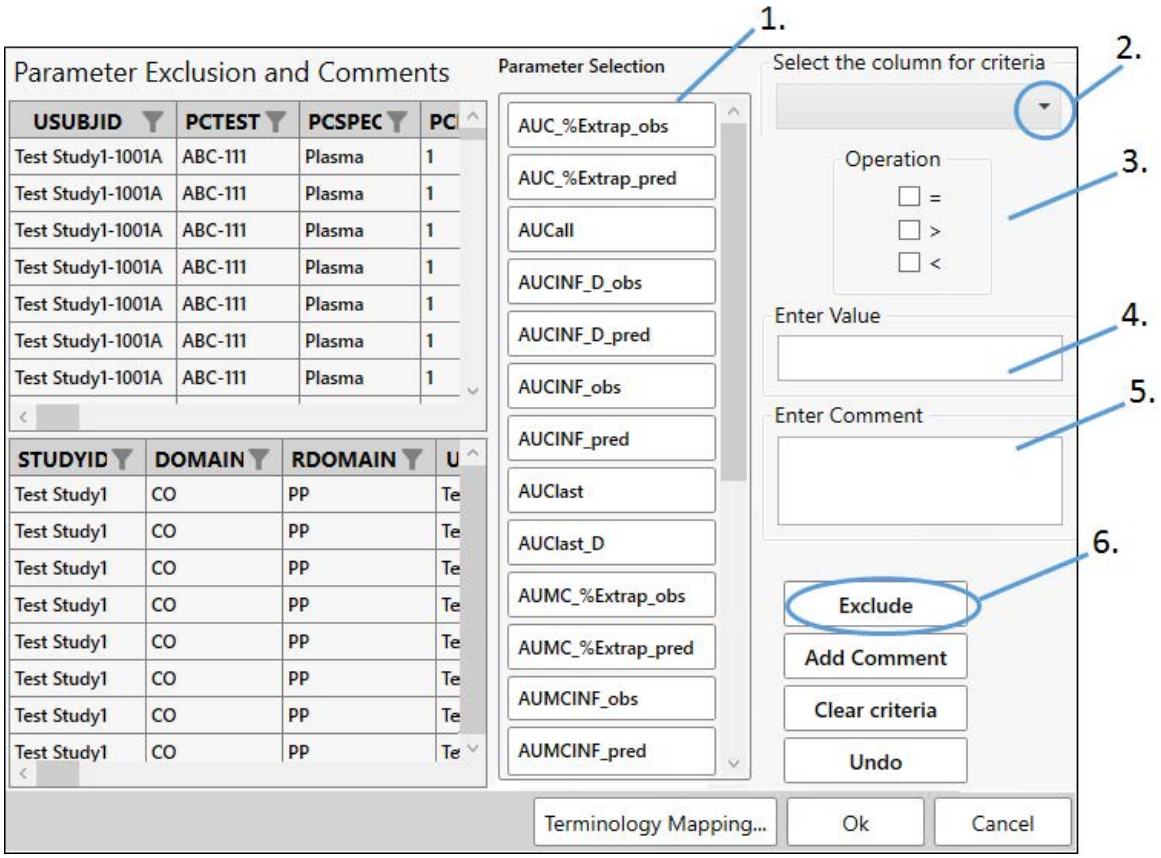
3. For **CTrough** and **Clr**, specify the occasion when the observed value is to be designated as the parameter by selecting from the list in the **Calculate For Profiles** column.
4. For **CTrough**, use the **Criteria** column to identify a particular time point.
5. Click **OK** to add the checked parameters to the list of selected parameters.

Exclude parameters

Manually select data

This process is the same as described in "Manually select data" in the PC creation section.

Use criteria to select parameter



Filter criteria can also be used to identify the parameters to exclude.

1. Under **Parameter Selection**, click the button for the parameter to exclude.
2. Select the variable on which to base the criteria.
3. Check the box(es) for the operator(s) to use in the criteria. Use combinations of two operators, if needed (e.g., check **<** and **=** to indicate the value is "less than or equal to."

4. Type the value in the **Enter Value** field.
5. Enter a reason for the exclusion in the **Enter Comment** field.
6. Click **Exclude**.
   If any of the selected parameters have comments in the CO domain, they need to be removed before the exclusion can be performed.

Note: Selecting **Parameter** in the **Select the column for criteria** pull-down list will result in the appearance of a second pull-down list labeled **Select parameter for criteria**, from which the parameter to use in the exclusion criteria is selected.

Select parameter (no criteria)

Selecting a parameter without specifying criteria will exclude all data points for that parameter.

1. Under **Parameter Selection**, click the button for the parameter to exclude.
2. Click **Exclude**.
   If any of the selected parameters have comments in the CO domain, they need to be removed before the exclusion can be performed.

To remove all the applied exclusions, click the **Undo** button.

To remove a specific exclusion, right-click the row and select **Undo**.

Click **Clear Criteria** to clear the fields and settings made on the page.

Add comments

Manually select data

This process is the same as described in "Manually select data" in the PC creation section.

Use criteria to select parameter

This process is the same as described in "Use criteria to select parameter" to exclude parameters, except click the **Comment** instead of **Exclude** button.

Select parameter (no criteria)

Selecting a parameter without specifying criteria will add the comment to all data points for that parameter.

1. Under **Parameter Selection**, click the button for the parameter.
2. Type the comment in the **Enter Comment** field.
3. Click **Comment**.
4. When finished with the domain specifications, click **OK**.

The **Terminology Mapping** button can be used to set the mapping of the matrix to the CDISC code list. (See "Terminology mapping" for more details.)

Validation of PP domain creation

Once **Submit** is clicked in the wizard, PK Submit performs numerous checks, including the following:

- POOLID values match entries in the Pool Definition dataset (POOLDEF).
- PPTESTCD is no longer than 8 characters and does not start with a number.
- PPTEST is no longer than 40 characters.
- The combination of PPTESTCD and PPTEST for each unique parameter name is unique.
- PPORRESU and PPSTRESCU are defined in the PKUNIT code list.
- When PPORRES is blank, PPSTAT is set to “NOT DONE”.
- When PPSTAT=NOT DONE, PPREASND is populated.
- When PCSTAT=NOT DONE, the following variables are null: PPORRES, PPSTRESC, PPORRESU, PPSTRESCU, PPSTRESN.
- PPRFTDTC is in a valid format.
- PPSPEC contains a value in the controlled terminology code list “Specimen Type”.
- PPSTINT and PPENINT are in ISO format.
- The SEND/SDTM and dataset variable type match.
- The following variables are populated: SEND: STUDYID, DOMAIN, USUBJID, PPSEQ, PPTESTCD, PPTEST, PPCAT, PPORRES, PPORRESU, PPSTRESC, PPSTRESN, PPSTRESU, PPSPEC, PPNOMDY (SEND only), PPRFTDTC.
- Variables conform with their controlled terms in the code list for SEND or SDTM.

A failure results in a displayed warning message and/or a message written to the Validation Report in the Documents folder.

Output

When the PP domain is created, the following worksheets are added to the Data folder.

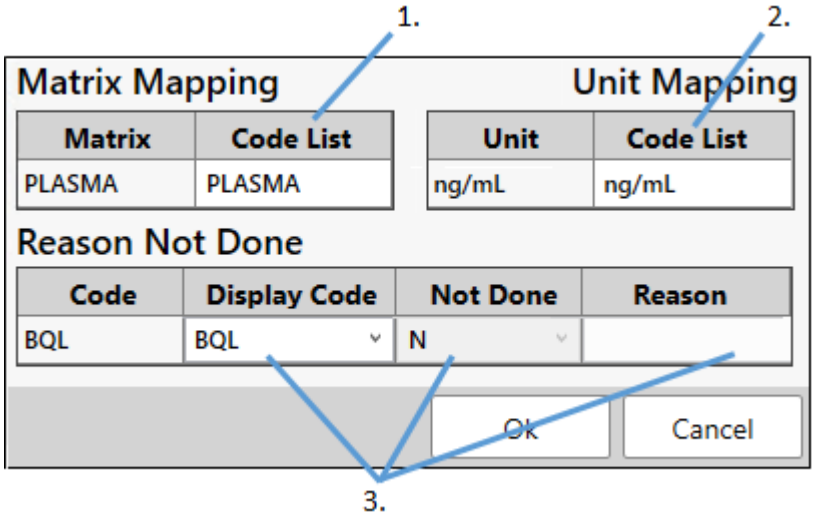
- PP (actual PP domain)
- SUPPPP (supplemental PP domain, SDTM standard only)
- ADPP (validation report, SDTM standard only with ADaM data imported)

Terminology mapping

If a variable is manually mapped, the database installed with PK Submit will remember the mapping and automatically map that variable the next time it is encountered. To see the complete terminology list and make changes to the automatic mapping, use the **Terminology Mapping** button, available when creating a PC or PP domain.

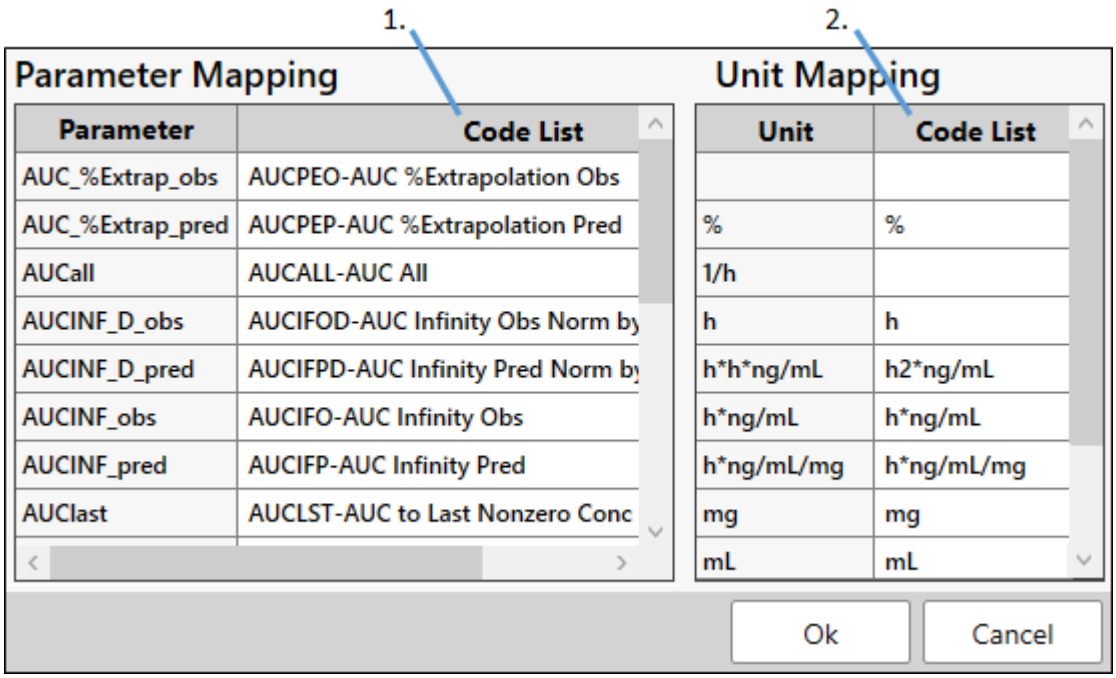
If there is an existing mapping, the CDISC code list will be pre-populated, otherwise, it will be empty/ blank.

For PC domain creation



1. In the *Controlled Terminology Mapping* dialog, set the mapping of the matrix (PCSPEC) to the CDISC code list by clicking the **Code List** cell and selecting the appropriate code from the menu.
2. Set the mapping of the unit (PCORRESU/PCSTRESU) to the CDISC code list by clicking the **Code List** cell and selecting the appropriate code from the menu.
3. Click **OK** to close the dialog and save the mapping information to the SQLite database.

For PP domain creation



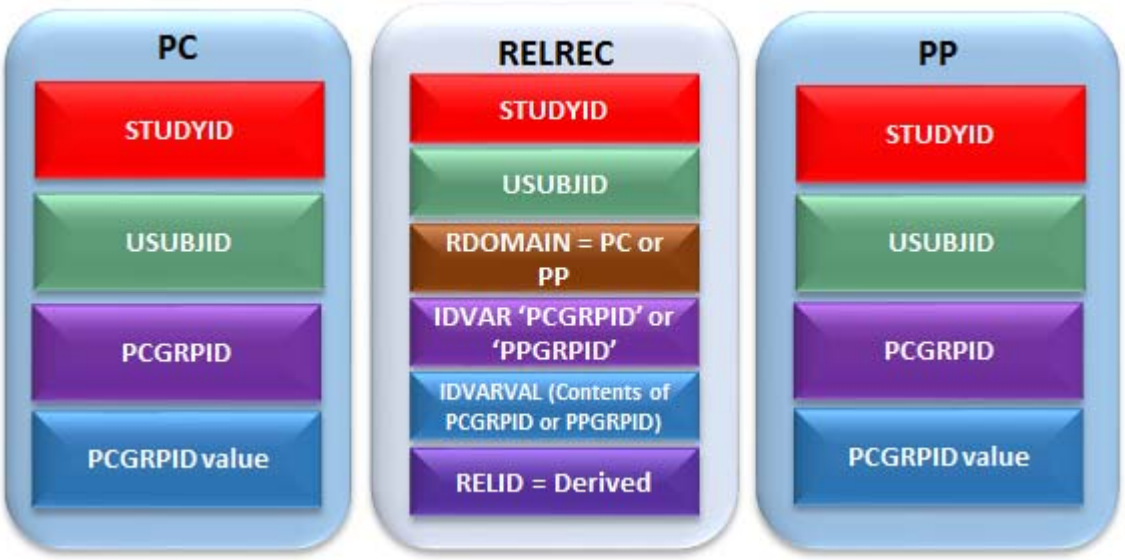
1. In the *Controlled Terminology Mapping* dialog, set the mapping of the parameter to the CDISC code list by clicking the **Code List** cell and selecting the appropriate code from the menu.
2. Set the mapping of the unit to the CDISC code list by clicking the **Code List** cell and selecting the appropriate code from the menu.
3. Click **OK** to close the dialog and save the mapping information to the SQLite database.

Create RELREC and POOLDEF Domains

When the **PK Submit > Create RELREC and POOLDEF Domains** menu item is selected, the RELREC and POOLDEF (Sparse analysis only) domains are immediately created and added to the Data folder.

POOLDEF is used to link multiple subjects to a single POOLID. The POOLID itself is created by concatenating the unique combination of all NCA sort variables (excluding the subject).

PK SUBMIT will create the RELREC domain using the many-to-many mapping method. This method links the PC.PCGRPID numbers with the PP.PPGRPID numbers by the RELID value. In the following image, the RELID=1 is used to link ALL records in the PC domain where PCGRPID= “Test Study1-1001A-ABC-111-1” to ALL records in the PP domain where PPGRPID=”Test Study1-1001A-ABC-111-1”.



Note: PK Submit will split all `.xpt` domains greater than 5 gigabytes (GB) in size into smaller datasets no larger than 5 GB.

Validation of POOLDEF domain creation

Once **PK Submit > Create RELREC and POOLDEF Domains** is selected from the main menu, PK Submit will perform the following checks:

Check that the POOLID values match between Pool Definition dataset (POOLDEF) and PP domain.

Check that the SEND and dataset variable type match.

Check that the following variables are populated: STUDYID, POOLID, USUBJID.

A failure results in a displayed warning message and/or a message written to the Validation Report in the Documents folder.

Validation of RELREC domain creation

Once **PK Submit > Create RELREC and POOLDEF Domains** is selected from the main menu, PK Submit will perform the following checks:

Check that the SEND/SDTM and dataset variable type match

Check that the following variables are populated: STUDYID, RDOMAIN, USUBJID, IDVAR, IDVARVAL, RELID, RELTYPE (SDTM only).

A failure results in a displayed warning message and/or a message written to the Validation Report in the Documents folder.

Create Submission Files

Select **PK Submit > Create Submission Files**.

In the dialog, optionally enter a study name, a description of the study and a protocol name to use in the files.

Click **OK**.

The following files for submission are generated, with all of the required fields populated, and stored in the Documents folder of the Phoenix project in subfolders, depending on their extension:

Define.xml file

Define.xslx file

Data Reviewer's Guide

Domain files in xpt format.

The Data Reviewer's Guide is a Word document that is based on the template available on the PhUSE website. It will vary depending on the standard selected. For SEND, the *Non-Clinical Study Data Reviewer's Guide* (nsdrg) is generated. For SDTM, the *Study Data Reviewer's Guide* (sdrg) is generated.

When STDM is the standard and AdaM data is imported, the output will also include a Define Adam.xlsx, Define ADaM.xml, and *Analysis Data Study Guide* (adrg) file

Export Submission Files

Select **PK Submit > Export Submission Files** menu item.

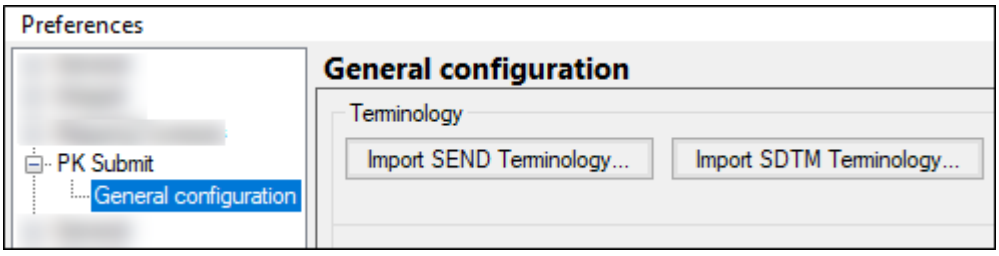
Use the *Browse for Folder* dialog to specify the location for the new files.

Click **OK**.

SAS xpt files are generated for all of the domains. In addition, copies of the Define.xml and *Data Reviewer's Guide* files will be included in the output folder, if they are present in the Phoenix project.

Preferences

PK Submit preferences, available to the user via the *Preferences* dialog (**Edit > Preferences**), consist of a General Configuration screen to allow the uploading of CDISC SEND- and SDTM-controlled terminology.



In the *Preferences* dialog, select **PK Submit > General Configuration**.

Choose the **Import SEND Terminology** or **Import SDTM Terminology** button.

In the file browser, navigate to and select the file containing the terminology settings. The file must be in Excel XLS format (*.xls).

The PK Submit SQLite database distributed with Phoenix is preloaded with SEND and SDTM Controlled Terminology code lists. If a different terminology set is imported, it will be stored in the SQLite database.

The SEND/Codelist code and Codelist name are listed below (the CDISC Submission Value is in parentheses):

C77529 Specimen (SPEC)
C85839 PK Parameters Code (PKPARMCD)
C85494 PK Units of Measure (PKUNIT)
C66789 Not Done (ND)
C66742 No Yes Response (NY)
C78737 Relationship Type (RELTYPE)

The SDTM/Codelist code and Codelist name are listed below (the CDISC Submission Value is in parentheses):

C78734 Specimen Type (SPECTYPE)
C85839 PK Parameters Code (PKPARMCD)
C85494 PK Units of Measure (PKUNIT)
C66789 Not Done (ND)
C66742 No Yes Response (NY)
C78733 Specimen Condition (SPECCOND)
C85492 Method (METHOD)
C78737 Relationship Type (RELTYPE)

CDISC time formats

Below are some important notes regarding the time formats used in CDISC.

- All the date, time, and collection time fields are in ISO 8601 format as defined by the CDISC standards.
- The format of CDISC data after import may differ depending upon the default local/regional ISO format for the environment in which Phoenix is running. The mm/dd/yyyy ISO date format may not be the default and may not even be an option in some regions.

Constructed variables

SEND 3.0

--SEQ: Sequential number identifying records within a dataset.
--STRESC: Copy of --ORRES.
--STRESN: Reports the numeric equivalent when --STREC contains a numeric result.
--STRESU: When --STRESC contains a numeric result, --ORRESU is reported in --STRESU.
--SPEC: Derived from the specimen name used during sample collection.
USUBJID: Concatenation of STUDYID-SUBJID.
PCTESTCD: "ANALYTE" + sequence number (0-9)
PCTPT: PCTPTNUM + Time Unit

PCTPTREF: "Time unit" + VISITDY + "Dose"

POOLID: A concatenation of all NCA sort key, separate each key with a dash "-".
--GRPID: A concatenation of all NCA sort key, separate each key with a dash "-".
PPCAT: Copy of PCTEST.
PPSCAT: "NON-COMPARTMENTAL" hardcode.
PPSTINT: Start time found in the partial area in the ISO format.
PPENINT: End time found in the partial area in the ISO format.
PPTPTREF: Copy of PCTPTREF.

SEND 3.1

--SEQ: Sequential number identifying records within a dataset.
--STRESC: Copy of --ORRES.
--STRESN: Reports the numeric equivalent when --STREC contains a numeric result.
--STRESU: When --STRESC contains a numeric result, --ORRESU is reported in --STRESU.
--SPEC: Derived from the specimen name used during sample collection.
USUBJID: Concatenation of STUDYID-SUBJID.
PCTESTCD: "ANALYTE" + sequence number (0-9)

PCTPT: PCTPTNUM + Time Unit

PCNOMLBL: "Time unit" + PCNOMDY

PCTPTREF: PCNOMLBL + "Dose".
POOLID: A concatenation of all NCA sort key, separate each key with a dash "-".
--GRPID: A concatenation of all NCA sort key, separate each key with a dash "-".
PPCAT: Copy of PCTEST.
PPSCAT: "NON-COMPARTMENTAL" hardcode.
PPSTINT: Start time found in the partial area in the ISO format.
PPENINT: End time found in the partial area in the ISO format.
PPTPTREF: Copy of PCTPTREF.
PPNOMDY: Copy of PCNOMDY.
PPNOMLBL: Copy of PCNOMLBL.

SDTM

--SEQ: Sequential number identifying records within a dataset.
--STRESC: Copy of --ORRES.
--STRESN: Reports the numeric equivalent when --STREC contains a numeric result.
--STRESU: When --STRESC contains a numeric result, --ORRESU is reported in --STRESU.
--SPEC: Derived from the specimen name used during sample collection.
USUBJID: Concatenation of STUDYID-SUBJID.
PCTESTCD: “ANALYTE” + sequence number (0-9)
PCTPT: PCTPTNUM + Time Unit

VISIT: “Time unit” + VISITDY

PCTPTREF: VISIT + “Dose”.
--GRPID: A concatenation of all NCA sort key, separate each key with a dash “**-**”.
PPCAT: Copy of PCTEST.
PPSCAT: “NON-COMPARTMENTAL” hardcode.
PPSTINT: Start time found in the partial area in the ISO format.
PPENINT: End time found in the partial area in the ISO format.

PK Submit Examples

PK Submit supports the automatic generation of a complete electronic PK regulatory submission package, including all necessary CDISC domains, during the normal process of setting up and executing an NCA.

The example below shows the basic steps to generating SEND 3.1 formatted submission-ready files.

See “SDTM example” for generating SDTM 3.2 formatted submission-ready files.

SEND example

This example uses the input of a PC.xpt and an EX.xpt file. Using PK Submit, a full set of CDISC domains in SEND 3.1 format will be generated and an NCA project will be created and set up to use the domains. At the end of the example, you will have a complete set of files for the study that are ready for electronic submission.

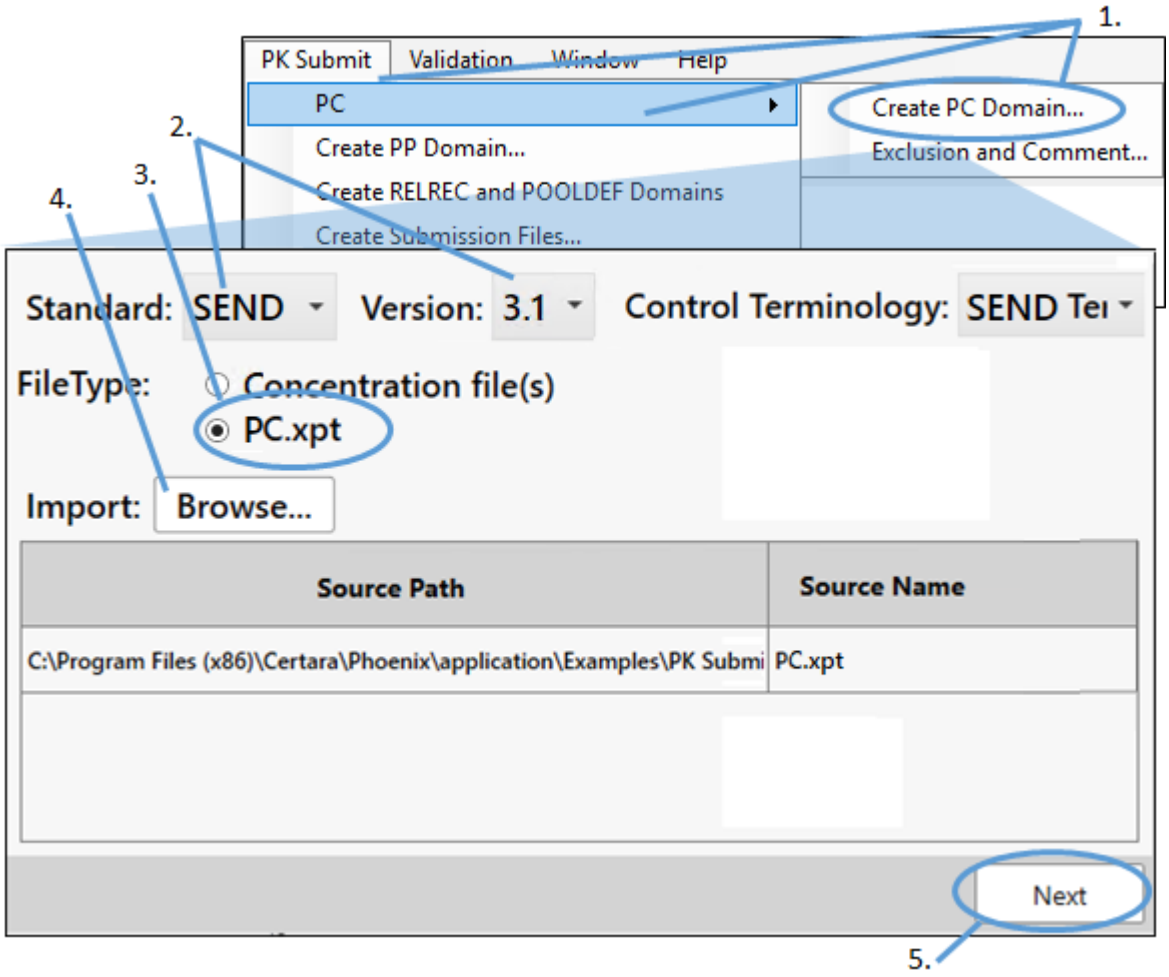
The major steps in this example include:

- Create the PC domain
- Create the PP domain
- Create RELREC domain
- Create files required for submission
- Export submission files

Create the PC domain

Specify the dataset for the PC domain

1. Select **PK Submit > PC > Create PC Domain** from the Phoenix menu.



2. In the *PK Submit* dialog, make sure the **Standard** and **Version** menus are set to **SEND** and **3.1**, respectively.
3. Select **PC.xpt** as the **FileType**.
4. Click **Browse**, navigate to `<Phoenix_install_dir>\application\Examples\PK Submit\Supporting files\Example1`, select **PC.xpt**, and click **Open**.
5. Click **Next**.

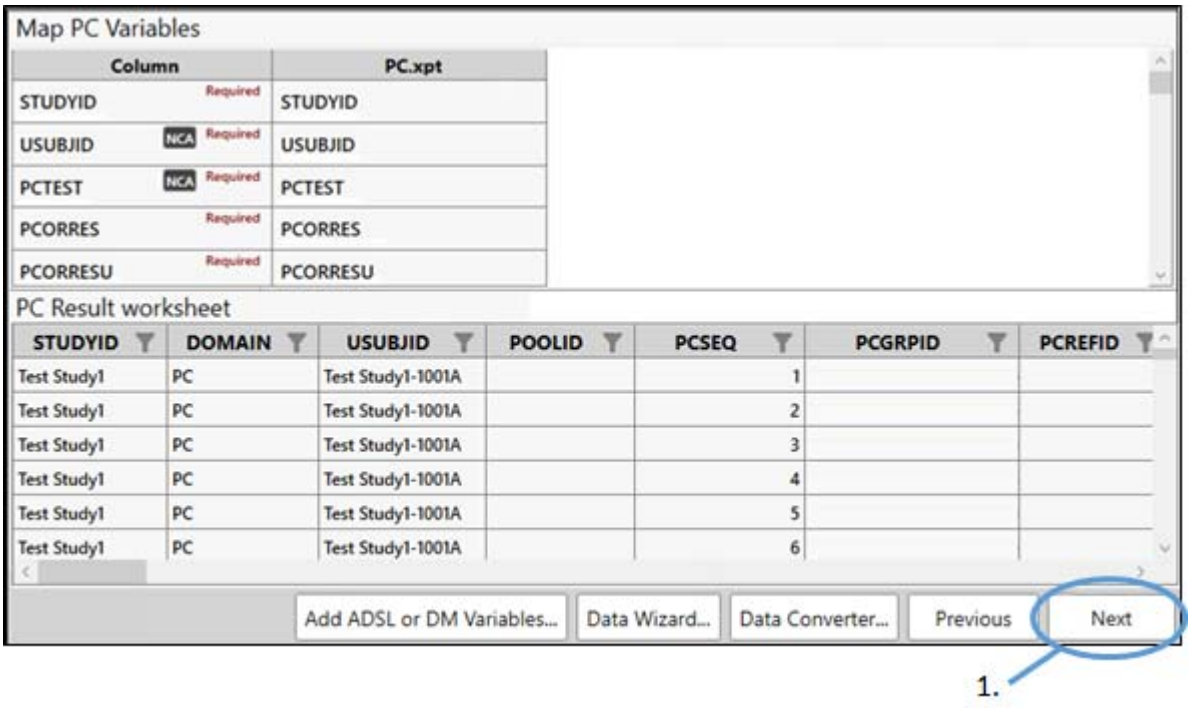
Map the variables

The next step in the process involves lining up variables in the input dataset with those in the PC domain. The variables are marked as either being required for the PC domain creation or optional. The example `PC.xpt` file we are using includes variables that are recognized by PK Submit as PC variables and, therefore, they are automatically mapped. There is no need for us to perform any manual mapping of the dataset variables to the PC variables.

Variables that are not required for the PC domain but are needed for the NCA can also be mapped at this point, such as Dose Amounts, Dose Units, and Routes of Administration. For this example, we will map these items in a later step.

Note: If a variable is manually mapped, the database installed with the application will remember the mapping and automatically map that variable the next time it is encountered.

All required variables must be mapped to complete the process. Our example input file contains all of the variables that are required for the PC domain so we can proceed to the next step.



1. Click **Next**.

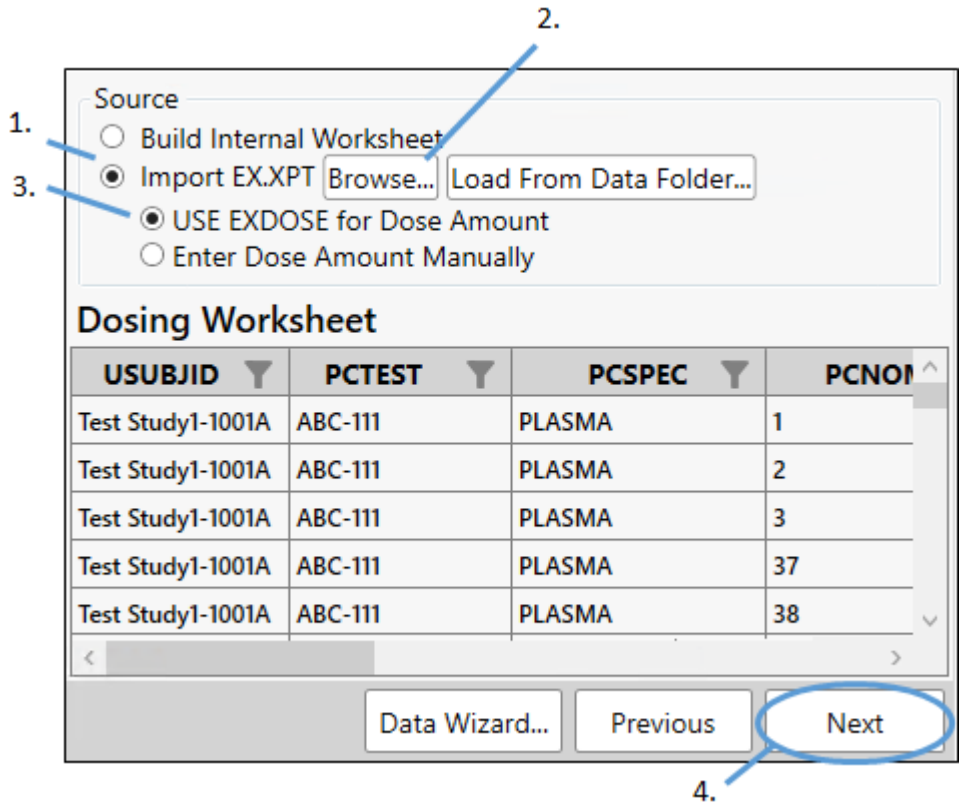
   During the PC domain creation process, PK Submit checks the data and will warn you of errors that will occur during the validation step. For example, if the USUBJID does not contain the studyID string, which is required for compliant PC domain, you will see a message and be given the option to have the PK Submit concatenate the study ID with the USUBJID to bring it into compliance.

Select NCA keys

1. For this example, we will use the default NCA keys. Click **Next**.

Merge dosing with concentration information

Dosing and concentration information can be merged by mapping the appropriate variables in the previous step, by entering values directly in the table, or by loading an EX**.**XPT file. For this example, we will load an example file.

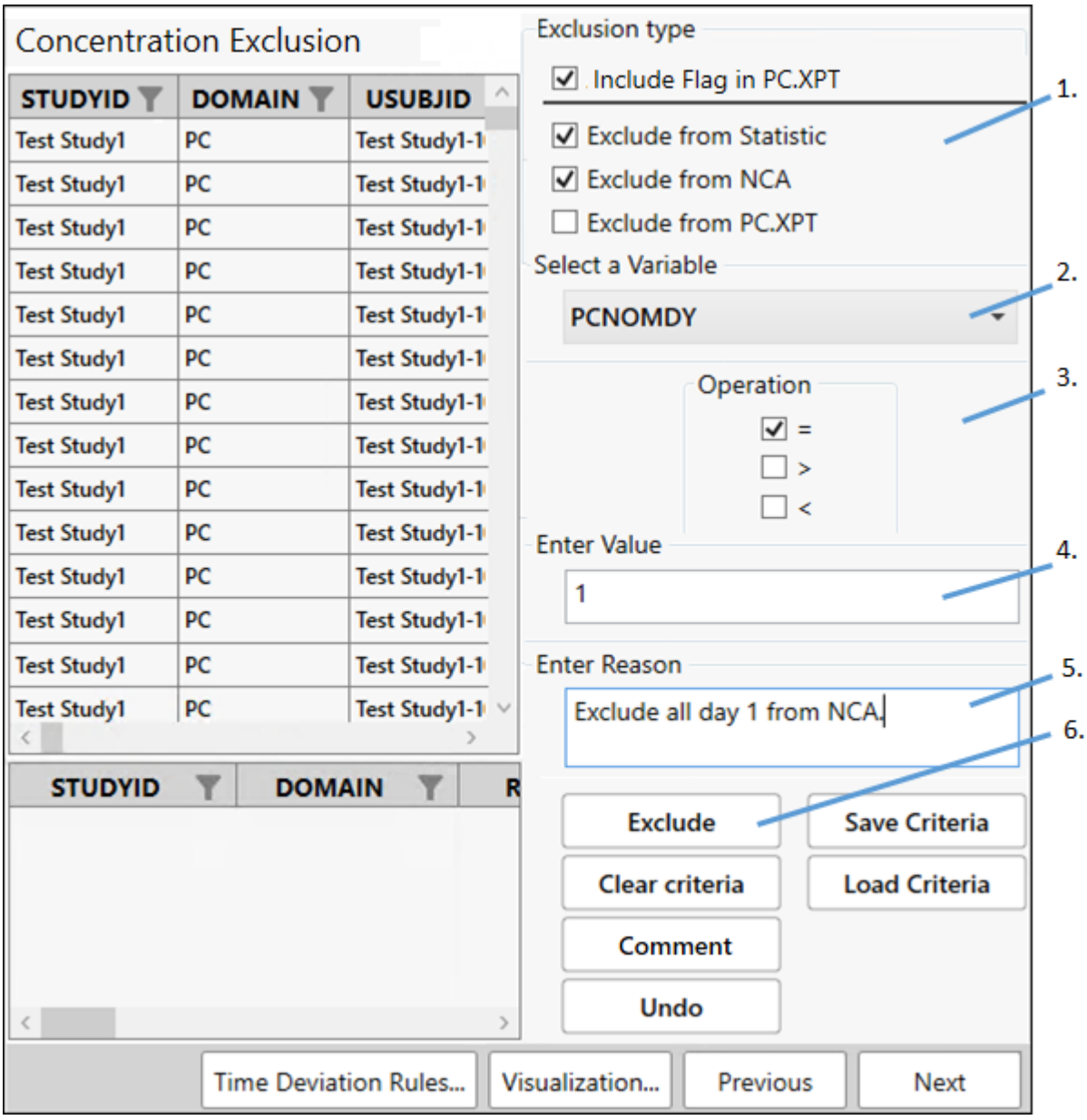


1. Select the **Import EX.XPT** option.
2. Select the **Use EXDOSE** for Dose Amount option.
3. Click **Browse**, navigate to `<Phoenix_install_dir>\application\Examples\PK Submit\Supporting files\Example1`, select **EX.xpt** and click **Open**.

   If the merge is performed successfully, PK Submit will tell you the number of rows of data were imported. Click **OK**.
4. Click **Next**.

Exclude data

Set up a filter to exclude all day 1 data from the NCA analysis.

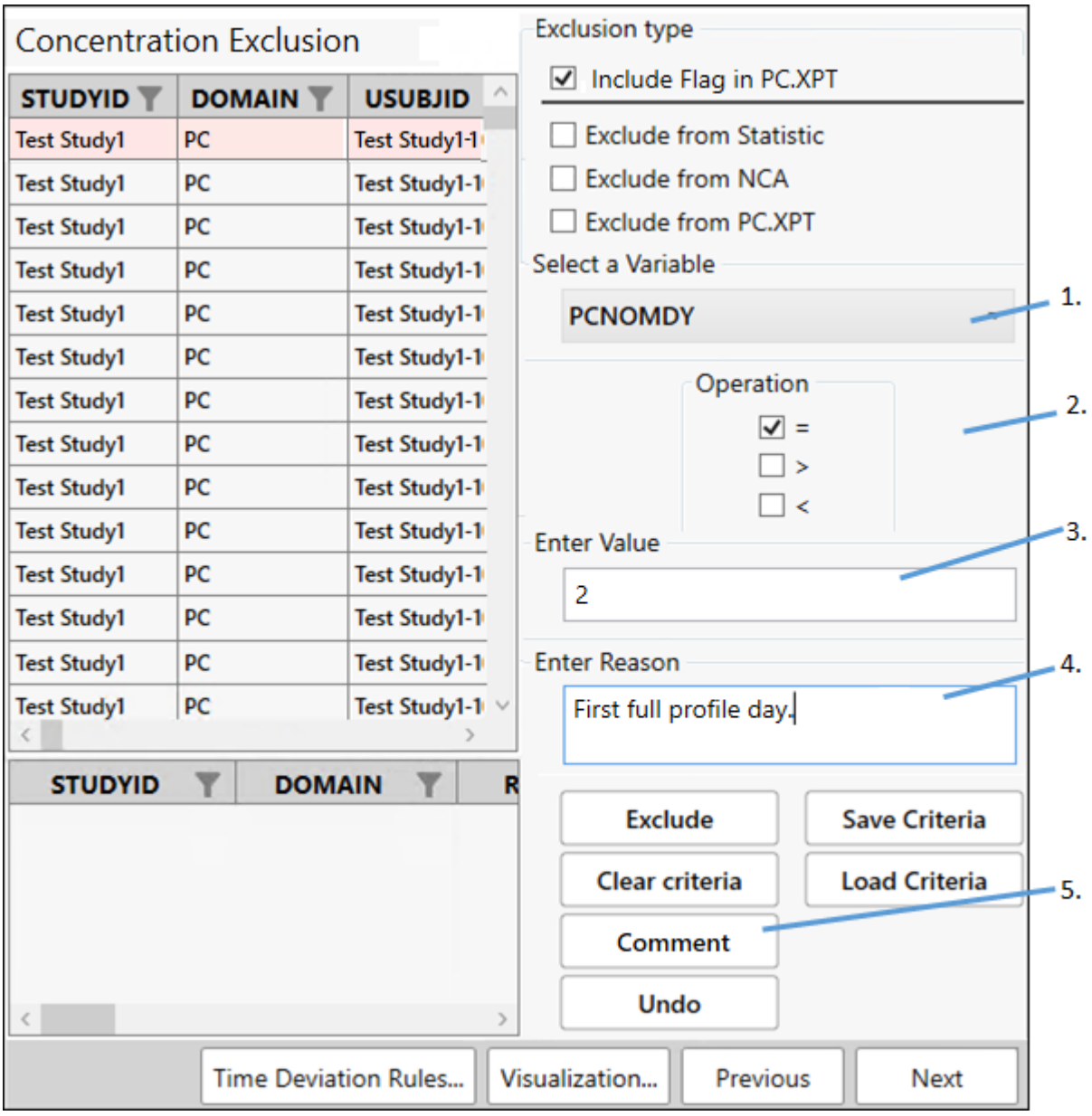


1. Check the **Exclude from Statistic** and **Exclude from NCA** boxes.
2. From the **Select a Variable** pulldown, scroll down the list and choose **PCNOMDY**.
3. Check the box for **=** under **Operation**.
4. In the **Enter Value** field, type `1`.
5. Type the following in the **Enter Reason or Comment** field:
   `Exclude all day 1 from NCA.`
6. Click **Exclude**.

   Rows that meet the criteria (row 1, in this example) will be shaded pink to indicate that they are marked for exclusion.

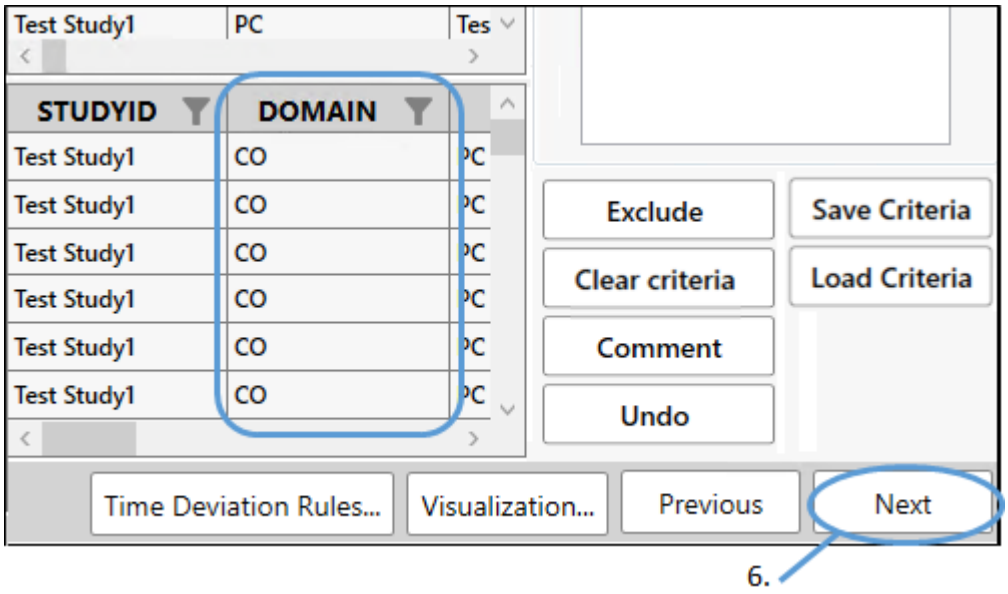
Add a comment

On the same Concentration Exclusion page, add a comment about the data collected on day 2.



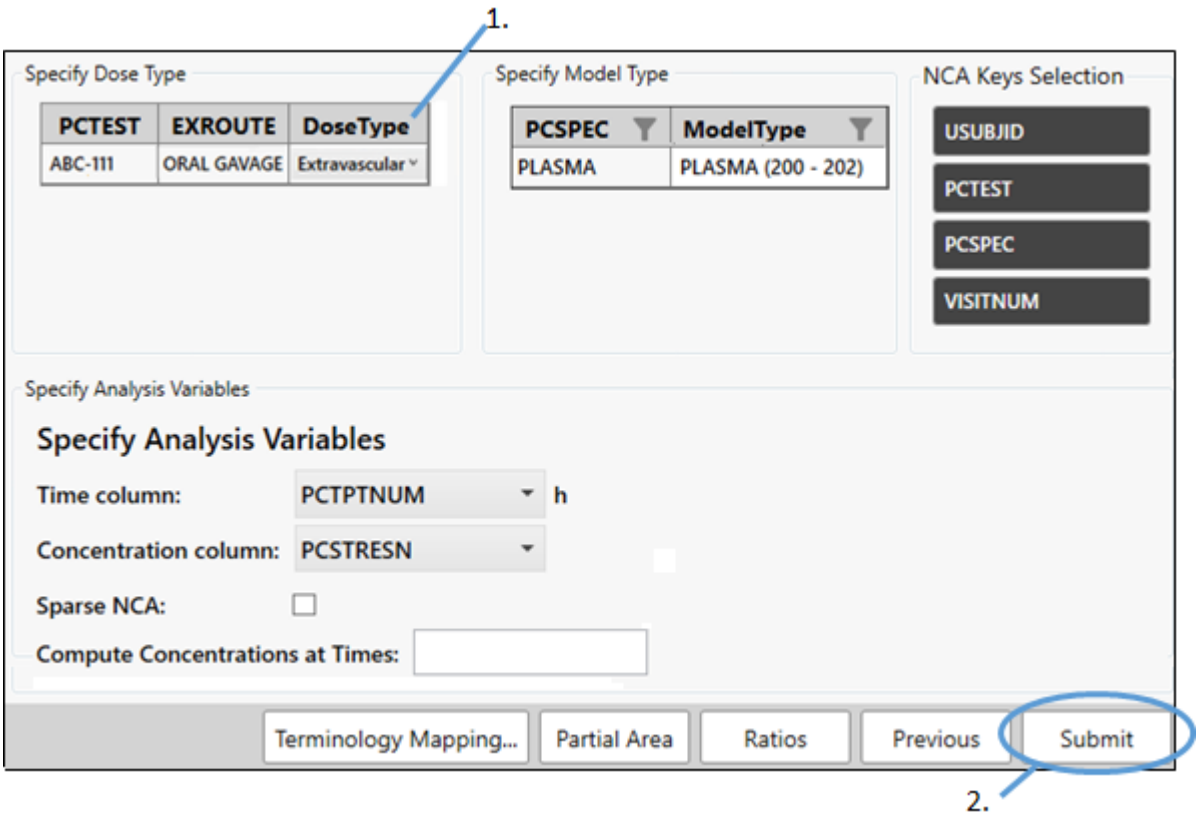
1. From the **Select a Variable** pulldown, scroll down the list and choose **PCNOMDY** again.
2. Check the box for **=** under **Operation**.
3. In the **Enter Value** field, type 2.
4. Type the following in the **Enter Reason or Comment** field:
   `First full profile day.`
5. Click **Comment**.

   Adding comments generates a CO domain.



6. Click **Next**.

Finish setting up NCA

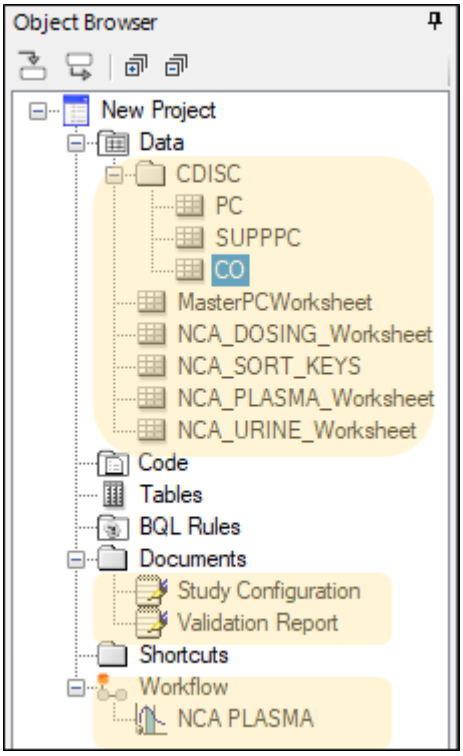


1. Select **Extravascular** from the **Dose Type** pulldown.

   The **Terminology Mapping** button will show how the terminology for specimen and units are being mapped. As mentioned earlier in the example, this mapping is remembered by the database and only needs to be mapped once. However, the complete terminology list is always available through the *Controlled Terminology Mapping* dialog for you to select from.

2. Click **Submit**.

The PC domain is complete and a Phoenix project is automatically created, with a workflow that has an NCA object preconfigured according to specifications made in PK Submit.

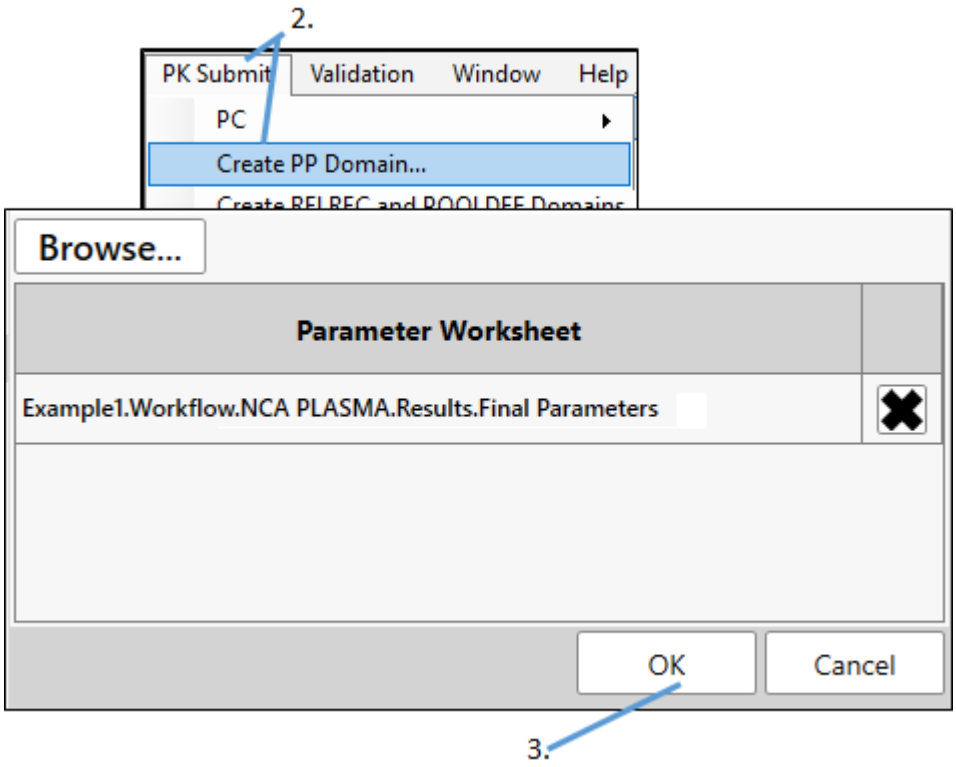


Create the PP domain

The PP domain can be generated from an NCA, typically the Final Parameters output worksheet. The NCA object set up by PK Submit is ready to execute. Unless you want to review the slope selector, you can simply run the NCA.

Specify the data for the PP domain

1. Rename the project as `Example1`.
2. Execute the NCA object.



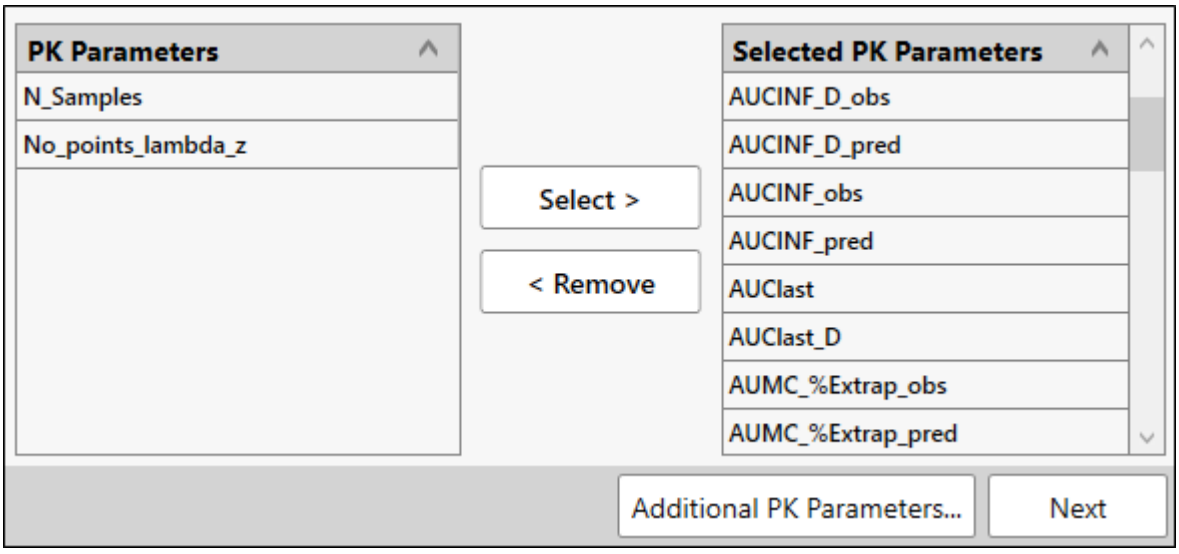
3. Select **PK Submit > Create PP Domain** from the Phoenix menu.

   PK Submit will automatically select the Final Parameters result worksheet when there is an open project with an executed NCA object available (such as in this example). Otherwise, use the Browse button.

4. Click **OK**.

Select PK parameters

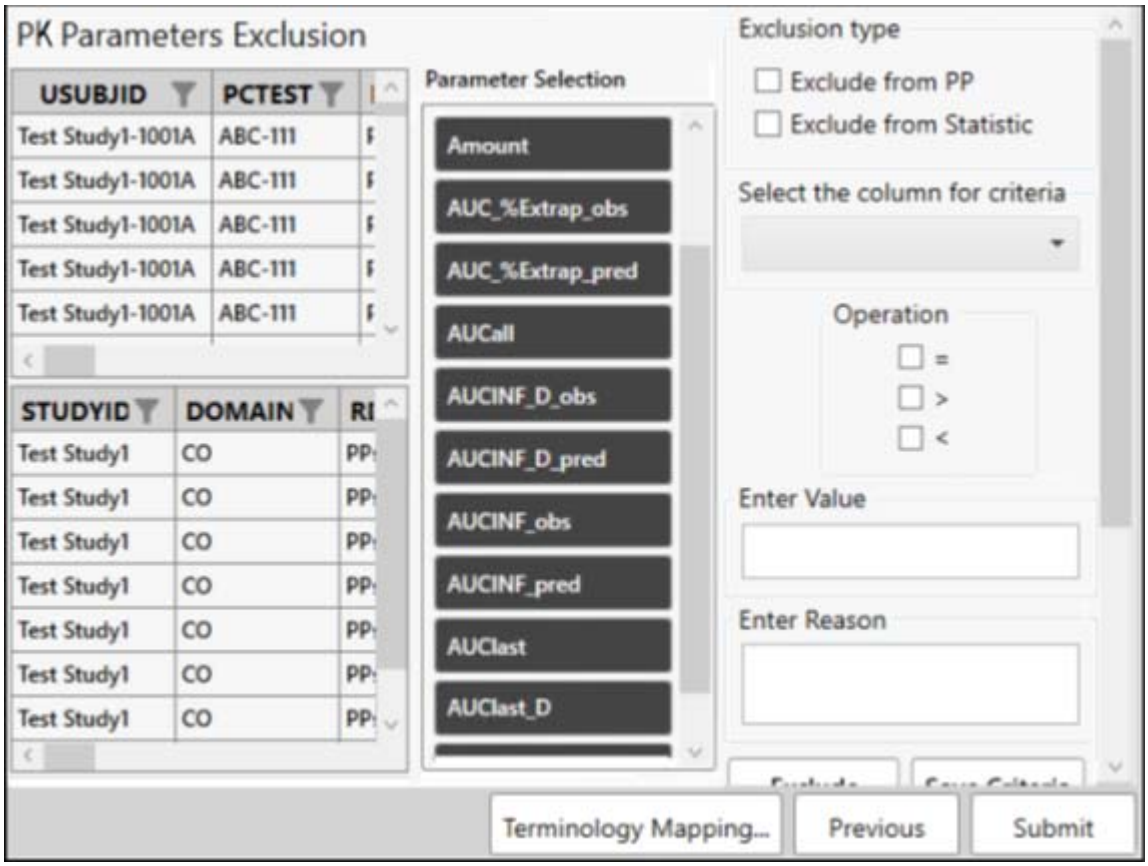
1. Using the **Select >** and **< Remove** buttons, move all of the parameters to the Selected PK Parameters list except for **N_Samples** and **No_points_lambda_z**.



2. Click **Next**.

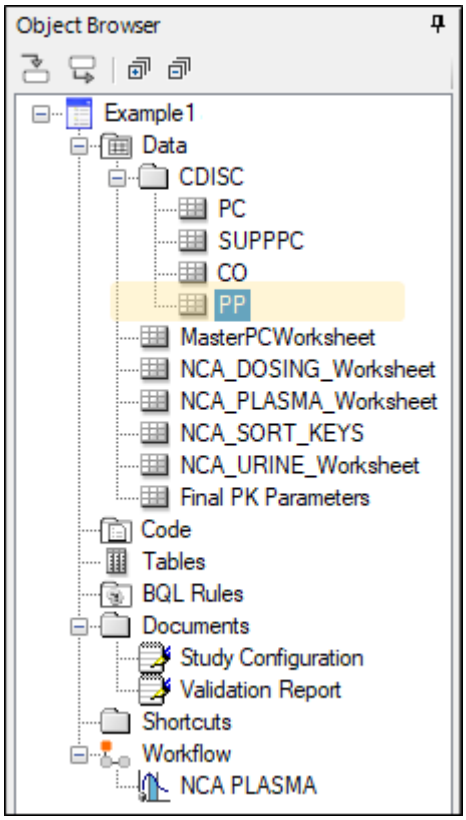
Exclude parameters

For this example, we will not set up any exclusion criteria.



1. Click **Submit**.

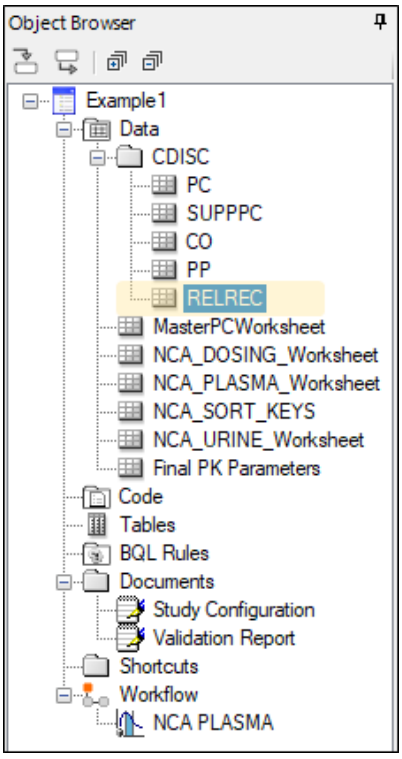
   The PP domain is created.



Create RELREC domain

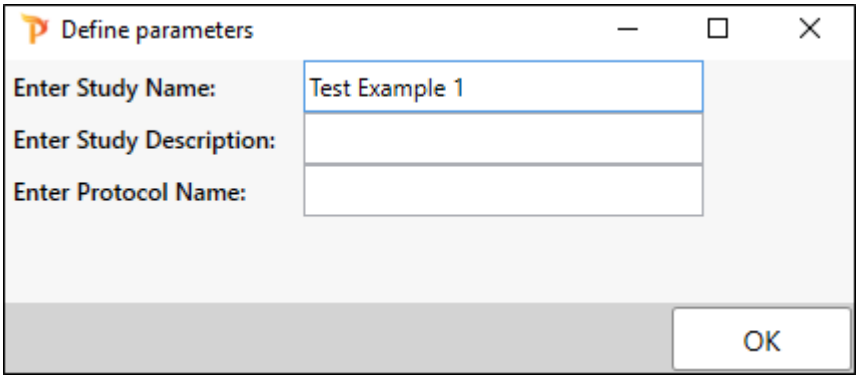
1. Select **PK Submit > Create RELREC and POOLDEF Domains** from the Phoenix menu.

Since this was not a sparse study, there will not be a POOLDEF domain.

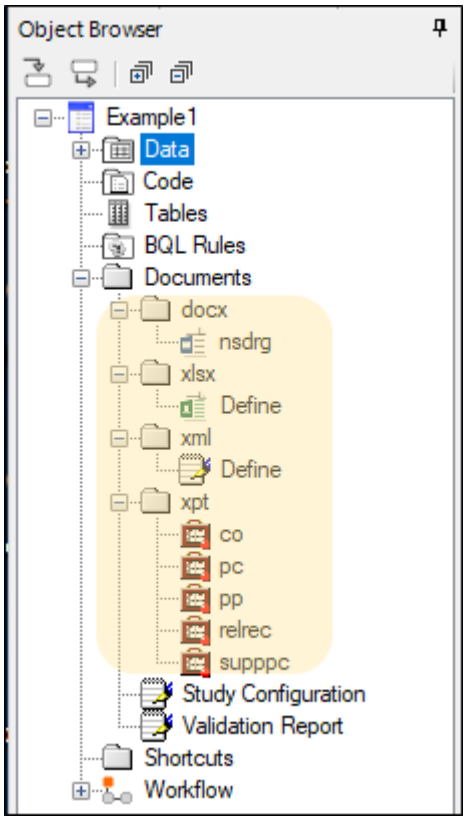


Create files required for submission

1. Select **PK Submit > Create Submission Files** from the Phoenix menu.



2. Enter `Test Example 1` as the **Study Name**.
3. Click **OK**.

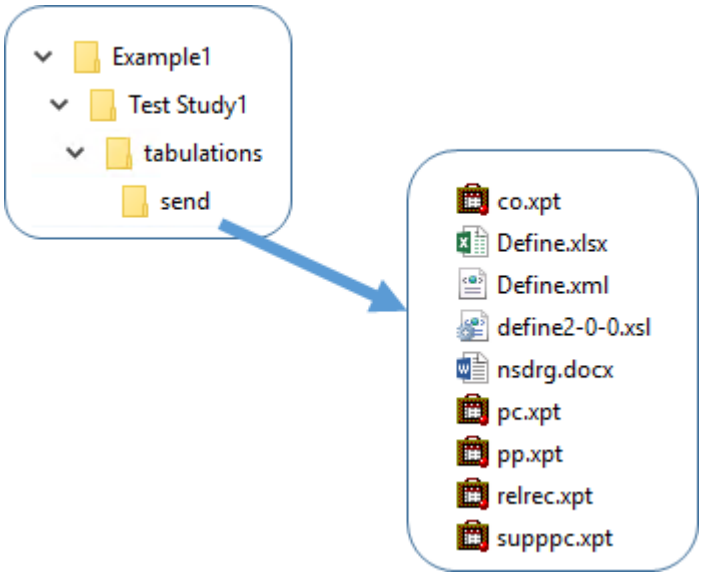


The Study Data Reviewer's Guide is created and stored in the **Documents > docx** subfolder of the Object Browser. The template for this document is available on the PhUSE website. PK Submit automatically populates the document with most of the information needed for submission.

The `Define.xlsx` file is created and stored in the **Documents > xlsx** subfolder. This Excel-formatted file contains all of the information you find in the `Define.xml` file for the study in the **Documents > xml** subfolder.

Export submission files

1. Select **PK Submit > Export Submission Files** from the Phoenix menu.
2. In the file browser, select the location in which to save the files and click **OK**.
   In the following image, a folder named Example1 was selected.



The study information is ready for electronic submission and the process is complete.

SDTM example

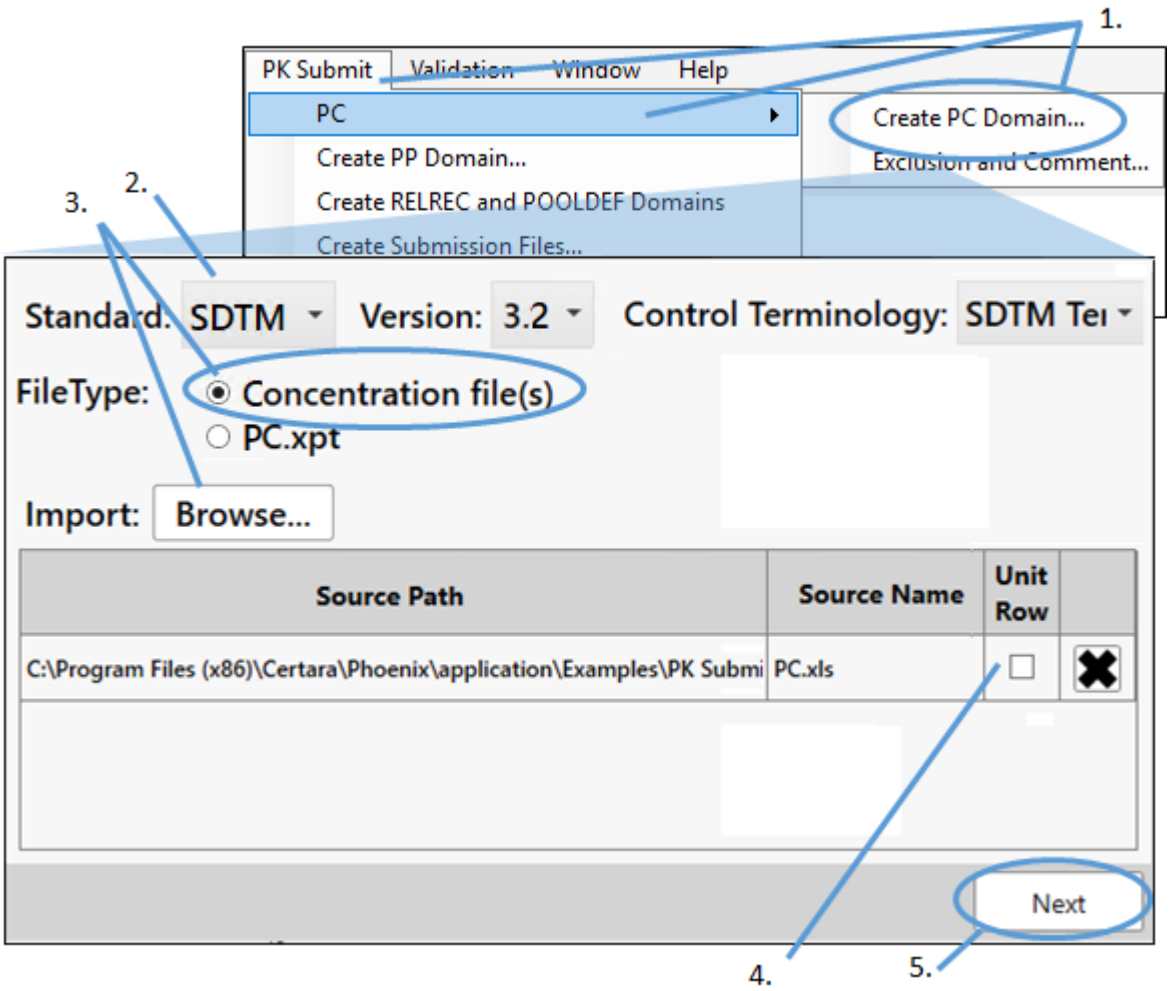
This example uses the input of a PC.xls file. Using PK Submit, a full set of CDISC domains in SDTM 3.2 format will be generated and an NCA project will be created and set up to use the domains. At the end of the example, you will have a complete set of files for the study that are ready for electronic submission.

The major steps in this example include:

Create the PC domain
Create the PP domain
Create RELREC domain
Create files required for submission
Export submission files

Create the PC domain

Specify the dataset for the PC domain

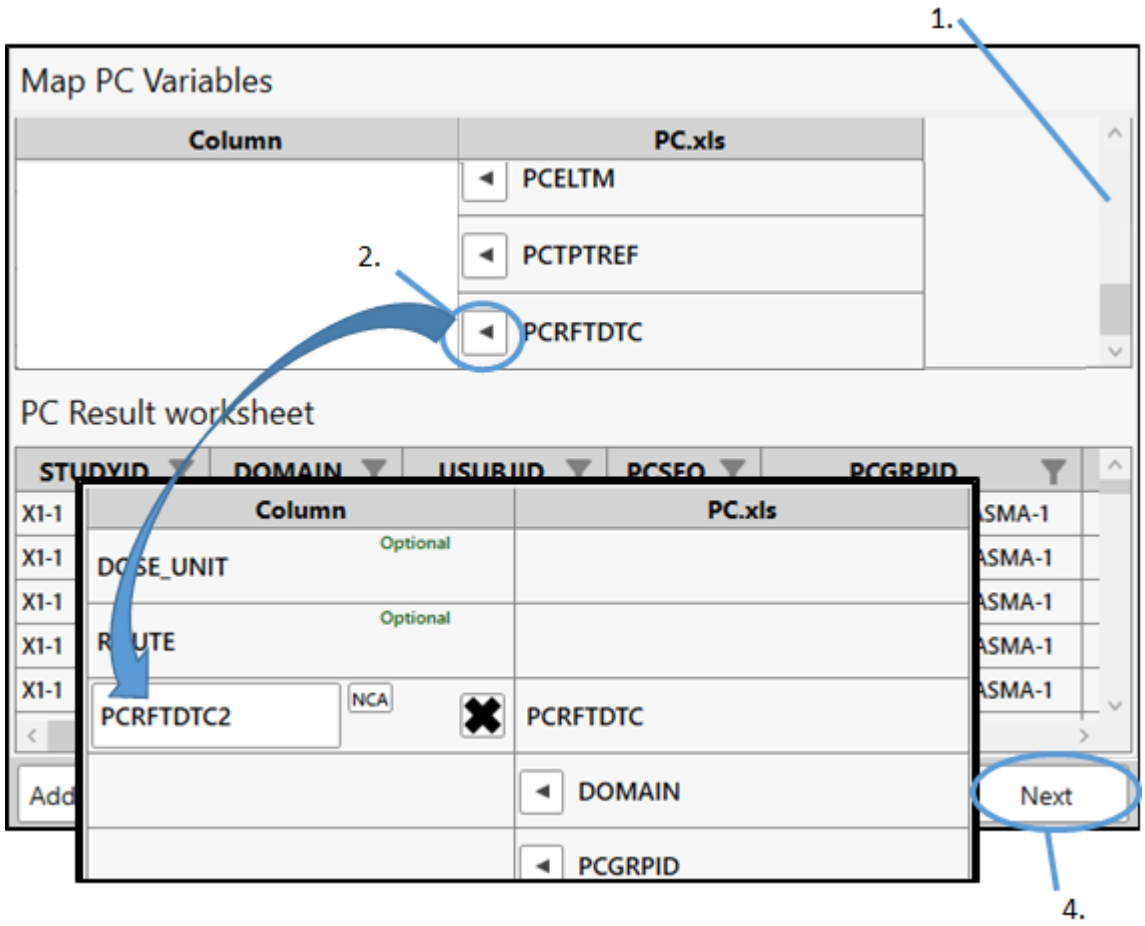


1. Select **PK Submit > PC > Create PC Domain** from the Phoenix menu.
2. In the *PK Submit* dialog, set the **Standard** and **Version** menus are set to **SDTM** and **3.2**, respectively.
3. With the **FileType** set to **Concentration file(s)**, click **Browse**, navigate to `<Phoenix_install_dir>\application\Examples\PK Submit\Supporting files\Example1`, select **PC.xls**, then click **Open**.
4. Check the **Unit Row** box to combine the first (column names) and second (units) rows of the Excel file.
5. Click **Next**.

Map the variables

The next step in the process involves lining up the variables in the input dataset with those in the PC domain. The variables are marked as either being required for the PC domain creation or optional. Many of the variables in the example `PC.xls` file are recognized by PK Submit as PC variables and, therefore, they are automatically mapped. There is one, however, that we need to manually map: PCRFTDTC.

1. Scroll down and locate **PCRFTDTC** in the PC.xls column



2. Click the left arrow in the PCRFTDTC cell.
   This moves the row up to the end of the mapped variables.
3. Scroll up to locate moved PCRFTDTC cell.
   The PCRFTDTC data is now mapped to a column named **PCRFTDTC2**.

Note: If a variable is manually mapped, PK Submit stores the mapping in a database to allow automatic mapping of the variable the next time it is encountered. The database file is `C:\Users\<user-name>\Documents\Certara\PKSubmit\PK Submit.db`.

All required variables are now mapped, so we can proceed to the next step.

4. Click **Next**.

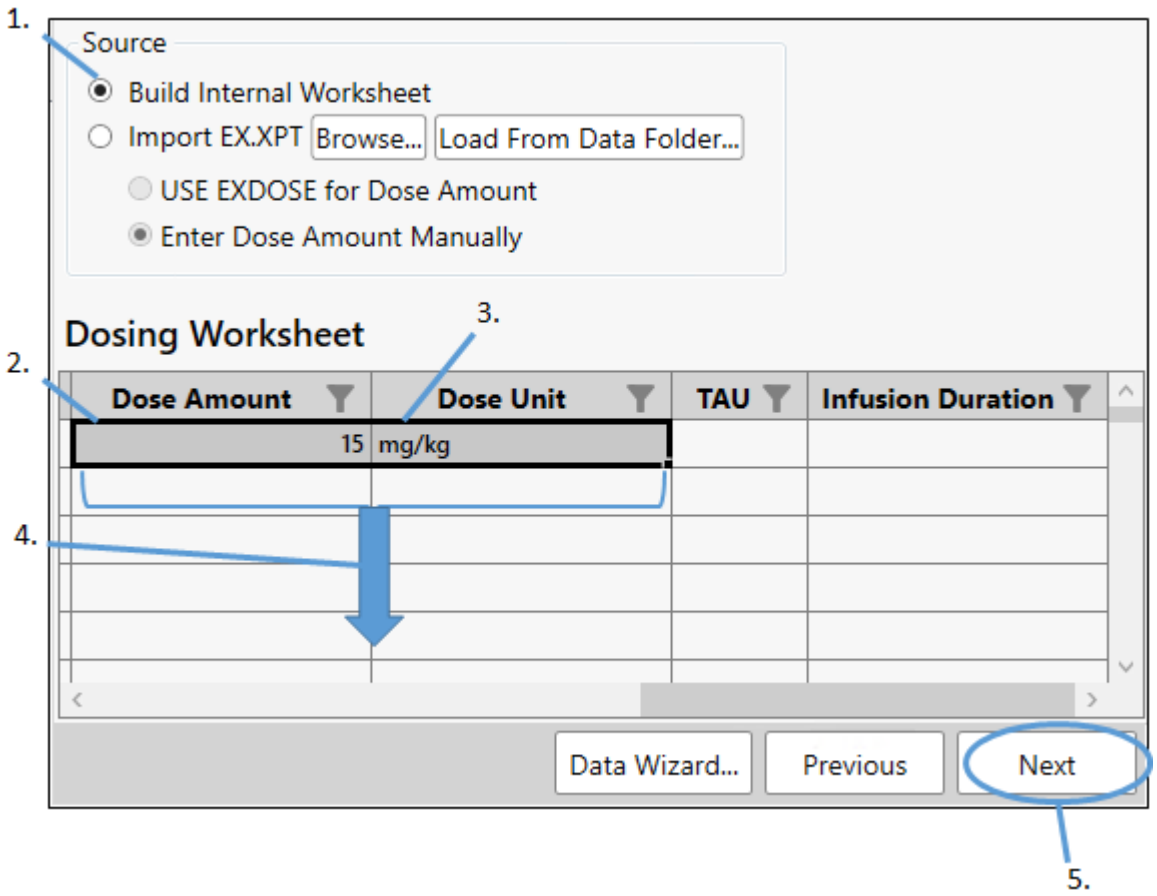
   During the PC domain creation process, PK Submit checks the data and will warn you of errors that will occur during the validation step. For example, if the USUBJID does not contain the studyID string, which is required for compliant PC domain, you will see a message and be given the option to have the PK Submit concatenate the study ID with the USUBJID to bring it into compliance.
5. Click **Yes** when asked about concatenating the study ID and USUBJID.

Select NCA keys

1. For this example, we will use the default NCA keys. Click **Next**.

Merge dosing with concentration information

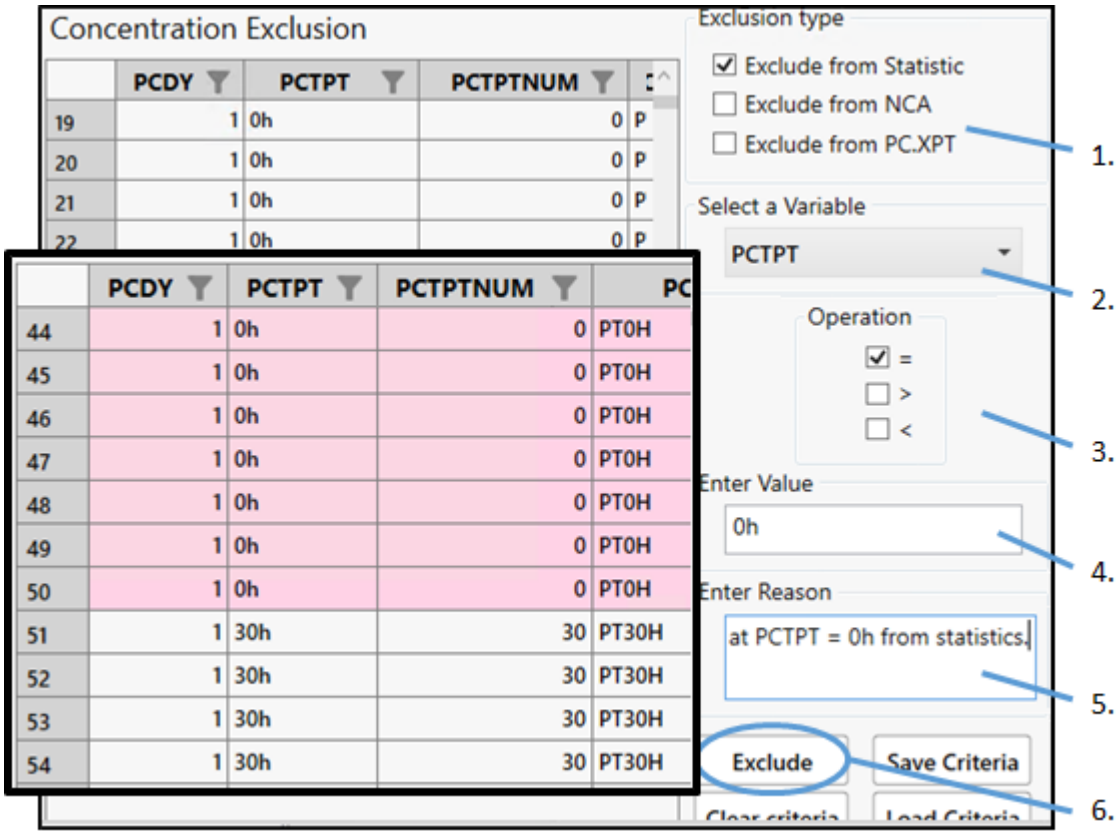
Dosing and concentration information can be merged by mapping the appropriate variables in the previous step, by entering values directly in the table, or by loading an `EX.xpt` file. For this example, we will enter our data directly.



1. Leave the **Build Internal Worksheet** option selected.
2. Locate the **Dose Amount** column in the Dosing Worksheet and enter `15` in the first cell.
3. In the **Dose Unit** column enter `mg/kg` in the first cell.
4. Select the two cells you entered information into and drag the lower right corner down to copy the values to all cells in the two columns.
5. Click **Next**.

Exclude data

Set up a filter to exclude data where PCTPT = 0h from the Statistics calculations.



1. Check the **Exclude from Statistics** box and clear other boxes at the top of the dialog.
2. From the **Select a Variable** pulldown, scroll down the list and choose **PCTPT**.
3. Check the box for **=** under **Operation**.
4. In the **Enter Value** field, type `0h`.
5. Type the following in the **Enter Reason** field:
   `Exclude data at PCTPT = 0h from statistics.`
6. Click **Exclude**.

   Rows that meet the criteria will be shaded pink to indicate that they are marked for exclusion.

Define a time deviation rule

In this example, we want to identify any data whose sample time deviation is either:

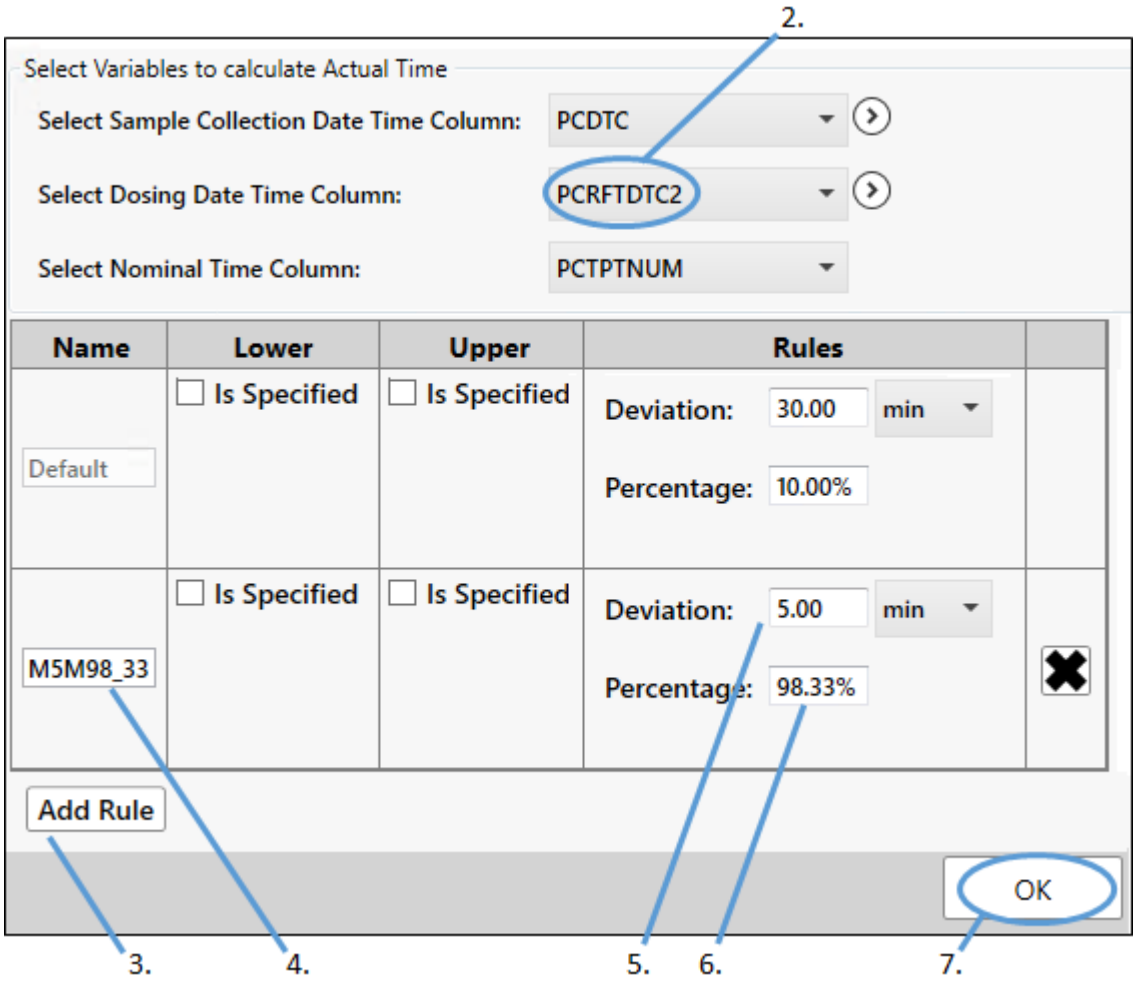
5 minutes or more
Or
98.33% or more of the time deviation

1. Click **Time Deviation Rules** at the bottom of the page.
2. From the **Select Dosing Data Time Column** menu, select **PCRFTDTC2**.
3. In the Rules column, click **Add Rule** near the bottom.
4. In the newly added row, enter `M5M98_33` as the **Name**.
5. In the Rules column, change the **Deviation** value to `5`.
6. In the Rules column, change the **Percentage** value to `98.33%`.

7. Click **OK**.

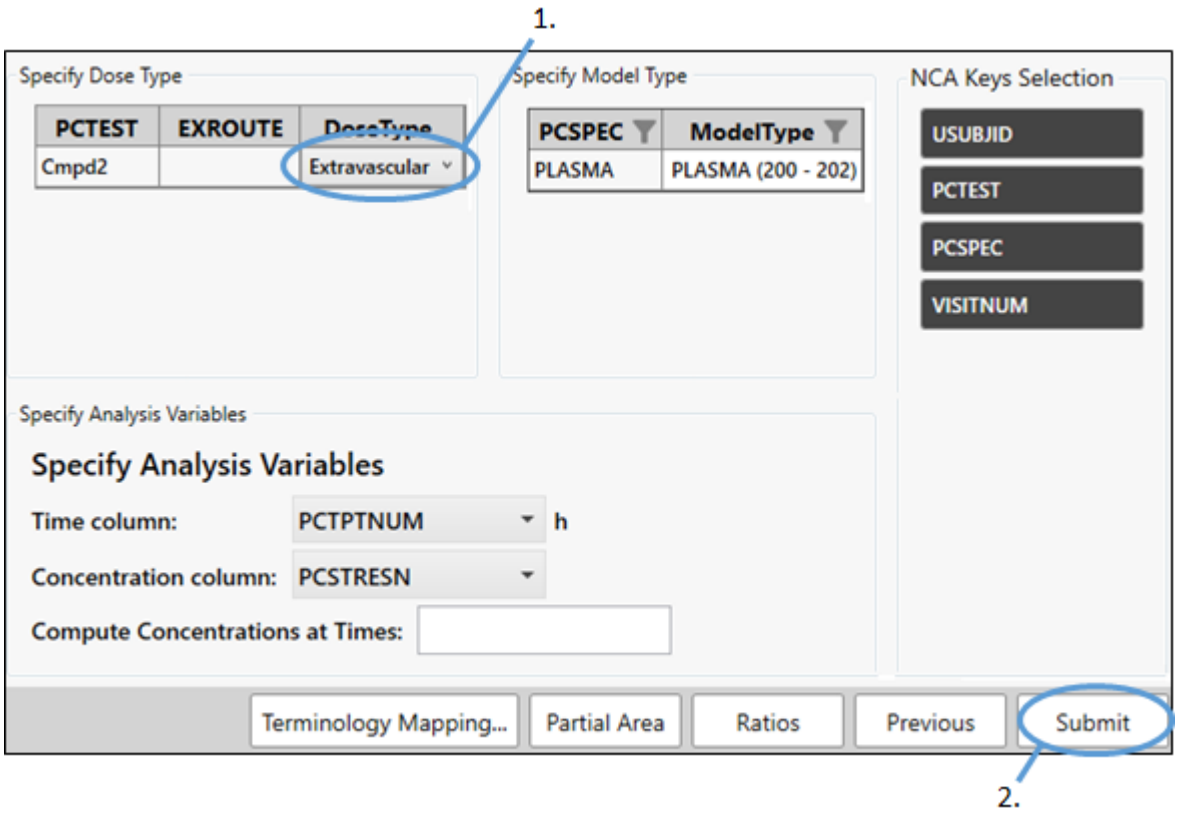
In the Data Exclusion table, scroll to the last few columns. The Time Deviation Rule computes values and appends columns for ActualTime, AnalysisEndTime, DeviationPK, PercentDeviation, and DeviationRuleApplied.

Scroll down the rows of data to find the data flagged in the DeviationRuleApplied column.



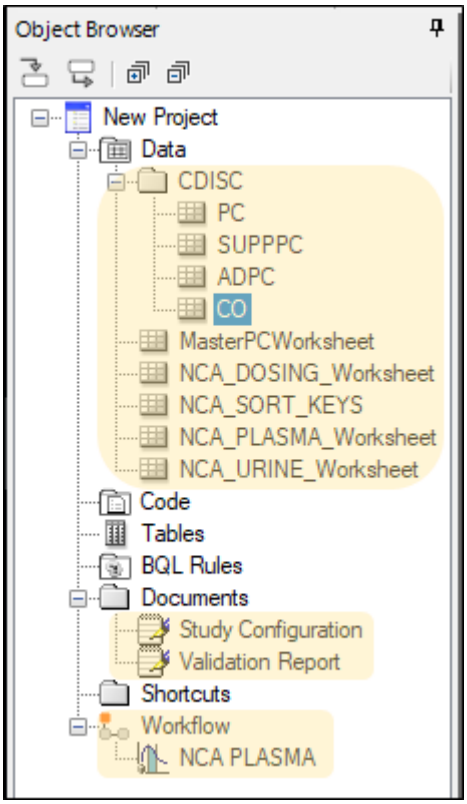
8. Click **Next**.

Finish setting up NCA



1. Select **Extravascular** from the **Dose Type** pulldown.
2. Click **Submit**.

The PC domain is complete and a Phoenix project is automatically created, with a workflow that has an NCA object preconfigured according to specifications made in PK Submit.

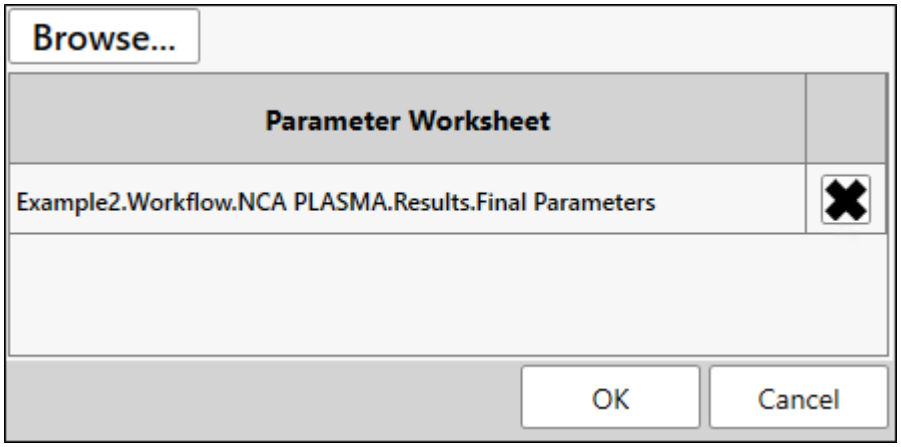


Create the PP domain

The PP domain can be generated from an NCA, typically the Final Parameters output worksheet. The NCA object set up by PK Submit is ready to execute. Unless you want to review the slope selector, you can simply run the NCA.

Specify the data for the PP domain

1. Rename the project as `Example2`.
2. Execute the NCA object.
3. Select **PK Submit > Create PP Domain** from the Phoenix menu.



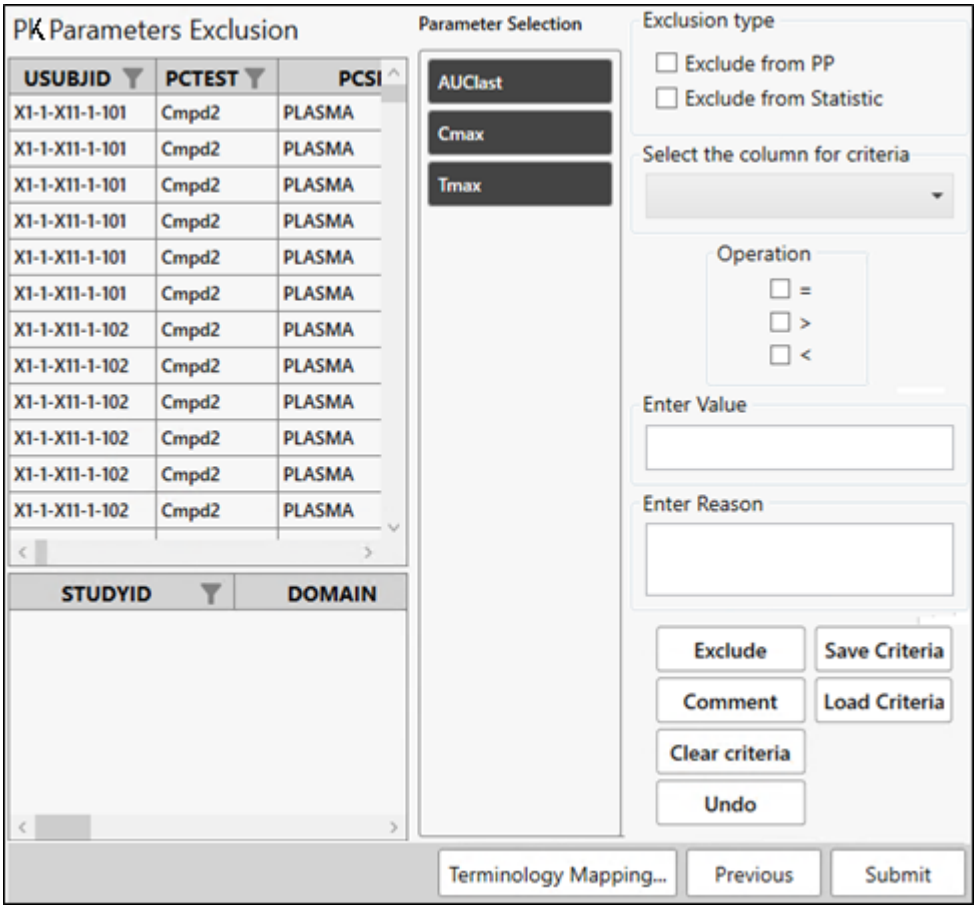
PK Submit will automatically select the Final Parameters result worksheet when there is an open project with an executed NCA object available (such as in this example). Otherwise, use the Browse button.

4. Click **OK**.

Select PK parameters

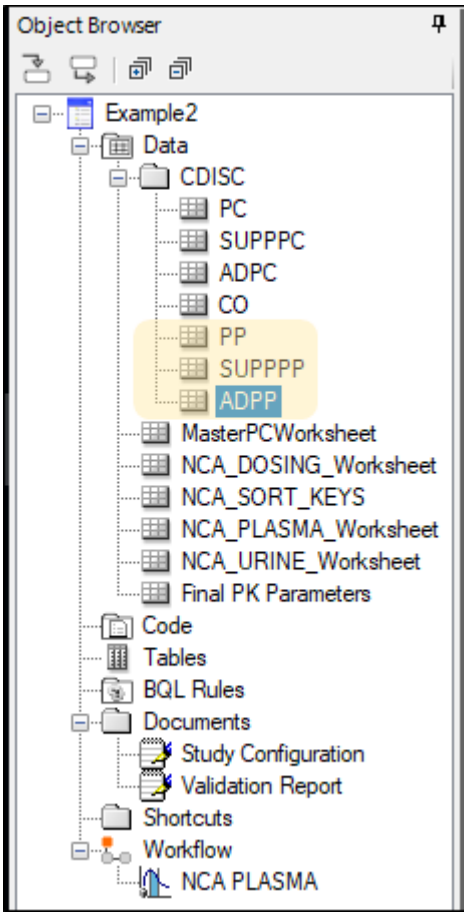
1. For this example, we will keep the default list of Selected PK Parameters and click **Next**.

Exclude parameters



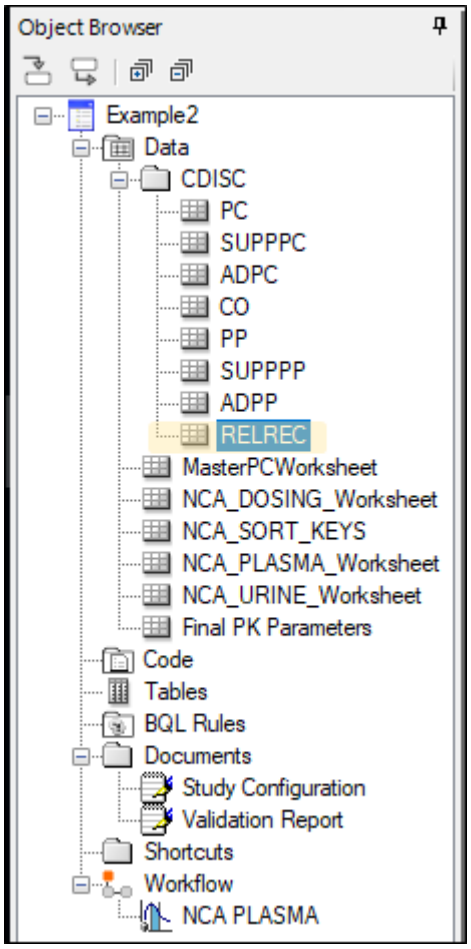
1. In the *PK Parameter Exclusion* page, click **Submit**.

   The PP domain is created.



Create RELREC domain

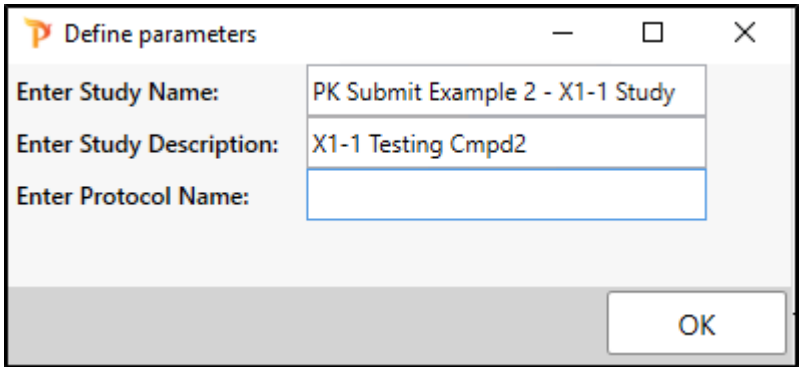
1. Select **PK Submit > Create RELREC and POOLDEF Domains** from the Phoenix menu.



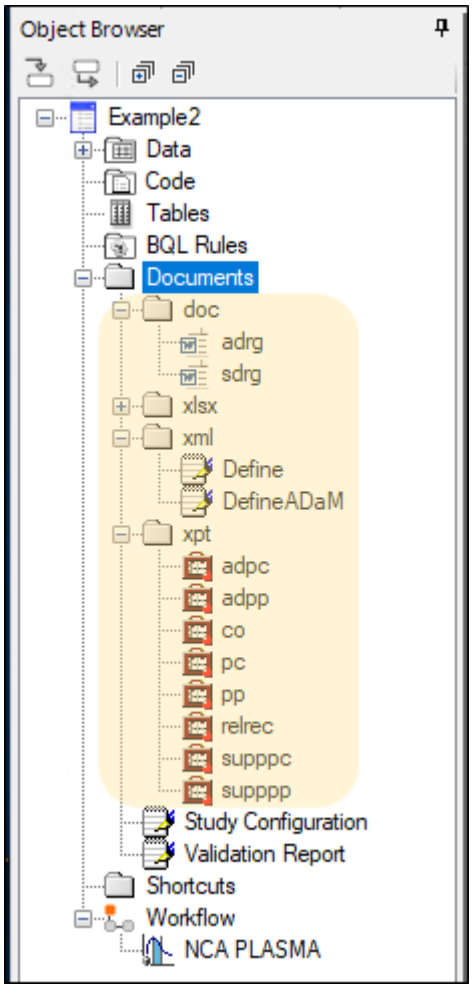
Since this was not a sparse study, no POOLDEF domain is generated.

Create files required for submission

1. Select **PK Submit > Create Submission Files** from the Phoenix menu.



2. Enter `PK Submit Example 2 - X1-1 Study` as the **Study Name**.
3. Enter `X1-1 Testing Cmpd2` as the **Study Description**.
4. Leave the **Protocol Name** blank.
5. Click **OK**.



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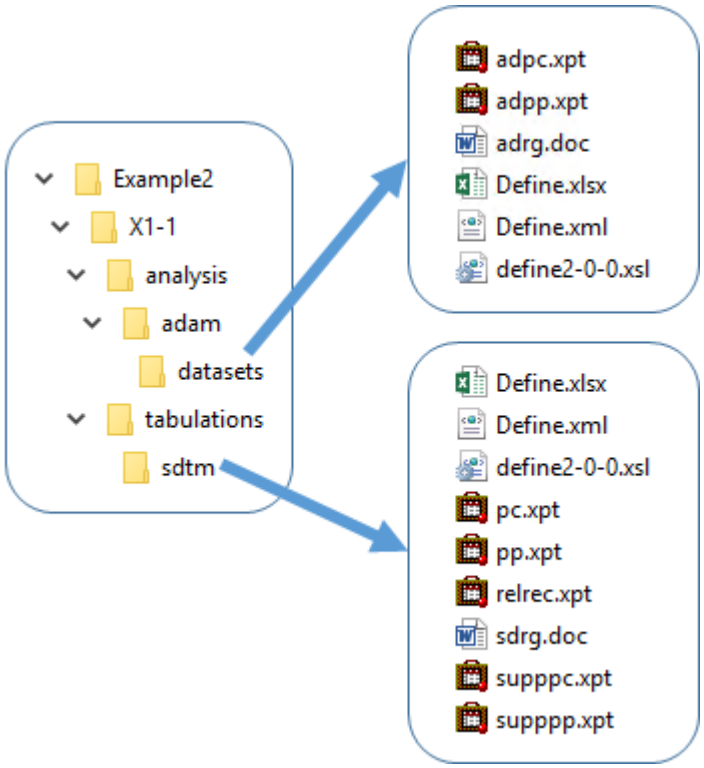
The `Define.xlsx` file is created and stored in the **Documents > xlsx** subfolder. This Excel-formatted file contains all of the information you find in the `Define.xml` file for the study in the **Documents > xml** subfolder.

Export submission files

1. Select **PK Submit > Export Submission Files** from the Phoenix menu.
2. In the file browser, select the location in which to save the files and click **OK**.
   In the following image, a folder named Example2 was selected.



The study information is ready for electronic submission and the process is complete.