

Pharsight® Phoenix® 1.4

Product Notification

Document Number: PHX029

Product Notification Date: 30-April-2015

Contents

Notification of Available Patch	1
LinMix Fixed Defect (affects Phoenix WinNonlin 6.4):	2
Custom Import Fixed Defect (affects Phoenix Connect 1.4):	2
Phoenix Model Object New Features (affect Phoenix WinNonlin 6.4 and Phoenix NLME 1.3):	3
Phoenix Model Object Fixed Defects (affect Phoenix WinNonlin 6.4 and Phoenix NLME 1.3):	5
Phoenix QT+ Fixed Defects (affect Phoenix QT+ 1.1):	11
To Download Patch PHX029:	12
To Confirm Patch PHX029 was Applied to Phoenix 1.4:	15
Pharsight® Customer Support	16

Notification of Available Patch

Defects have been identified since the release of Phoenix® 1.4 which affect Phoenix WinNonlin, Phoenix NLME, Phoenix Connect, and Phoenix QT+ users. A patch (Patch PHX029) is available from the Support website to correct these issues. Phoenix WinNonlin users need to apply this patch only if the Phoenix Model Object (i.e., Naïve Pool engine for PK/PD modeling) and/or the Bioequivalence Wizard Object are used. All Phoenix NLME, Phoenix Connect, and Phoenix QT+ users should apply this patch.

Phoenix® 1.4 - Product Notification

Both the 32-bit and 64-bit Phoenix executables will be updated when this patch is applied.

Notes: Phoenix Connect users who use the CDISC functionality should also review **Product Notification PHX030** and install the related patch to CDISC-related defects.

Phoenix WinNonlin Validation Suite 4.0 (for use in validating Phoenix WinNonlin 6.4, part of Phoenix 1.4) customers should refer to Product Notification PHXWNLVS014 for details on testing the functionality affected by this PHX029 patch.

The following defects are fixed and the following new functionalities are implemented in the patch related to this Product Notification PHX029:

LinMix Fixed Defect (affects Phoenix WinNonlin 6.4):

LinMix Estimates and Contrasts could be incorrect when levels contained both numbers and text (QC 14808, 14949): In Phoenix 1.4, if the variable used for the Estimate or Contrast had levels that contained both numbers and text, the Estimates/Contrast output could be incorrect due to erroneous sorting. In the Estimates and Contrast grid where the user enters his coefficients, the sorting is numerical, so "40 NA" comes before "110 NA". The error also occurs when the text comes before the number, as in "NA 40" and "NA 110". This is inconsistent with the sorting done during processing which is alphabetical, so "110 NA" comes before "40 NA". This defect is corrected by Patch PHX029 in that alphanumeric sorting is now used in the Estimates and Contrast grid. With Patch PHX029 installed, the Estimates and Contrast grid will be reordered if needed upon loading existing projects.

Custom Import Fixed Defect (affects Phoenix Connect 1.4):

Result Filters: Import did not handle .dat files properly (QC 14693): The Phoenix Connect NONMEM, PsN, R, SAS, and S-PLUS plug-ins have a Result Filters tab that allows the user to define filters that determine whether files of a certain name or size are returned to Phoenix as a shortcut, a binary file, a complete copy, or not returned at all. On the "Result Filter" tab for the third-party plug-ins (NONMEM, PsN, R, SAS, and S-PLUS), if the "File Pattern" matches .dat files and the "Import Format" is set to "Import", the .dat files were imported incorrectly, with all data in a single column. This defect is corrected by Patch PHX029 by changing the column delimiter to [space] for .dat files.

Phoenix Model Object New Features (affect Phoenix WinNonlin 6.4 and Phoenix NLME 1.3):

When "Infusions possible?" is checked, the tool now accepts rate OR dose and duration (QC 8261): In Patch PHX029, this improvement has only been included at the engine level. To use this feature, the user must go to the Model Text tab and use the User-Provided Extra Column Definition Text to specify which columns in the dataset to use for A1 and Duration. For example, if you want to map the "dose" column to A1 and "InfTime" column to duration, you would specify the following:

dose(A1<-"dose", duration = "InfTime")

Note that a command-line user can also use the dose and duration by writing the statement as above.

Standard errors of predicted values are now included on Residuals output for Naive Pooled model fits (QC 11956): After applying the PHX029 Patch, the output results from fitting models using the Naive Pooled engine will display standard errors of the model prediction at each time point (and each subject, if there are multiple subjects). The standard errors are displayed in the residual worksheet results in a column labelled 'PRELSE'. Because the output structure is shared among all the Phoenix Model methods, this column will also appear but will be blank when using other engines (e.g., FOCE).

Usability has been improved for ADDL and SS variables (QC 14147): Data specification of steady state conditions have been enhanced and improved. These changes include:

- Capability to specify different SS and ADDL dosing regimens at different times within the same patient.
- Automatic computation of the overall cycle length.
- Capability of the SS cycle to contain up to 10 different formulations superimposed.
- Capability to combine SS and ADDL, with covariate setting.
- Better alignment of the definitions of ADDL and SS with other tools (e.g., NONMEM).

Detailed Explanation of Changes:

Steady-state dosing can be specified.

Consider this input data file:

id	time	SSOffset	A1	Aa	SS	II
1	0		100	30	1	8
1	0	3	50	60	2	8

Phoenix® 1.4 - Product Notification

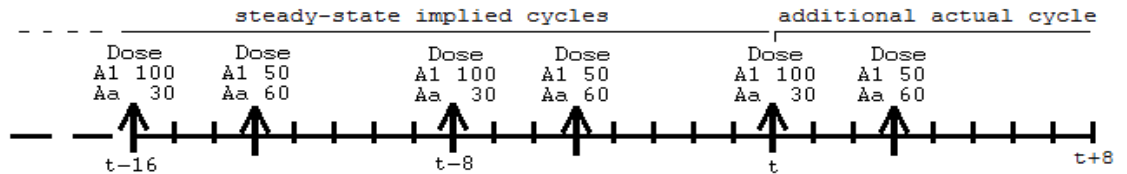
The column definition text file contains these lines

```
sscol(SS)
iicol(II)
ssoffcol(SSOffset)
```

where sscol(SS) indicates that there is a column named SS (meaning steady-state), and iicol(II) indicates that there is a column named II (meaning interdose interval). The SS column contains values 1 or 2 (or nothing). Note: rows in which SS is 2 can only follow rows in which SS is 1 or 2.

When the first row is encountered, at time 0, the model will undergo a cycle of II time units (in this case 8), where each iteration of the cycle consists of a dose of 100 to A1, and a dose of 30 to Aa, followed by 8 hours until the next repetition. This cycle is conceptually repeated sufficient times to bring the model to steady state, ending at time 0, because 0 is the time on the row. Then, at that time, the doses are repeated one more time.

Multiple cycles can be superimposed, as shown by the second row, in which SS is 2, indicating an 8 time-unit cycle with a dose of 50 to A1 and 60 to Aa. However, the doses are not given at time 0. They start at time 3, because there is a datum 3 in the SSOffset column. So the cycle looks like this:



Up to nine SS=2 rows can follow an SS=1 row. In addition, the interdose interval (II) values do not all have to be the same. However, the least common multiple of the interdose intervals must not be more than ten times the longest one. This prevents combinations of interdose intervals like 24 and 23 (for which the least common multiple would be 552 time units).

Additional doses can be specified by the following:

id	time	A1	Aa	II	ADDL
1	0	100	30	8	10
1	3	50	60	8	10

The column definition text file contains these lines

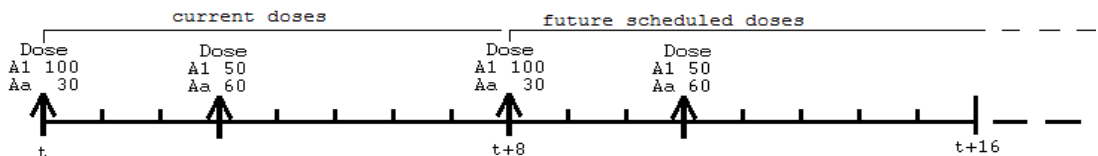
```
addlcol(ADDL)
iicol(II)
```

where addlcol(ADDL) indicates that there is a column named ADDL (meaning additional), and iicol(II) indicates that there is a column named II (meaning interdose interval).

When the first row is encountered, at time 0, first the doses into A1 of 100 and Aa of 30 are performed, and then 10 more of those doses are scheduled into the future, at 8 time-unit intervals, because ADDL = 10 and II = 8.

Then when the second row is encountered at time 3, first the doses into A1 of 50 and Aa of 60 are performed, and then 10 more of those doses are scheduled into the future, at 8 time-unit intervals.

Together the ADDL doses look like this:



Combined Steady-state and Additional Dosing

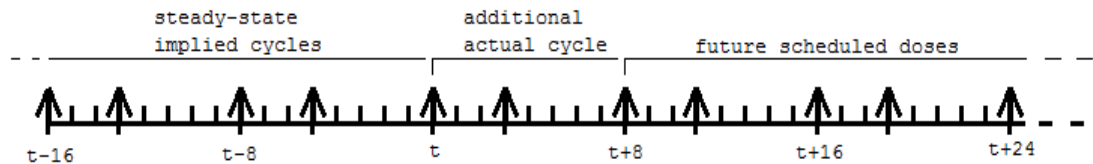
Phoenix® 1.4 - Product Notification

SS and ADDL dosing may be combined, as in the following:

id	time	SSOffset	A1	Aa	SS	II	ADDL
1	0		100	30	1	8	10
1	0	3	50	60	2	8	10

where the column definitions are:

sscol(SS)
iicol(II)
ssoffset(SSOffset)
addlcol(ADDL)



Covariates may be included on SS or ADDL lines
But observations will be ignored.

Command-line argument /modeltext has been implemented to inform what is the name of the model text file, so that it can be included in dmp.txt (QC 14565).

Plugin.DME version information now appears in the Settings file (QC 14863): In addition to the Phoenix version build number, the Settings file for the Phoenix Model Object now includes the version of the DME plug-in, so that it is clear that the Phoenix Model Object with patch PHX029 was executed.

Phoenix Model Object Fixed Defects (affect Phoenix WinNonlin 6.4 and Phoenix NLME 1.3):

Phoenix model displayed as out-of-date upon execution (QC 14266, 14421): The use of the **Freeze PK** option in an individual model could result, after a model was run, in the Phoenix model object remaining in an out-of-date status.

Freezing PK parameters that had random effects prior to checking Sequential PK/PD could lead to a state where Sequential PK/PD could not be executed (QC 14278): In Phoenix 1.4, random effects on frozen fixed effects were allowed. If the model was also a sequential PK/PD model and if the “Sequential PK/PD?” checkbox was unselected and re-selected, the following problems were encountered:

- The Random Effects mapping grid would no longer allow the random effect parameters to be mapped.
- The covariate statement from the Model Text would be deleted.

Phoenix® 1.4 - Product Notification

- An error about undefined random effects would be encountered upon execution.

To fix these issues in the PHX029 patch, random effects on frozen fixed effects are no longer allowed in the model text from Built-in or Graphical models. This change was made because the mean of any random effect will move to compensate for any misspecification of its corresponding fixed effect, which essentially unfreezes the fixed effect. If the user insists on having random effects on a frozen fixed effect, this can be done in a textual model.

If a Built-in or Graphical model created with a previous version, such as Phoenix 1.4, had random effects on frozen fixed effects, the random effect will be automatically removed from the model text when the project is loaded in Phoenix 1.4 with the PHX029 patch applied. Consequently, projects may run differently in Phoenix 1.4 vs Phoenix 1.4 with the PHX029 patch.

This new behavior may cause confusion because the UI may appear as if random effects on fixed effects are supported. For example, if a user selects random effects for PK parameters first, then freezes the corresponding fixed effects, it will appear in the UI as if random effects on fixed effects are allowed, since both checkboxes are selected, but the model text will not have these random effects.

Further confusion may also arise because the UI allows “Sequential PK/PD?” to be selected without having any random effects in the model. In this case, the model will execute without error, even though it is not a true sequential PK/PD model, because random effects from the PK model are not being used. The “Ran” checkboxes for the corresponding fixed effects must be selected prior to selecting the “Sequential PK/PD?” checkbox in order to run as a true sequential PK/PD model.

If a user wants to run a sequential PK/PD model and, due to loading an existing PHX 1.4 project or due to freezing fixed effects prior to checking “Sequential PK/PD?”, the UI is in a state where “Sequential PK/PD” is selected, and the “Freeze PK?” checkbox or the “Freeze” checkboxes for the fixed effects are selected and disabled (thereby removing the random effects from the model text), the user must first unselect “Sequential PK/PD”, unselect the “Freeze PK?” checkbox or the “Freeze” checkboxes for the fixed effects, select the “Ran” checkboxes for the corresponding fixed effects (if not already selected), then re-select “Sequential PK/PD?” and map the random effects on the Random Effects mapping panel on the Setup tab.

Error in application stating that access to path is denied has been corrected (QC 14439/CRM 147624): In Phoenix 1.4, executing a Phoenix Model object

would occasionally throw an error indicating that access to a path was denied. The user was often able to re-execute successfully after a few minutes.

Error Message "Execution failed: Drag/drop registration did not succeed" has been corrected (QC 14542): In Phoenix 1.4, if a Phoenix Text Model was flagged as out-of-date (upgraded) on loading a project from a prior Phoenix version, then the text was updated during execution. If the user had viewed the text model and navigated away, an error occurred on execution because the text of the model in the viewing window was being updated in a background thread, which caused the error "Execution failed: Drag/drop registration did not succeed".

Simulation (Add Sim Table) now works with multi-level, count and time to event data (QC 14546): Users can model observations as multiple categories (0,1,2, up to 10) with various link functions, time to event (censoring, interval censoring), or counts (like the number of seizures over a period of time). However, when performing simulations with models with these types of responses, no output was being produced in the simulation tables in Phoenix 1.4. This defect is corrected by Patch PHX029 so that simulation tables can now be used with any design (dosage, times) and any type of observation. Design conditions do not need to be the same as the observed data. The user can use the input data as a design template and then the simulated observations will be in allpcdata.csv. The user can also specify a separate simulation table that outputs simulated observation over a specified time grid. In 'Sim/Pred Check' mode, data is generated for all observation types except time-to-event. The VPC plots that are created automatically are only really meaningful for Gaussian observations. The user is advised to post-process the generated tables to produce meaningful diagnostics, e.g., observed versus predicted probabilities of a logistic or multiple categories model.

The 'dobefore' and 'doafter' statements worked only with observed data and not at the user defined simulated sampling times (QC 14547): In Phoenix 1.4, Pharsight Modeling Language (PML) statements 'dobefore' and 'doafter' did not trigger at user-defined simulation sampling times in simulation tables, i.e., rows were not created at these sampling times.

Event statements in simulation tables caused Phoenix to become unresponsive (QC 14555): When using Sim./Pred. Check run mode with a model with an event statement in Phoenix 1.4, the Status Window would open but there would be no further processing shown. The "Stop Execution" button could be used to regain control, but there would not be any results. In Phoenix 1.4 with Patch PHX029 applied, the run successfully completes.

The system appeared to halt if there was a while(1) statement when performing a simulation (QC 14558): In Phoenix 1.4, while(1) statements

Phoenix® 1.4 - Product Notification

worked during data fitting because a subject would stop as soon as it ran out of data points, but it would run indefinitely during a simulation because of the unknown amount of time. This defect is corrected by Patch PHX029 so that simulations will now complete for models having the ‘while(1)’ statement.

Initial Estimates plot did not work for sequential PK/PD models (QC 14567):

There was a new option in Phoenix 1.4 to perform PK/PD Sequential modeling where a PK portion of the model is frozen and the PD portion is fit. However, to obtain the same plasma concentration prediction as from an individual PK model fit, the PK random effects were converted into covariates and then the PD portion of the model was evaluated. When this option was selected, the initial Estimates live-plot window did not work for sequential models.

‘Variable Undefined’ Error when using Sequential PK/PD and "Freeze PK?" checkboxes on Structure tab has been corrected (QC 14575):

In Phoenix 1.4, if "Freeze PK?" was checked, it still allowed random effects to appear in the PK structural parameter definition. This caused an invalid ‘Variable undefined’ error, and the model did not run. This defect is corrected by Patch PHX029, and built-in and graphical models no longer allow frozen fixed effects to have associated random effects in the model text. See QC 14278 above for a similar defect regarding individual “Freeze” checkboxes and details on how existing Phoenix 1.4 projects can be affected.

Model failure due to multiple definitions of variables has been corrected (QC 14576):

In Phoenix 1.4, the program did not allow having structural parameters and fixed effects of the same name. If this occurred, a ‘Variable multiple definition’ error appeared, and the user was required to give separate names to the fixed effects to distinguish them from the structural parameters. This was not the case in Phoenix 1.3 and thus, older models could fail in Phoenix 1.4 when they previously passed. This defect is corrected by Patch PHX029, so that now the structural parameters can be named the same as the fixed effects, provided the structural parameter has no random effect or covariate effects (as in the case of an individual model).

PK/Indirect could get into a state where the stderr results for an epsilon were associated with the wrong observation (QC 14577):

In the infrequent situation where a model has more than one observe statement, such as EObs and CObs, and one of the observe statements has no mapped data, it is normal for the standard error step to fail. However, if the Naive Pool method is used, and standard error is requested, it has another way to estimate the standard errors by using the variance inflation factors. When this occurred in Phoenix 1.4, it was possible for the standard error of epsilon to be associated with the wrong observation.

Models that ran in PHX 1.3 stopped in PHX 1.4 after about 100 iterations with "NLME7.exe has stopped working" has been corrected (QC 14580/CRM 149397): In Phoenix 1.4, if a model contained more than a five random effects and requested standard errors, it would crash after generating standard errors. This was the result of a memory allocation problem in reading the variance-covariance matrix.

The static BQL option within the Phoenix Model has been corrected (QC 14581): In Phoenix 1.4, the concept of a "static bql" was introduced. For example, if an observe statement contained ", bql=0.1", and the mapping for that observation did not contain a BQL column, it meant that any observed value below 0.1 such as 0.09 was treated as simply below 0.1. However, observations that were exactly as the number entered (e.g., 0.1) were treated as non-BQL for non-time-based models such as Emax.

Incorrect simulation results when there were frozen fixed effects has been corrected (QC 14595): In Phoenix 1.4, in individual simulations, if some fixed effects were frozen, some fixed effects were initialized to the wrong values and incorrect results were presented in Ind. Simulation plot and worksheet and in Rawsimout. For population models, the simulation would not run in particular cases where PK was unfrozen in the structural model, but the PK fixed effects were individually frozen by themselves.

Several defects with the dmp.txt file have been corrected: In Phoenix 1.4, additional fields were added to the R-friendly dmp.txt file, including covariances, idtable (containing subject-specific data), and residuals. The following defects, affecting only NLME users, existed in the dmp.txt file in Phoenix 1.4, but are corrected by Patch PHX029: .

- **The dmp.txtfile did not contain residuals if stderr failed (QC 14657):** However, if the standard error step was not requested, or it was requested but failed, the idtable and residuals were not output to the file.
- **In dmp.txt file, in idTable, frozen fixed effects caused etas to be misaligned (QC 14882):** If a model contained frozen fixed effects, the eta values in the idTable were misaligned and did not match the random effects.
- **Incorrect Log-Likelihood information in dmp.txt file (QC 14892):** In the dmp.txt file, in the LL per subject, when MPI was used, valid numbers only appeared for subjects processed on process 0. The issue occurred with engines FO, FOCE-EB, FOCE-ELS, and IT2S with MPI and with QRPEN with and without MPI. Individual subject log likelihoods were not computed for Naive Pooled. This defect is corrected by Patch PHX029 and log-likelihood (LL) values are now printed for every individual in the dmp.txt.

Frozen epsilon caused mismatch of output in VCV matrix (QC 14716): In Phoenix 1.4, if a Phoenix Model Object had epsilon frozen, then the Variance-Covariance matrix in the output was not taking into account the frozen epsilons and the matrix elements were in incorrect positions in the matrix.

Theta output worksheet did not contain any standard errors even though Fischer Score was requested and was successful (QC 14732): In Phoenix 1.4, when an NLME user was fitting a population model and requesting the Fischer Score standard error, it was possible that the Hessian standard errors failed but the Fischer Score succeeded. However, in this case the Fischer Score standard errors were printed in the supportive output 'std_error.asc', but were not displayed in the Theta output worksheet which only printed blank standard errors.

Phoenix Model Object: User-Provided Extra Column Definition was broken for Dosing (QC 14845): In Phoenix 1.4, user-provided extra column definition text for the Dosing worksheet was not being included in the column definition text.

Model failed when using Date and Time option (QC 14865): In Phoenix 1.4, when an NLME user was fitting population models, the user had the choice to use date and time instead of numerical relative time. When this option was used, models failed to execute.

Freezing a non-diagonal Omega block generated an error (QC 14900): In Phoenix 1.4, when an NLME user was fitting a population model with a full block matrix for the random effects with the option to freeze the full block, the system produced a code-generation error ("Model execution failed or cancelled") and no output was created. This error did not occur when freezing a diagonal omega block.

Stratified bootstrap did not work for data with Reset column (QC 14925): In Phoenix 1.4, when an NLME user was running stratified bootstrap for data including Reset column (i.e., the input data contains resets), the Phoenix Model Object failed the resampling.

Epsilons were not generated randomly in stochastic simulation (QC 14927): In Phoenix 1.4 when generating simulation tables with a model that did not have random effects, the first simulated observation of every odd replicate was a repetition, not random. In Phoenix 1.4 with Patch PHX029 applied, the model will simulate unique random values for all replicates.

When Fisher Score was used as Method for Stderr, Core Output showed variance instead of standard deviation (QC 14940): In Phoenix 1.4, when an

Phoenix® 1.4 - Product Notification

NLME user was fitting a population model and requesting the Standard Error method be Fischer Score, the system was displaying the variance instead of standard deviation in the results Core Output.

Dispersion formula in the Count statement has been corrected for the NLME user (QC 14971): In Phoenix 1.4, the dispersion formula in the Count statement was $\text{Var} = \text{mean} * (1 + \alpha^{\text{power}})$. Patch PHX029 corrects this to $\text{Var} = \text{mean} * (1 + \text{mean} * \alpha^{\text{power}})$.

Error in rnegbin function for sampling from a negative binomial has been corrected (QC 14980): Simulation of observations from the count statement was not performed in Phoenix 1.4, and the rnegbin function for sampling from the count statement in the presence of overdispersion was incorrect.

Failure of standard error computation is now shown as blank (QC 14983): In Phoenix 1.4, the Theta outputs (Theta, Theta Correlation, Theta Covariance, and VarCovar worksheets) were displaying zeroes for Stderr if the standard error computation failed. With Patch PHX029, this has been updated to instead display blank cells to clarify that the computation failed. Because CV% and the confidence interval depend on Stderr, they will also now be blank in the Theta output. This new format is also reflected in the dmp.txt file that can be easily uploaded into R. However, with this new format, R scripts should account for missing variance-covariance values.

Phoenix QT+ Fixed Defects (affect Phoenix QT+ 1.1):

QT Transformation Object - Delta Delta values were incorrect when using time matched correction and crossover placebo correction together (QC 14424): In Phoenix 1.4, if both a baseline time matched correction and a crossover placebo correction were used together, the user could get null delta delta values, unless the order of the data happened to be a certain way.

Heart Rate Correction (HRC) - Backward compatibility was broken for HRC objects between QT+ 1.0 and QT+ 1.1 (QC 14436): On re-execution of a Heart Rate Correction object that was created in Phoenix 1.3 using Phoenix QT+ 1.0 and creating "Mean Sum of Squares" output, an "Object reference not set to an instance of an object." error was generated in Phoenix 1.4 (QT+ 1.1).

The CQTc module was updated due to NLME changes in patch PHX029 (QC 14786): The Concentration-QTc module utilizes the NLME engine for model fitting. Due to the implementation of QC 11956 (see page 3 above), the CQTc module was updated to work properly when the patch is applied.

Phoenix® 1.4 - Product Notification

To Download Patch PHX029:

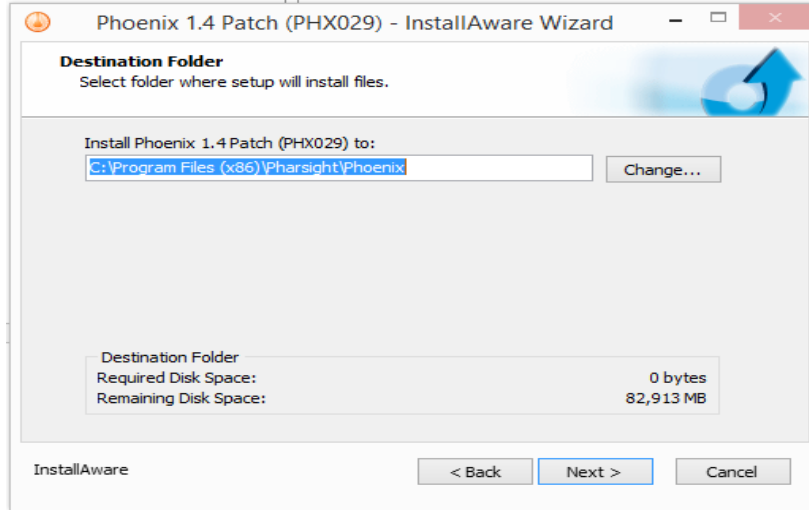
Patch PHX029: To apply patch PHX029, Phoenix 1.4 must already be installed on the machine, then follow these steps:

1. Close Phoenix, if it is currently running.
2. Open a web browser, and login to www.certara.com/support . If you don't already have a login, you can create one by providing your contact information.
3. Navigate to the Product Downloads area, and select the Phoenix 1.4 Release Version.
4. Download the zip file named "Phoenix_1.4_product_notification.zip".
5. After the download is complete, extract the zip file using right-click → Extract All.
6. Execute PHX029_PHX1.4_Patch.exe. The following screen will appear. Click the 'Next >' button.



Phoenix® 1.4 - Product Notification

7. If necessary, modify the destination folder where Phoenix 1.4 is installed and click the 'Next >' button.

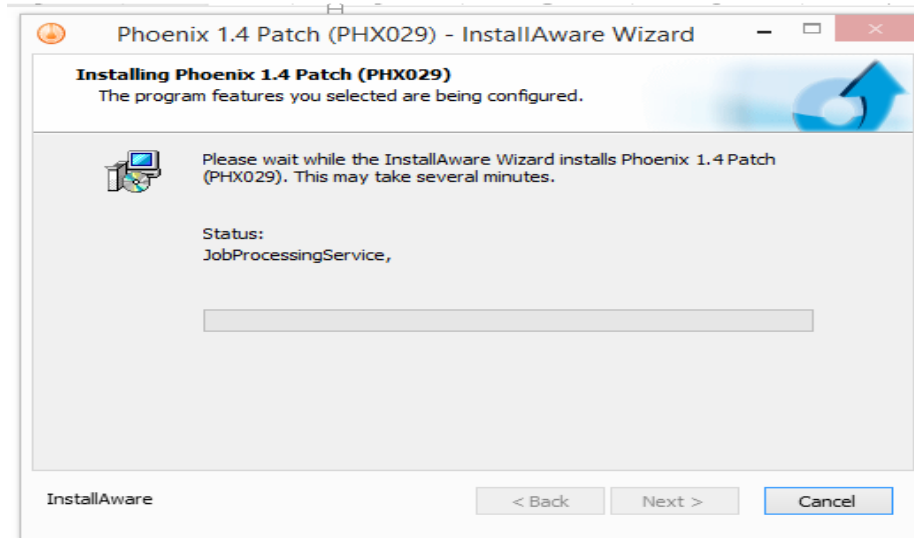


8. Click the 'Next >' button.



Phoenix® 1.4 - Product Notification

9. Wait while the patch installer installs the updated files.



10. Click the 'Finish' button.

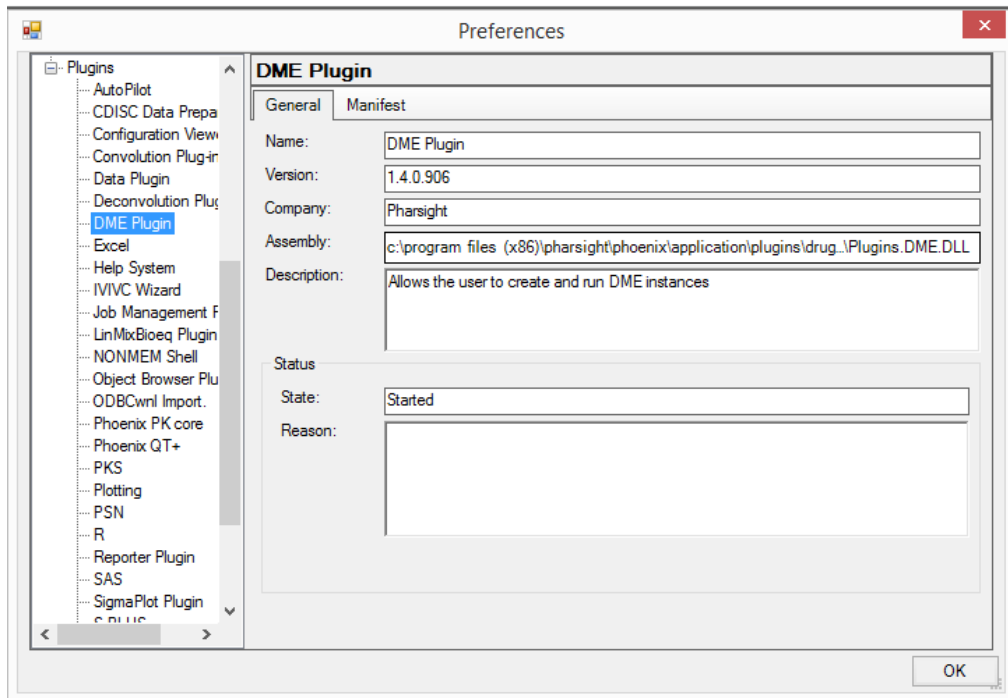


Phoenix® 1.4 - Product Notification

To Confirm Patch PHX029 was Applied to Phoenix 1.4:

To confirm that this patch has been applied:

- Launch the Phoenix application
- Go to Edit>Preferences
- Expand the Plugins section
- Click on DME plugin
- Confirm the version is 1.4.0.906 (prior to installation of the patch, the version was 1.4.0.0)



Pharsight® Customer Support

Technical support

Consult the product documentation to address questions. If further assistance is needed, contact Pharsight technical support through e-mail, our web site, phone, fax, or mail.

E-mail: pharsight.support@certara.com (fastest response time)

Web: www.certara.com/support

Phone: 1-919-852-4620

Fax: 1-919-859-6871

Mail: Pharsight Corporation
5520 Dillard Dr., Suite 260
Cary, North Carolina 27518

For the most efficient service, e-mail a complete description of the problem, including copies of the input data, output files, and any screen shots that show the reported error.

Customer feedback

Please submit requests for product enhancements and defect corrections through e-mail, fax, or through Pharsight's customer support web site:

E-mail: pharsight.support@certara.com

Web: www.certara.com/support

Fax: 1-919-859-6871

User Forum

Get tips and discuss Pharsight products with other users at www.certara.com/forums.