MW\Pharm version 3.60 (date 30/06/2004)

(Update of version 3.50)

Instructions:

Unzip the file MW360UPD.ZIP in the directory containing MW\Pharm (usually C:\APO, which is the default directory).
If you want to keep the original version 3.50, copy the following files to a safe place: APO2PR.EXE, APO2PR.ENG, APO2PR.NED, APO2PR.DEU and APO.BAT.
Any other file is unaffected by this update.

Extensions:

1.1. A new method for the calculation of creatinine clearance during simulation and fitting of a medication history has been added. The method used in earlier versions is the default method ('using formula'). The new method can be chosen in the option menu, calculation options, B,'Renal clearance calculation', changing from 'using formula' (original method) to 'exact'.
The 'exact' method simulates the creatinine level based on creatinine production (as derived from the equations by Cockcroft&Gault, Jelliffe I or II, according to the selected method), creatinine removal by extracorporeal clearance, and renal creatinine clearance. The latter is now calculated for each interval between creatinine measurements, assuming a linear increase or decrease between the time points of measurements.

1.2. The window providing information of the values in the graphs (activated by <F6> in both graphic screens) has been extended with concentration or amount (as selected in the options menu, calculation options) in the peripheral compartment and in total body. Also, units have been added for each value.

1.3. Medication history screen: one or more consecutive lines can be selected, copied, pasted and deleted by the following commands:
<Ctrl><DownArray> : select the line at the cursor position. The selected lines are highlighted. The selection is cleared by any other key.
<Ctrl>C : copy the selected lines.
<Ctrl>X : copy the selected lines, and delete.
<Ctrl>V : paste the copied lines at the cursor position (may be in a different medication history).

1.4. Extension of Bayesian fitting of the medication history with Bayesian and non-Bayesian parameters. In case of a Bayesian fitting, each parameter can be assigned a status:
- fixed: parameter is treated as a constant during fitting (in case of a population analysis the initial value is assigned to each subject);
- Bayesian: parameter is treated as a Bayesian variable, i.e. its value is compared to

the population mean in the Bayesian objective function (identical to ‘variable’ status in the versions up to 3.50);
- non-Bayesian (status not available in versions up to 3.50): parameter is not taken into account in the Bayesian objective function, but it is fitted as a ‘free’ parameter. This status can be applied to parameters that do not have typical properties for a population, e.g. time weighting parameter T½_weight (see 1.5), scaling factor gamma (see 1.6), or concentration at time zero (c0), or to parameters for which population mean and/or standard deviation are unknown (see also 3.9).

1.5. Extension of Bayesian fitting of the medication history with time-weighting factor. In case of changing patient parameters it may be preferred to give more weight to the more recent measurements. This can be performed by entering a value for T½_weight (unit: days), i.e. the ‘half-life’ of the relative weight of the measurements. The parameter can be treated as a constant value, or can be fitted either Bayesian or non-Bayesian (variable). Since T½_weight is a typical value for a patient under specific conditions, fitting as a non-Bayesian parameter is the default status for T½_weight. The parameter T½_weight can also be estimated in a population analysis.
The current value of T½_weight can be removed by entering 0 (i.e. no time weighting).

1.6. Extension of Bayesian fitting of the medication history with a scaling factor for the residual error (gamma). Weighting of the measurements is performed by taking into account the assay error pattern (polynomial function). This approach assumes that the residual error is solely due to assay errors, and that model misspecification, including changing patient characteristics, does not play a role. In practice, residual error is usually larger than the estimated assay error, thus invalidating this assumption. Assuming that the ratio between the residual error and the assay error is constant, this larger error can be accounted for by entering a value for this ratio, gamma. This factor gamma has typically a value between 1 (equal errors, and similar to the fitting if gamma is not entered, and to the fitting in earlier versions) and, say 4 (in case of a very precise assay and the large deviation of the model assumptions, e.g. due to changing patient condition). The parameter gamma can also be estimated in a population analysis.
The current value of gamma can be removed by entering 0 (i.e. no gamma factor, or gamma factor is 1).

1.7. Population analysis by the Bayesian Iterative two-stage procedure can also be performed taking into account the existing population set. The final result of the population analysis is a weighted average between the existing population set and the Bayesian population estimates obtained from the selected patients, using the number of patients as the weighting factor. Therefore this procedure can be applied only in cases where the number of patients from which the existing population parameter set was estimated, is known. Alternatively an arbitrary number can be assigned to the existing population set (e.g. equal to the number of patients in the patient selection), but this does not result in an objective final population parameter set, of course.
This approach is recommended in cases where the number of patients is too low to

allow a reliable population analysis. Of course the resulting population parameters are dependent on the existing population set. As a result, the method should be applied only in cases where the existing population set is sufficiently plausible.

1.8. A Monte Carlo simulation can be performed using a patient selection as a template (in version 3.50 the template was a single patient, and each patient in the Monte Carlo data set was identical with respect to patient characteristics, dosing and time of measurements). The generation of Monte Carlo data sets can be started from the KinPop menu by <F4>, after making of loading a patient selection.
See also separate instruction for this option.

1.9. KinPop: In case of a population analysis on a single Monte Carlo data set, the 'true value' of the population parameters (mean and standard deviations) and of the individual patients are shown to allow a judgement of the results of the Monte Carlo analysis.

1.10. Drug data screen: the unit 'nmol/l' can be chosen for concentrations.

1.11. Default height and weight for children: for children the default height and weight, as expected from age, are filled automatically in the appropriate fields if these fields have not been edited, i.e. if they contain the default values, as indicated by the dark green colour (edited values are shown in a light green value).
The default value are calculated from the following empirical equations:

Weight (kg) = 3.5 + Age * (7.84 + Age * (-1.87 + Age * (0.239 + Age * (-0.0125 + Age * 0.0002346))))

(minimum value 3.5 kg, maximum value 70 kg)

Height (cm) = 50 + 24 * Age ^ 0.575

(minimum value 50 cm, maximum value 175 cm)

(these equations were also used in version 3.50 and earlier to calculated LBM in case of body height lower than 152.4 cm (5 feet)).

1.12. Patient status screen: Default height and weight are shown on the screen within [ ], and can be selected by entering '0' for height or weight, respectively. This applies to the default value of 70 kg and 175 cm for adults, and the default values for children described under 1.11.

1.13. Limited Sampling Strategy: A new module to determine the optimal sampling times for the assessment of AUC from 1 to 4 measurements has been added. This module is described in a separate document.

1.14. Drug data screen: a new field has been added for storing text to the record, e.g. for a reference to the source of the drug data.

Corrections:

2.1. Saving and retrieving extreme body weight (>300kg) now handled correctly.

2.2. Date and time indicator along the X-axis in the graphics of the medication history has been improved (in earlier versions the indication was not correct in some cases).

2.3. Multiple extracorporeal clearance in the medication history is now handled correctly. In version 3.50 a second extracorporeal clearance was not always taken into account (this became apparent by the graph of the creatinine level, which should show a drop during each period of extracorporeal clearance).

2.4. Starting KinBes from the 'Kin... menu' is now possible. In earlier versions starting KinBes could fail.

2.5. KinFit performs now correct weighting using a polynomial function in cases where the unit of concentration is not the standard unit 'mg/l'.

2.6. Data sets made by Monte Carlo analysis can be given an 8-character name (in earlier versions an 8-character name was not recognised in KinPop; only names up to 5 characters were handled correctly).

2.7. Forms for printing can be edited within the program (in earlier versions the editor program EDIT.COM could not be found.

2.8. Graph of medication history: Confidence intervals are now shown correctly (in earlier versions the time axis was not correct if the total time of the axis exceeded that of the calculated profile).

2.9. Graph of medication history: Export of confidence intervals to an export file corrected. In earlier version the values for lower and upper values of the confidence interval were exported at time points that were not the same as for the concentration values.

2.10. Starting the program with data in a different directory is now enabled. The function added in version 3.50 (see note 1.1. to version 3.50) did not function properly. In addition, a subdirectory name can be used without a full path.

2.11. Drug data screen: If the molecular weight is changed when the unit of dose or concentration is in molar units, the conversion is performed correctly (In earlier versions the conversion could be erroneous, if the unit field was not changed). Note: Changing the molecular weight is not recommended since it affects all molar values (not the mg values!) related to dose or concentration, including the concentration measurements in the medication history (because these values are stored in the database in mg/l, irrespective of the selected unit).

2.12. KinPop works now properly with any number of parameters (in earlier

versions, more than 8 parameters could result in a runtime error, or an ‘insufficient memory’ message).

2.13. Printing is now possible when the program runs under Windows XP. In earlier versions the printing module ResPrint was not loaded under Windows XP (as can be checked in the Option menu, Print and screen options; see lower line, at right).

2.14. Export and import of patient and drug data records is now available under Windows XP. In version 3.50 this option did not work running under Windows XP.

2.15. Importing of patient data has been improved; in version 3.50 identical records were not recognised in case of mixed lower and upper case characters in patient name or patient number. The import is now case-insensitive.

2.16. Medication history: duration of infusion (Tinf) is now stored in the patient database in the usual precision. In version 3.50 and older values were rounded to multiples of 0.1 hour (in case of duration of infusion of 0.5 hour or less, rounded to zero, and interpreted as bolus administration).

2.17. Medication history: a medication history with a line containing a value for extracorporeal clearance but not for the duration (in column Tinf) is now stored and retrieved correctly. In version 3.50 and older this situation resulted in a disrupted patient record. Note that this situation is checked for by pressing <F10> to continue the process (only by pressing <F1> and saving the patient record this error could occur).

2.18. Medication history: in exceptional cases the calculation was retarded considerably, in Windows XP resulting in pausing the program and requiring a key stroke to continue; this situation could occur if the calculated plasma concentration was virtually but not exactly equal to zero. This anomaly has been corrected.

Other changes:

3.1. During simulation and fitting of a medication history with changing body weight, the actual LBM, LBMc, and BSA are now calculated at each time point (in earlier versions these parameters were calculated only at the time points of a weight observation, and interpolated between these time points). The difference with earlier versions is very small.

3.2. In the graph of the creatinine level (upper panel in the graph of the medication history) the creatinine level measurements are indicated by a small circle.

3.3. The fitting procedure of the medication history can be switched off by choosing as algorithm ‘no fitting’ (instead of Marquardt or Simplex). This allows, e.g., an evaluation of a particular set of parameter values.

3.4. The calculation of the confidence interval of the predicted concentration profile

after fitting of the medication history has been modified. The degrees of freedom (df) is now calculated as:

a) if all parameters are either fixed or Bayesian, the degrees of freedom is infinity, i.e. a normal distribution is used instead of a Student t-distribution.
b) If one or more parameters is a non-Bayesian parameter (see 1.4):

$df = N_{meas} + N_{Bayesian} - N_p$

where N_{meas} is the number of measurements, $N_{Bayesian}$ is the number of Bayesian parameters, and N_p is the total number of variable parameters (Bayesian and non-Bayesian; see 1.4).
(in version 3.50 df was estimated by an empirical equation).

3.5. Extension of Bayesian fitting of the medication history for parameters describing the situation at time zero: c0, d0_po, and d0_im. Since these parameters have typical values for a patient under specific conditions, fitting as a non-Bayesian parameter is the default status (see 1.4).

3.6. KinPop: The order of the screens showing the results has been modified, and can be chosen from the KinPop menu (selection A to D), allowing easier access to these screens.

3.7. KinPop: The graphic screens showing the final fit of the individual patients are shown faster, without actual fitting of the parameters. The parameters shown on the screen are now exactly equal to that used for the final population estimates.

3.8. KinPop: The calculation of the 'dispersion factor' df95, and consequently df(mean), has been modified in case of less than 20 subjects. In this case the calculation of df95 would require extrapolated beyond the extreme values, i.e. the lowest and higher value of the individual patient parameters. To avoid this extrapolation, the df95 is calculated in a slightly different way, i.e. by dividing the difference between the two extreme values by twice the Z-value corresponding to the actual confidence level associated to these extreme values (in other cases, the difference between the interpolated values enclosing the symmetrical 95% confidence interval is divided by twice the Z-value associated with a 95% confidence interval). In case this alternative calculation is used, i.e. in case of less than 20 subjects, df95 is denoted as 'df50*'.

3.9. Medication history fitting and KinPop: In case of a missing value for the standard deviation of a particular parameter, the default status for this parameter is 'fixed'. This can be changed, if desired, to 'non-Bayesian' (see 1.4). The status 'Bayesian' is no longer allowed. In earlier versions the default status was 'Bayesian', and, as a result of the missing standard deviation, only a 'relative Bayesian' procedure could be performed, which cannot be regarded as a true Bayesian procedure. In contrast, the new method is purely 'Bayesian': either the parameter is assumed to be fixed, or it is treated as a 'free' parameter without constraints.

3.10. KinPop: After the first cycle, the individual parameters obtained in the previous

cycle are now used as initial estimates for the next cycle. In earlier versions the initial estimates were set to the current population estimates. Usually, the new procedure results in a faster convergence to the final population estimates.

3.11. KinPop: The stop criterion has been slightly modified, i.e. the process is stopped only if the relative change of all population means and standard deviations are less than the chosen criterion (default 0.0001). In earlier versions only the population means were considered. Usually, the new procedure requires more cycles to convergence, but results may be expected to be more accurate.

3.12. KinPop: The stop criterion has been slightly modified, i.e. the process is stopped in case of oscillating population means and standard deviation at the highest log-likelihood. In earlier versions the process could stop at the lowest log-likelihood. In practice these oscillations are rather unusual, however.