PK-Works

Dedicated Software for

Pharmacokinetic Simulation

&

Dosing Regimen Individualization

(User's Manual)

Author: Munther R. Al Shami, BSc Pharm, PhD.

Contents

Description 3

Interactive PK Modelling 3

Individualization of Dosing Regimen 15

Individualization in Disease States 15

Renal Failure 16

Liver Dysfunction 16

Targeting Ranges for *SRDF*s 19

Description

PK-Works is applied pharmacokinetic *(PK)* software that has been developed to cater for a wide range of needs for scholars and clinical practitioners in the domain of *PKs*. It has emerged as full-fledged system addressing basic *PK* situations as well as those that has neither been adequately dealt with in the *PK* literature nor by any other similar application software. These include the *PKs of intermittent infusion, missed doses, PK* of *sustained release dosage form (SRDFs), targeting of drugs plasma ranges and individualization of dosing regimen with particular emphasis on kidney failure and hepatic dysfunction.*

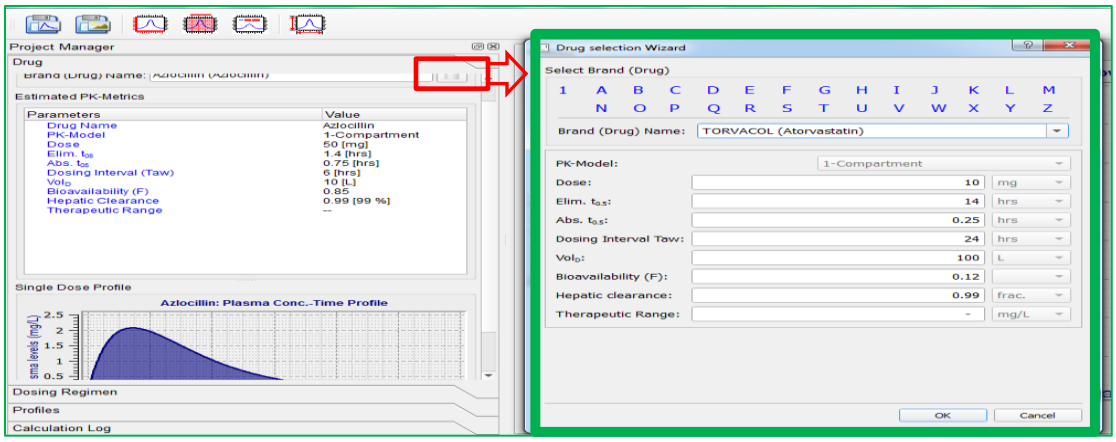
Unlike any other software, *PK-Works* has been supplemented by an extensive *PK* database covering more than 1,450 drugs substances and 38,000 brand products that are in use in the Russian Federation, European Union, Japan, the United States and Canada.

The compilation of the *PK* metrics of generic drugs was based on information supplied by major drug information databases including the American Hospital Formulary Service, Martindale Extra Pharmacopeia, LexiComp, and the *USP-DI*.

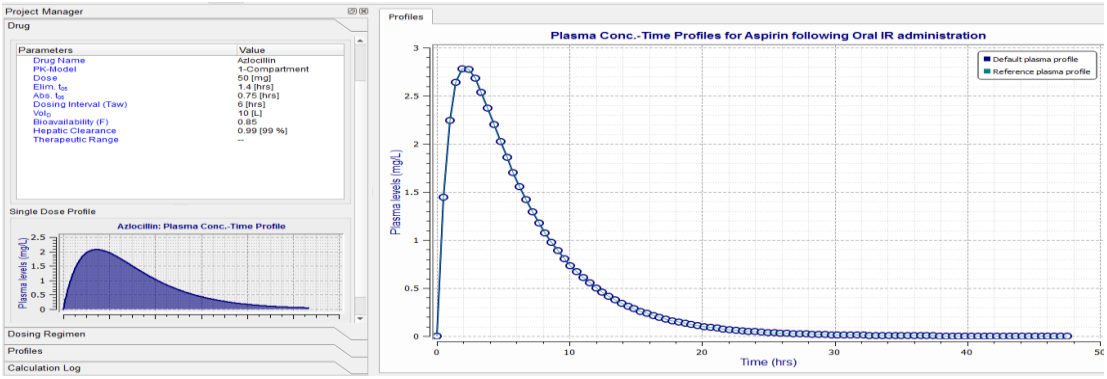
Since the *PK* profiles for all generics is not always available, user are informed of such instances and are requested to use reliable *PK* metrics for further processing of their drugs of interest. Such limitation in system is strictly related to the availability of these metrics in the scientific literature and will be subject to continual resolution in the future editions of the system.

Interactive PK Modelling

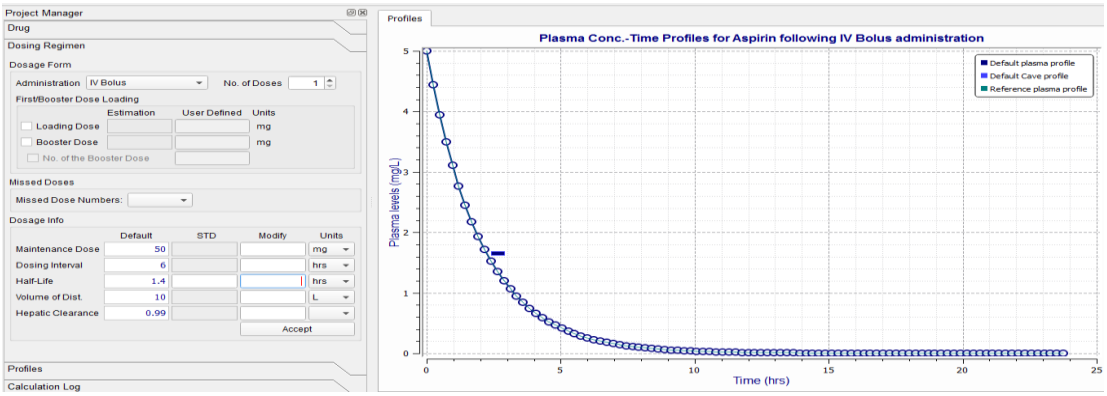
Drug selection: user may select the drug of interest from *PK-Works* database that contains *PK* information for all drug molecules available in the *USA* and Canada (about 1,450 drugs). It also contains names of about 38,000 branded drug products. Clicking on the database button (marked with RED) will cause the display of the drug selection dialogue box marked with the **GREEN** border line:



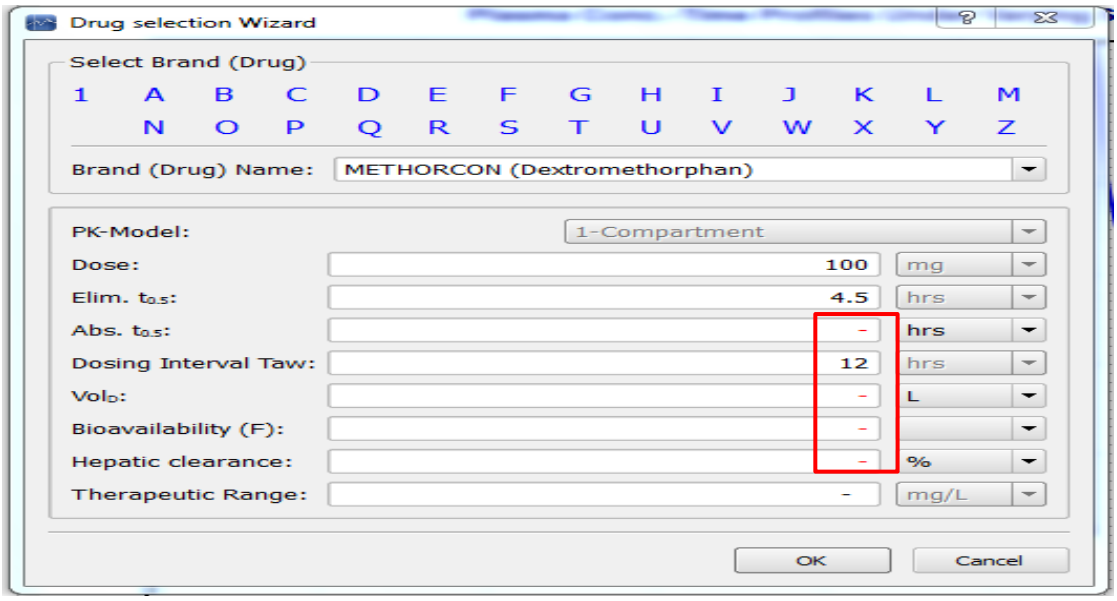
Once user has selected the drug of interest, the system displays its oral single dose as a *default* profile:



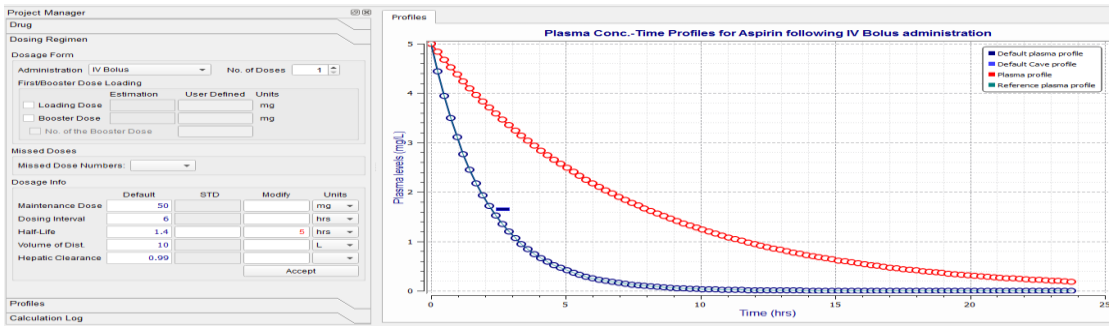
A single dose IV bolus plasma profile could be readily simulated if selected by the user.



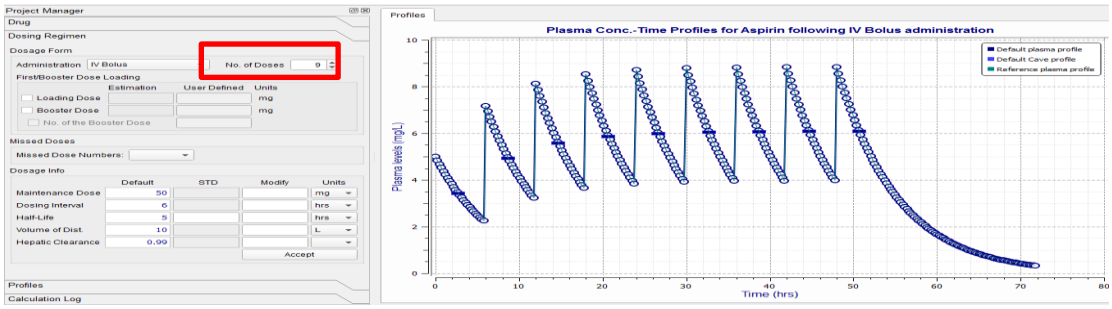
In some instances, information pertaining to the *PK* metrics for some drugs may not be complete. Hence, users are required to enter values for such parameters (marked with RED) as shown hereunder:



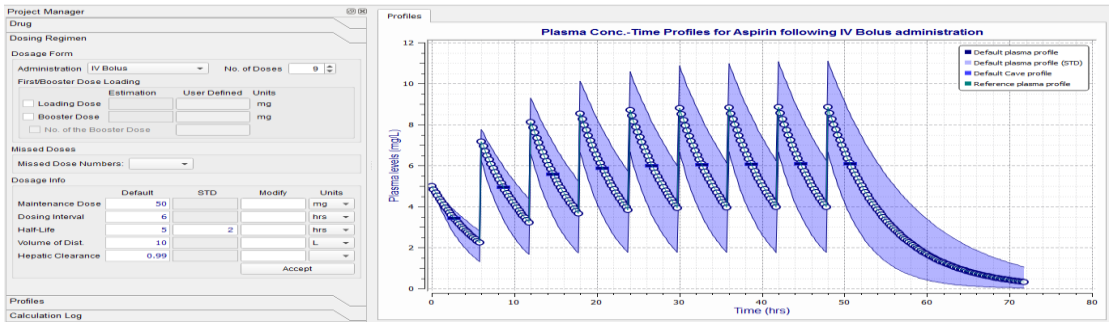
User may alter any of the simulation parameters (e.g. $t_{0.5}$). The system will display the new profile caused by such alteration in RED. If user accepts the new output, simulation will proceed with the new profile.



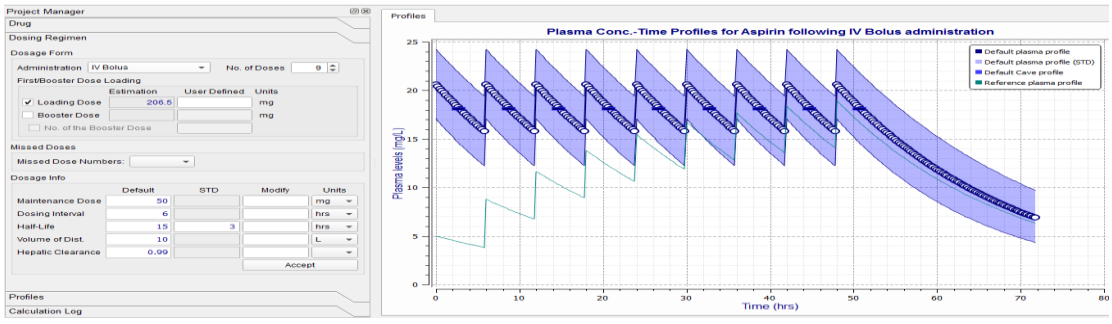
Multiple dosing: could be easily simulated by defining the number of administered doses.



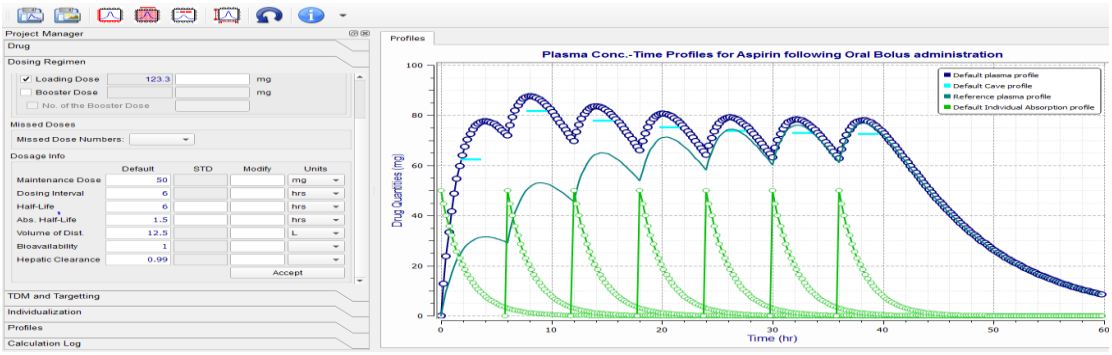
Likely plasma levels: variability, expressed as *StDev*, associated with *PK* metrics for the elimination or absorption rate constants are provided by the system will display the likely plasma levels.



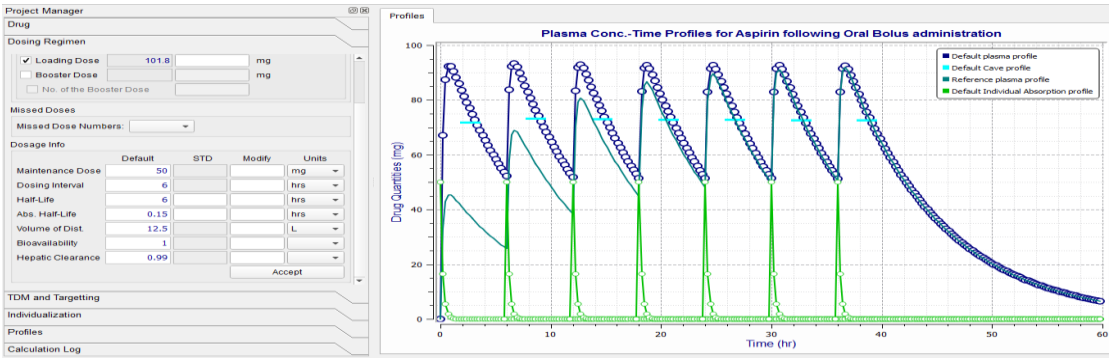
Dose loading: for drugs with relative long $t_{0.5}$, a loading dose may be estimated by the system. Such a dose will produce steady state (*SS*) plasma levels as shown below.



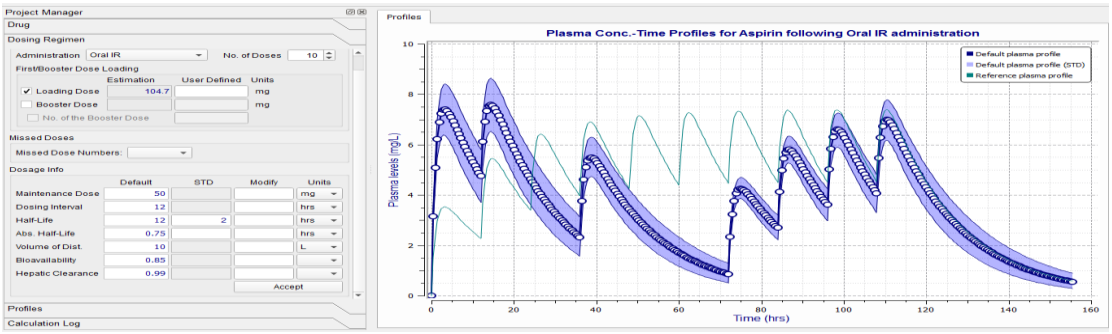
As shown above ***PK-Works*** will generate a typical *SS* plasma profile upon the administration of an IV bolus loading dose. However, in case of oral bolus dosing regimen, such typical profile will appear distorted as shown in the below diagram. The unique features of this diagram are caused by significant accumulation of the drug in the absorption domain. Such diagram will typically be generated for poorly absorbed drugs, especially when the dosing interval is relatively short.



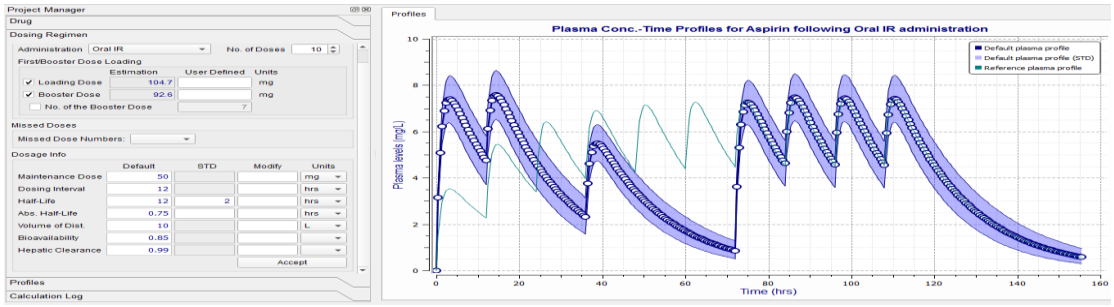
Such apparent distortion will disappear in cases of drugs that are rapidly absorbed or when doses are spaced apart as demonstrated in the below diagram:



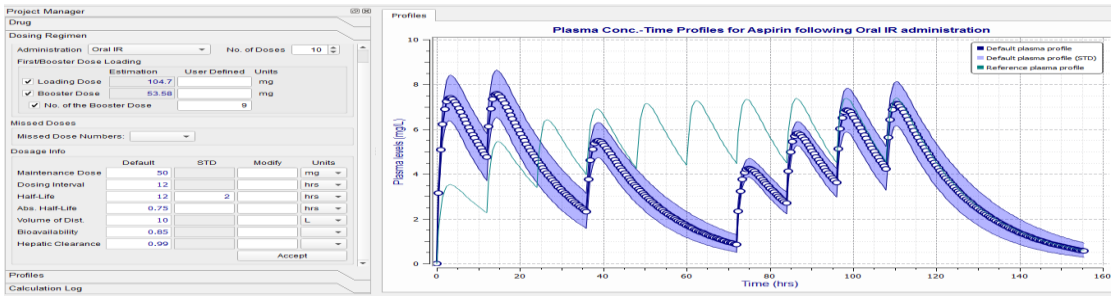
Missing doses: if one or more dose(s) were missed, the resulting plasma profile will be readily provided by the system. Such profile will demonstrate significant diminution of plasma levels which may require the administration of a booster dose.



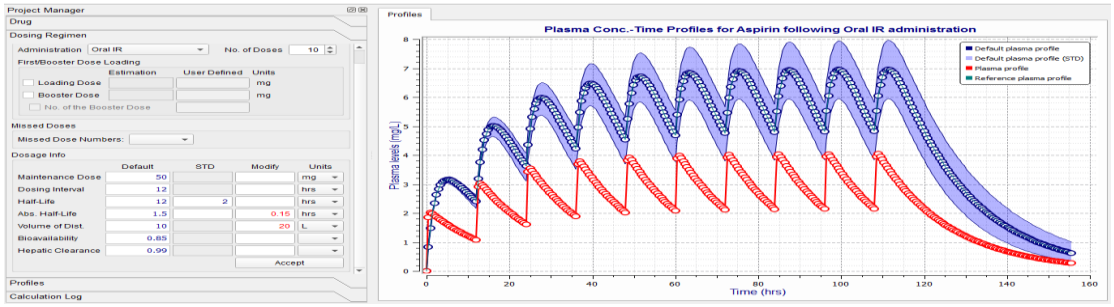
Dose boosting: the system will estimate the required dose that will restores plasma concentration to *SS* levels. Boosting dose will be estimated (by default) after the last missing occurrence as shown below.



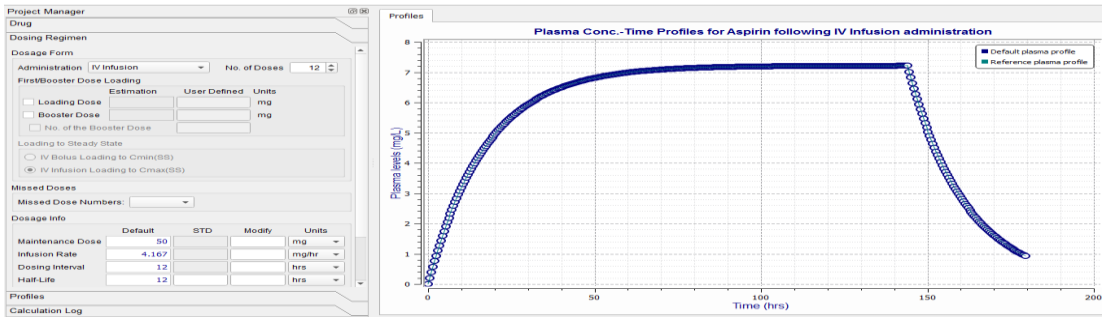
User may estimate the booster dose at any dose number (N) at which patient has reported missed dose.



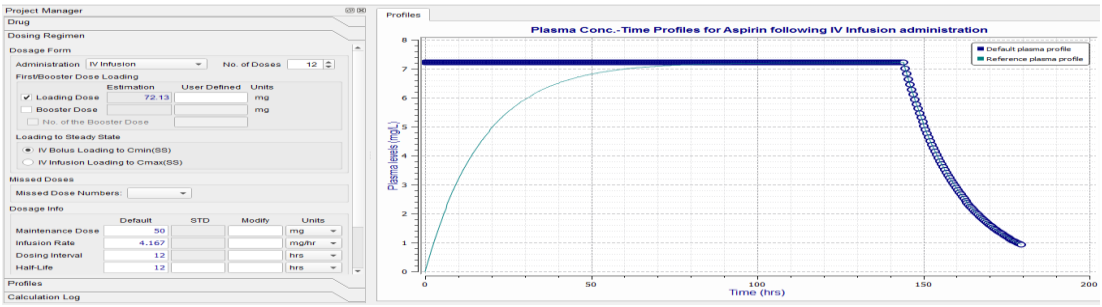
User's selected PK metrics: the system accepts alternative metrics if user does not trust the validity of the default metrics provided by the system. In the case provided hereunder, two parameters have been altered, namely, $t_{0.5\alpha}$ and V_d.



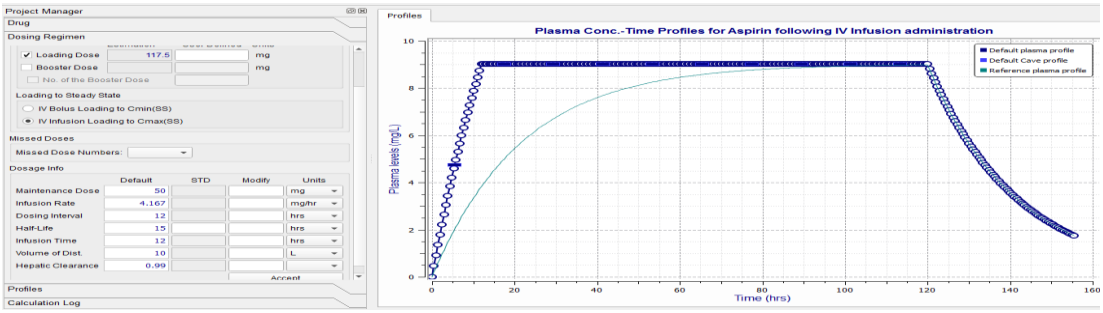
Dose loading for continuous infusion: the only valid estimate for dose loading that is provide in the literature is that related to continuous infusion. Setting the dosing interval equivalent to the infusion time will produce a plasma profile that is identical to that obtained by continuous infusion



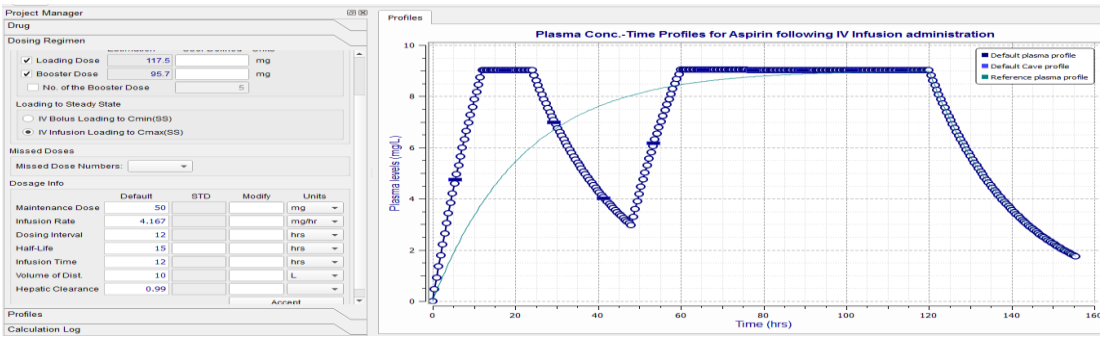
Intravenous bolus dosing which is widely reported in the literature is provided hereunder:



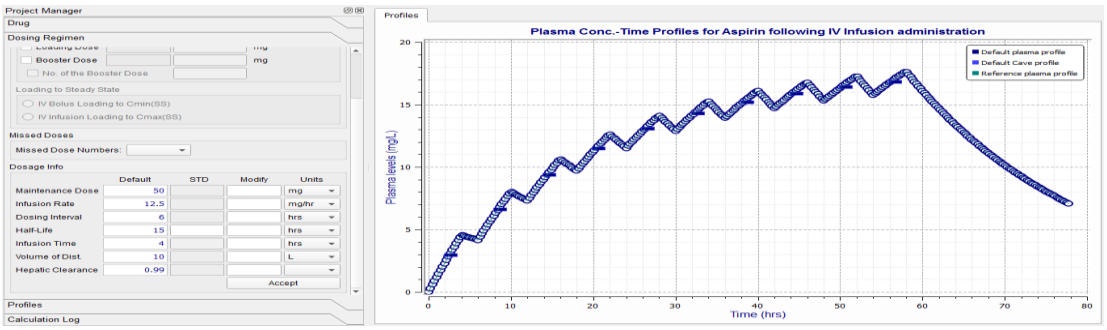
A less common approach is infusion loading based the infusion rate that will produce *SS* plasma levels towards the end of infusion time. The profile generated by this approach is provided hereunder:



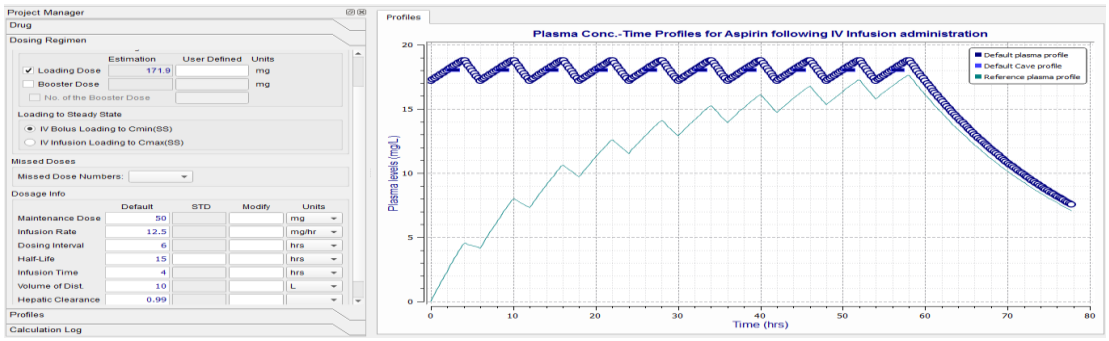
Boosting for missing doses in the case of continuous infusion by the infusion loading approach:

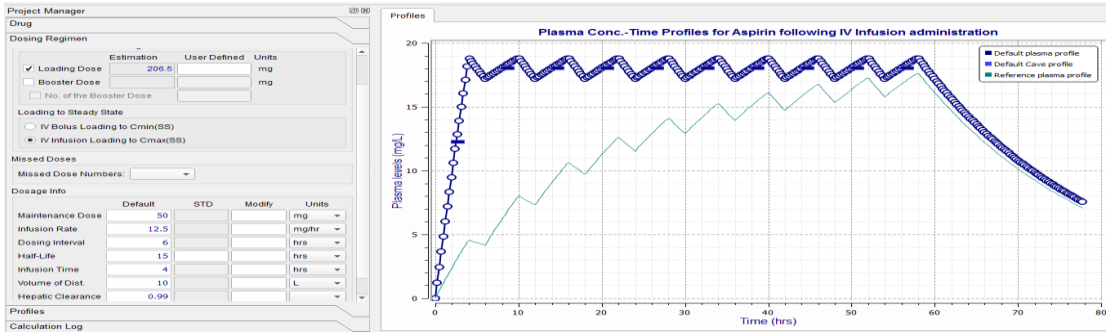


Intermittent infusion: ***PK-Works*** offers unique chance to entertain varying scenarios for intermittent infusion. A typical profile is shown below.

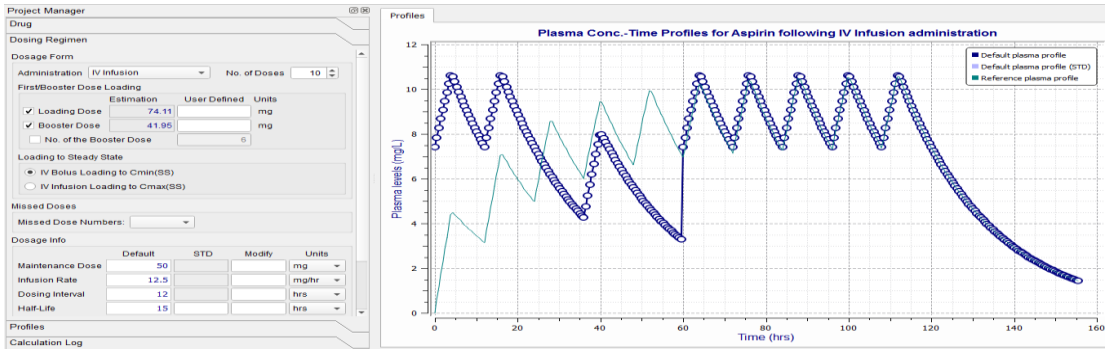


However, no valid method has been indicated for dose loading or for intermittent infusion. ***PK-Works*** offers two unique methods for such loading, namely, IV bolus and IV infusion loading. These are respectively provided in the below two diagrams.

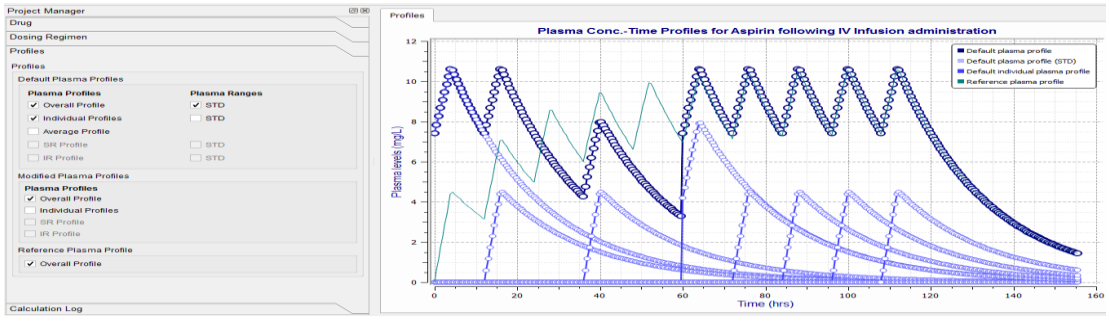




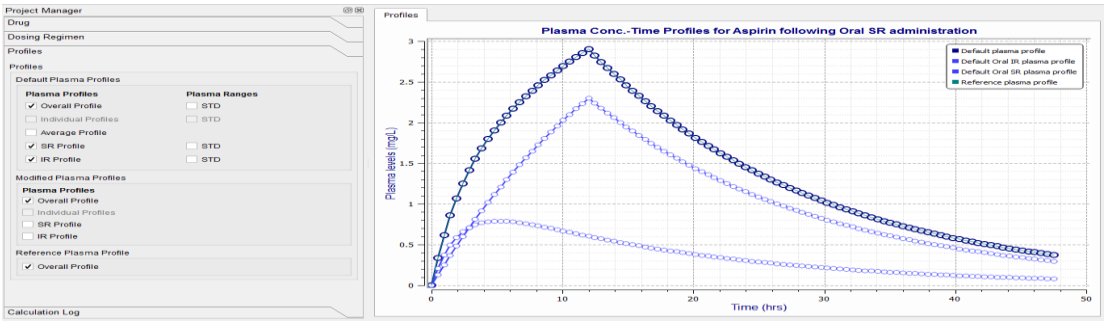
The same applies to dose boosting in the case of missed doses.

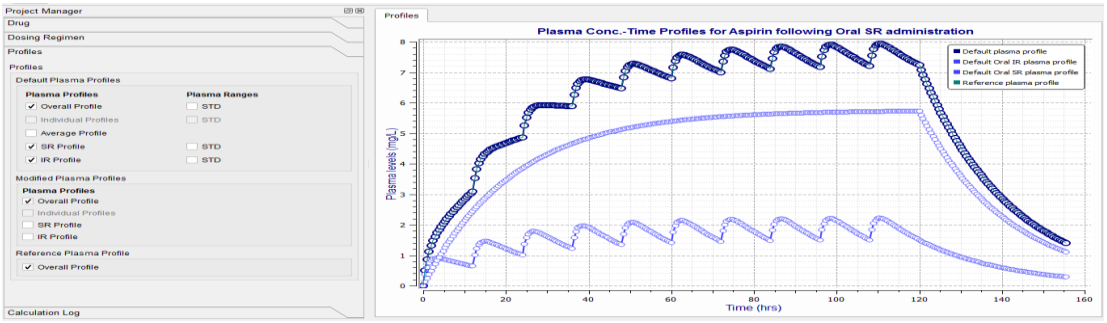


As shown below, individual maintenance, loading and booster doses in the case of intermittent infusion are also generated by the system.

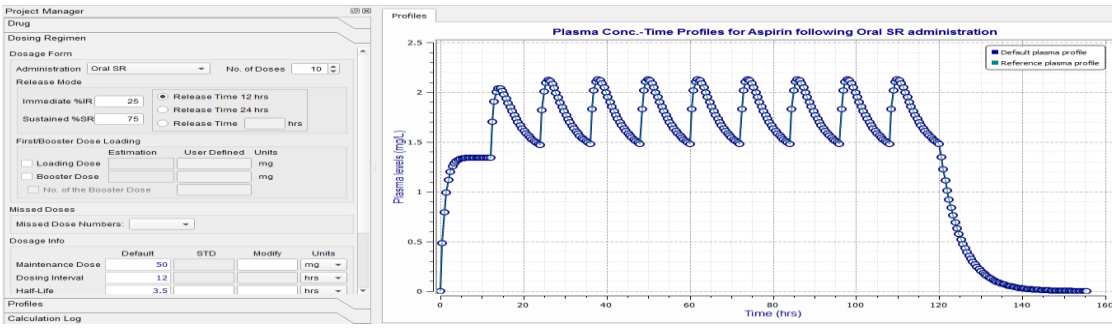


PK* of *SR* dosage forms (*SRDFs*)**: There is no evidence that the *PK* of SRDFs has been adequately dealt with in the entire *PK*. By contrast, ***PK-Works offers unique possibility to simulate single or multiple profiles. The presence of an immediate release portion in the *SR* form is accurately accounted for by the system.

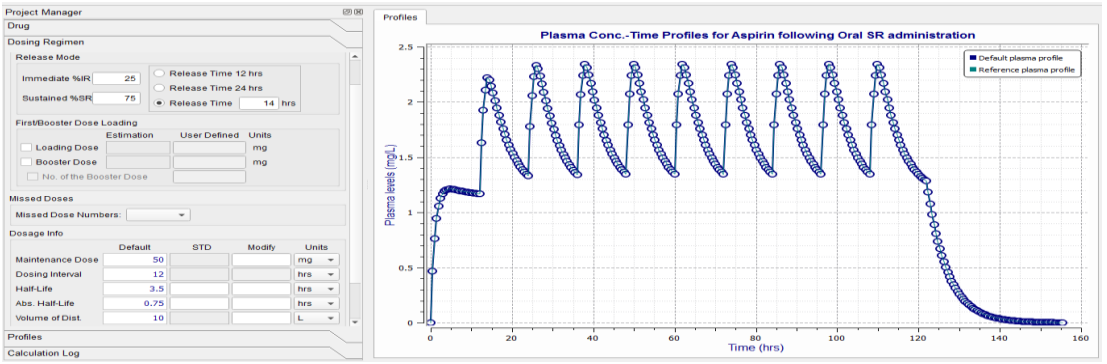




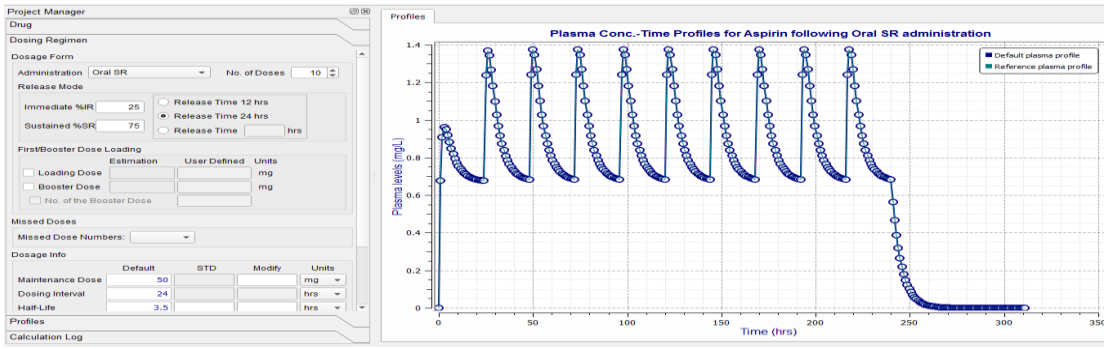
SRDFs are available with manufacturer's claim that drug release occurs within 12 or 24 hours. User may select enter the actual release time as indicated by in-vitro dissolution testing. The diagram below shows plasma profiles obtained by a 12-hours release form.



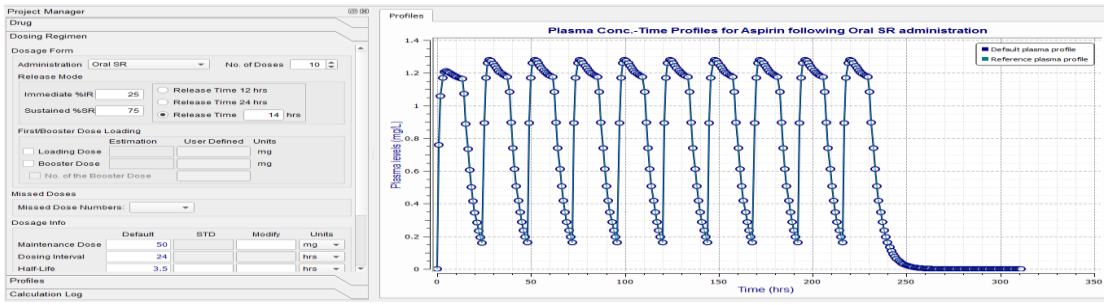
As demonstrated in the below diagram, only slight alteration in the peak-to-trough fluctuation will occur in the plasma profiles is the drugs was release in 14 hours.

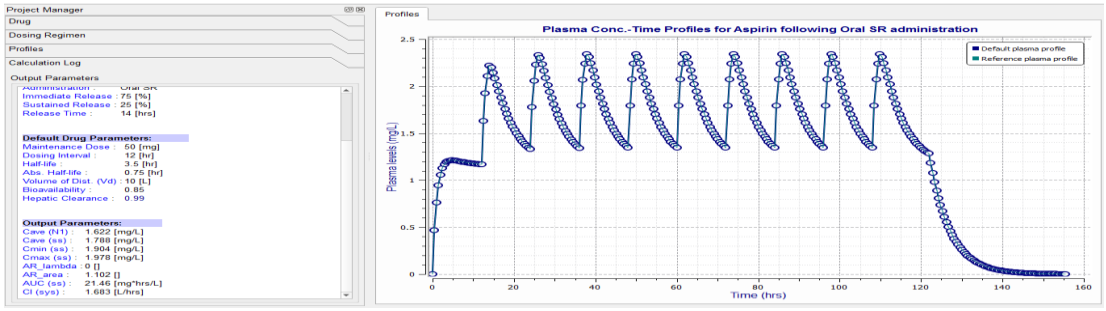


As demonstrated hereunder, compared with 12-hours *SRDF*, peak-to-trough values associated with the 24-hours forms, are almost doubled.

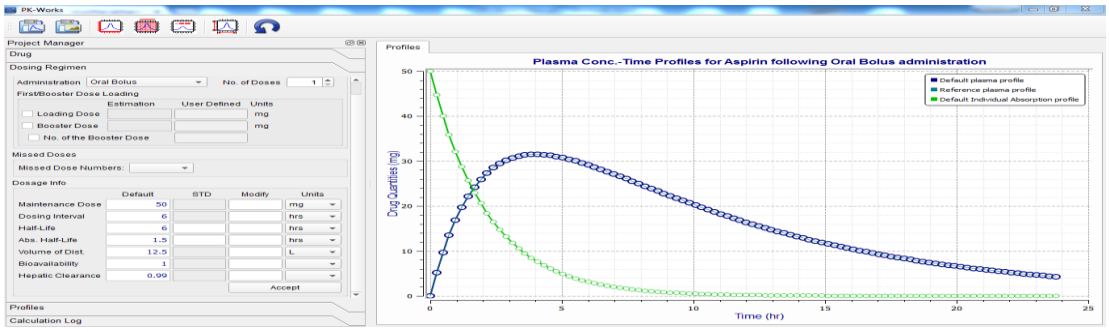


Interestingly, a reasonable peak-to-trough pattern will be significantly distorted If the actual release time for the 24-hours forms is set at a realistic value of 14 hours. This implies that the prime property of the extended release form will be severely violated.

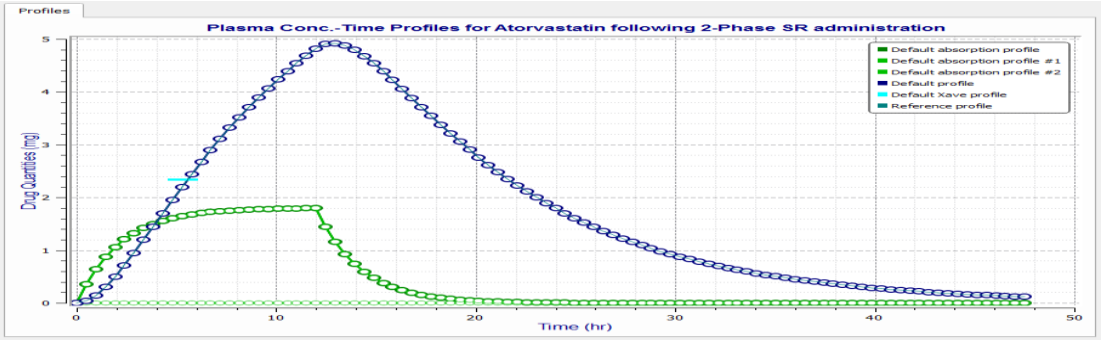




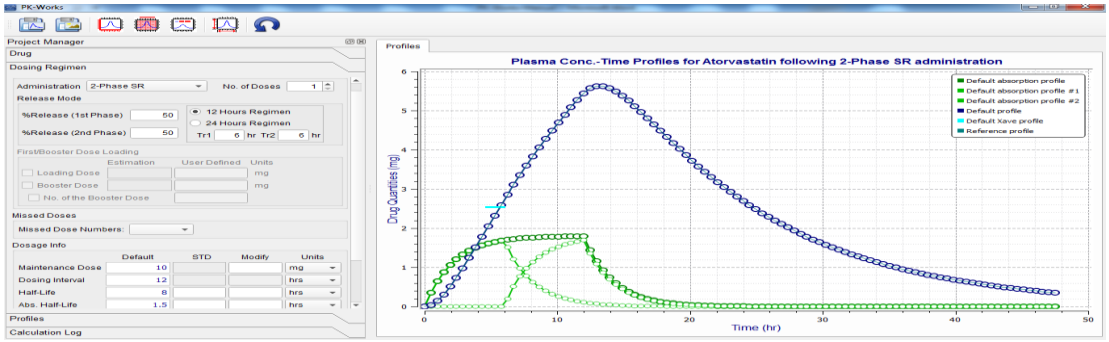
Elucidation of drugs kinetics in the absorption domain: this is indicated by the graphical display of drugs quantity in the absorption domain or the gastro-intestinal tract *(GIT).* This applies to any other extravascular route of administration and allows assessment of the percent of drugs remaining to be absorbed for one-compartment model drugs which was earlier attempted by Wagner-Nelson. It may be readily demonstrated that this approach is operationally equivalent to sigma-minus method.



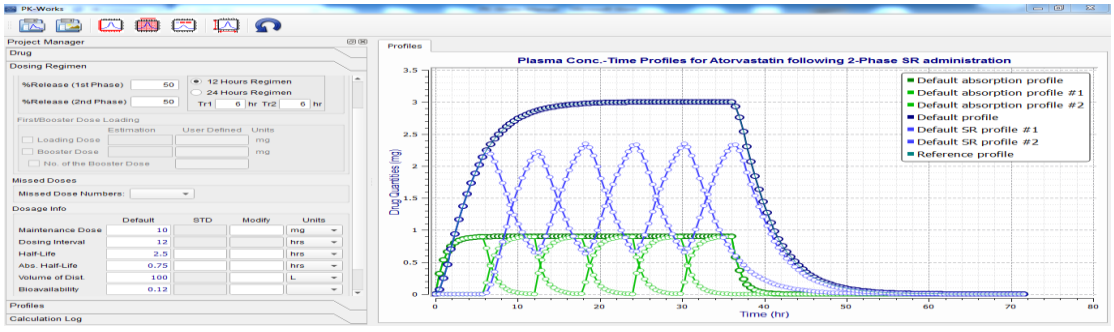
As shown in the below diagram, neither of the above methods appears to be suited for the assessment of the percent of drug remaining to be absorbed. This is related to the confounding effect of drug release of *SR* forms into the *GIT*. Notwithstanding, application of Wagner-Nelson method for the estimation of the absorption rate from the plasma profile could be valid upon the cessation of drug release from the *SR* dosage form as shown in the BLUE profile provided hereunder.



The validity of the above said is ascertained by drug profiles in the absorption domain when drug release occurs in two distinct phases.

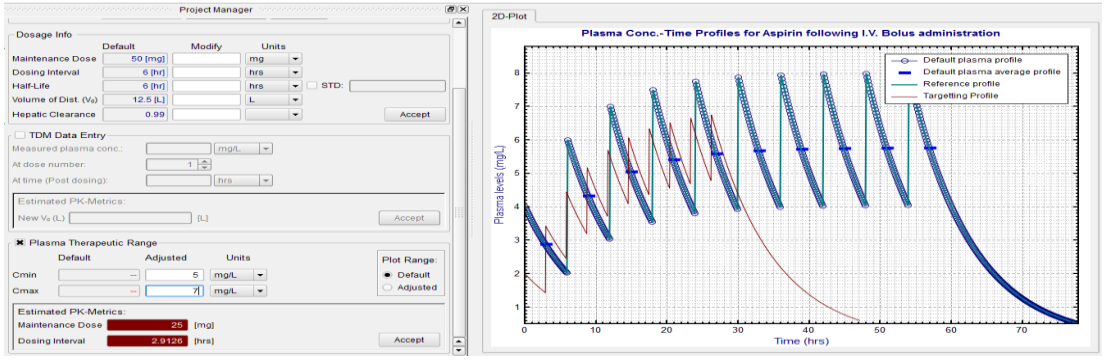


Bearing in mind the prime objective of Wagner-Nelson method, for a one-compartment model drugs, is the characterization of drugs absorption process. This is only feasible for *IR* oral forms, or after the cessation of drugs release from the *SR* dosage form, after the administration of a single dose. It is evident, from the above diagram, that such method could be used for *SR* cases.

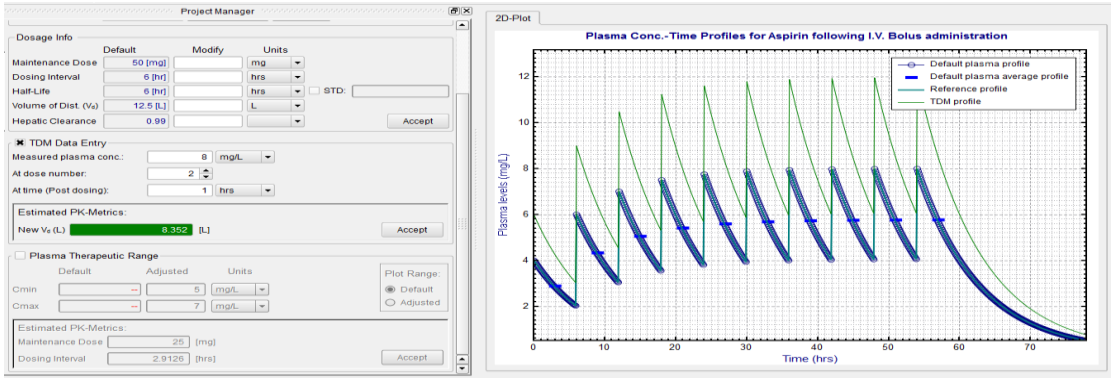


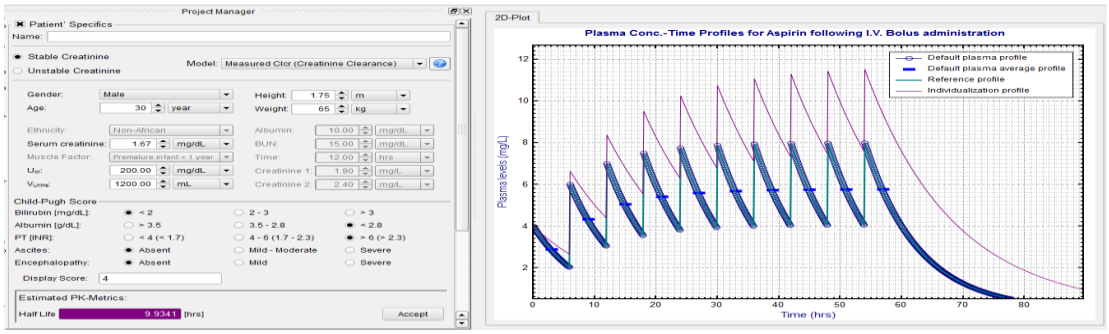
The above diagram represents multiple dosing profiles of two-phase 12-hours *SR* form with 50% of the dose released in two 6-hours periods. ***PK-Works*** offers detailed display of all kinetic events in the systemic circulation (profiles in **BLUE**) as well as in the absorption domain or the GIT (profiles in **GREEN**).

Targeting plasma ranges: this is another unprecedented aspect of *PK-Works*. In cases of drugs with well-defined therapeutic windows, user may enter the upper toxic and the lower effective or therapeutic levels. These will prompt the system display the dosing regimen (dose and dosing frequency) that will produce such levels. This is indicated by the profile and values displayed in **BROWN** hereunder.

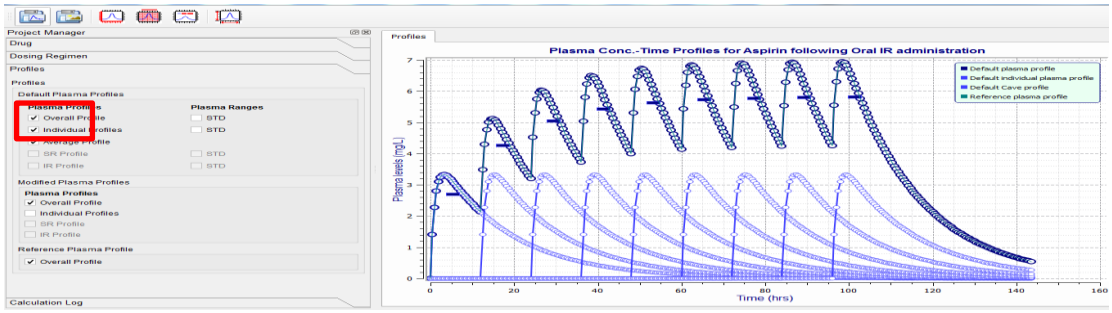


TDM-based adjustment: If plasma concentration data or values obtained through drug monitoring utility are available, these could be submitted to the system. *PK-Works* will readily display a new plasma profile (in **GREEN**) by assigning a modified value for the volume of distribution (V_d). The generation of these profiles is based on the assumption that the default value for the V_d may not be accurate. This assumption is operationally equivalent to inaccurately used bioavailability parameter.

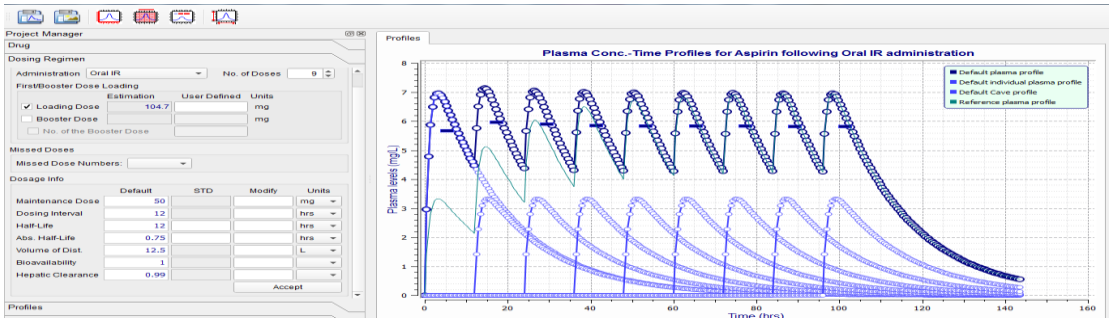




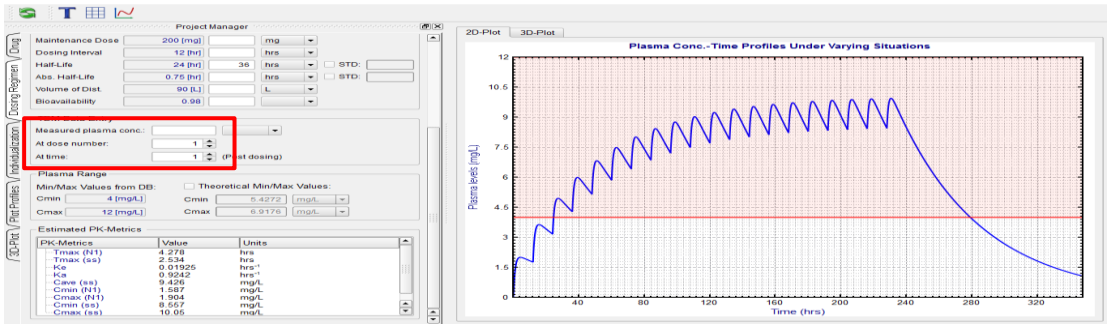
Diagrammatic display of system output: *PK-Works* offers a unique opportunity to visualize all drug profile in the body as required by users. This is explained consider the below diagram:



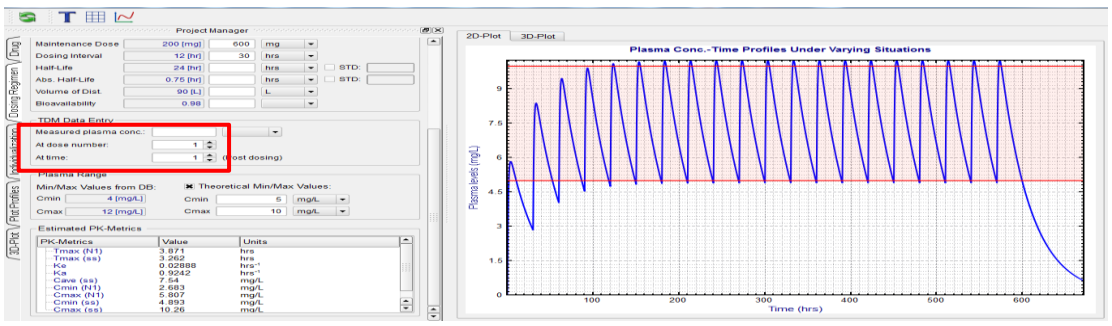
Clicking on the "Plasma Profiles" options are provided for user to display any profile of interest. The default profiles is always provide in light **GREEN** as shown hereunder, so that users may appreciate the impact of modifying simulation parameters on all profiles offered by the system.



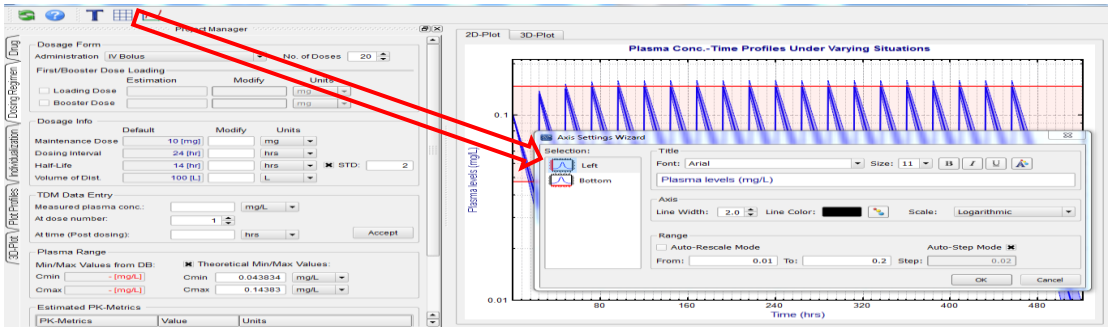
PK-Works defines the therapeutic range for drugs with well-defined therapeutic windows (*Carbamazepine*) provided that such values are available in the system database. Theoretical ranges estimated on the bases of the simulation parameters are also displayed along with the reported values in the literature.



Alternative therapeutic ranges may be defined the user. In which case, the system determines the ideal dosing regimen that will produce such user-defined ranges. Such Ideal Regimen may be altered to practical or feasible dosing regimens.



In addition to the possibility of customizing plasma concentration-time plots, plasma profile could be displayed on either the rectilinear or the semi-logarithmic scales.



Individualization of Dosing Regimen

The previous reflections on the theoretical PK modelling does not enjoy its relevance due to this very property (theoretical); rather it has also to do with the very essence of DRI. As for example, if the information available to the clinical practitioner indicates that the elimination half-life is different from that provided by the system, then once such parameter is modified, a new profile will be instantaneously generated by the system with altered half-life. The same applies to all other PK characteristic. Also, as demonstrated above, if the variability (expressed as variation Standard Deviation or coefficient of variation) of any PK metric is known, then availing such information to the system will also produce a profile reflecting or incorporating such variability. Such scenarios represent a wide range of individualization as experienced in clinical practice such as the extent of bioavailability or the absorption rate constant or volume of distribution.

In addition, is individualization is interpreted as a modification of dosing regimen, on the basis of some characteristic of the patient such as age or other physical attributes, ***PK-Works*** readily account for such instances. For example, it is an established fact that any regular maintenance dose is based on some average characteristic of the whole population such as body surface area (BSA) which is often equated by $1.73m^2$. Hence, an individualized maintenance dose could be readily estimated since BSA represents one of the standard outputs of ***PK-Works***.

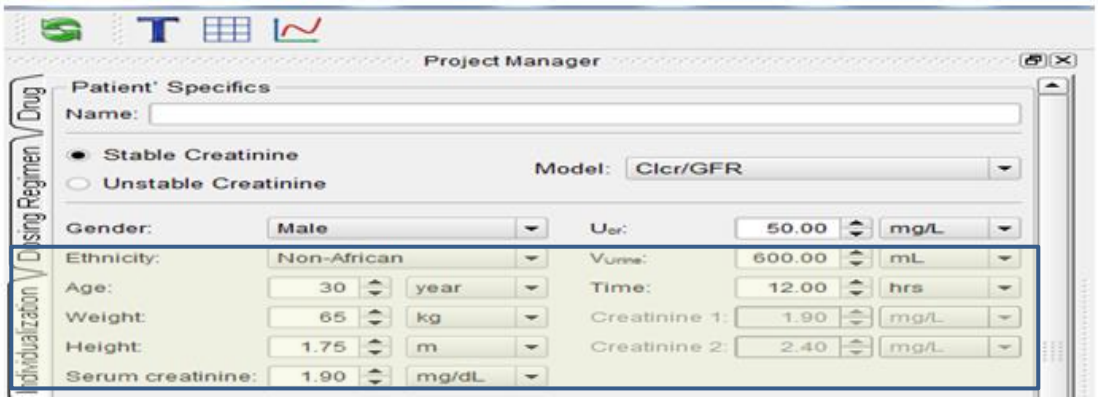
Inter-individuals differences are often associated with significant differences in ADME of many drugs. This is the case with highly variable drugs where more than 40% coefficient of variation is quite likely. Such differences are generally reflected in the drugs plasma levels. In clinical set-up where TDM service is available, user may enter feedback offered by such service and ***PK-Works*** will adjust the plasma profile accordingly. This is shown in the following two diagrams:

Individualization in Disease States

DRI is often associated with two specific disease conditions, namely, kidney failure and liver dysfunction. This necessitated that ***PK-Works*** be equipped with functionality to assess the impact of varying intensities of such disease conditions on the overall performance of drugs in the body.

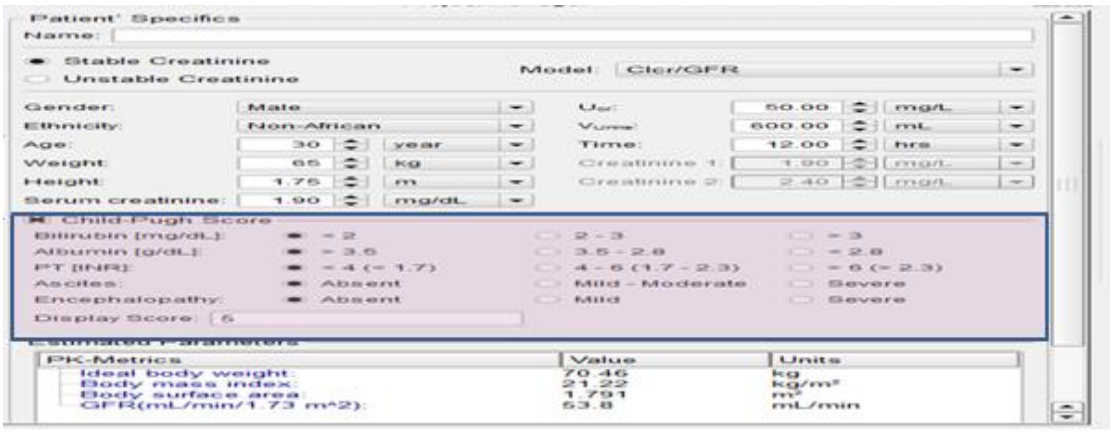
Renal Failure

For drugs that are partially or totally eliminated via the kidneys, ***PK-Works*** utilizes serum or urinary creatinine values to account for all likely scenarios of altered renal function. Cases where stable or unstable serum creatinine levels are present, these are used to estimate the percent decline in this function.



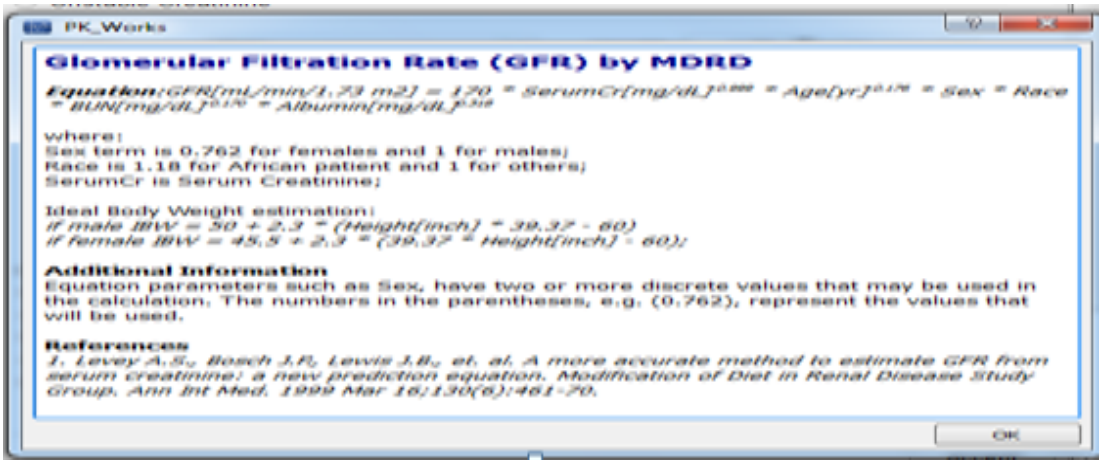
Liver Dysfunction

The above applies to liver dysfunction where Child-Pugh score is utilized to assess the percent decline in such function.

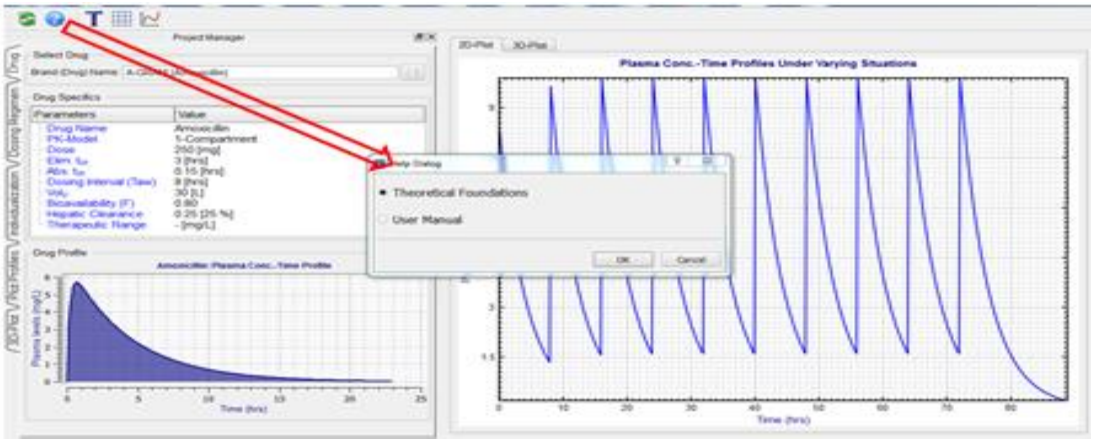


The overall impact of either liver dysfunction or renal disease states on the elimination properties of drugs is estimated and the plasma profile based on the altered rate constants is re-plotted.

User may choose the procedure suited to assess renal function, as indicated by creatinine clearance. Nine such procedures are employed by the system.



PK-Works is supplemented by an elaborate description of the mathematical foundation employed for the construction of the system as well as a User's Manual.



Novel Mathematics: some aspect of the mathematics foundation used in *PK-Works* is quite novel. Hence, it will not be available in the conventional *PK*. These are related to targeting of therapeutic plasma levels, area estimation in the case of intravenous infusion, the *PK* of missing doses and one- or two-phase *SR* forms.

Average Plasma Concentration (C_{av})

The average plasma concentration at different dosing interval could be defined upon the integration of the first equation (C_{pl}). Due to its therapeutic efficacy, the average plasma level is more important than just defining C_{max} and C_{min}.

$$AUC_{0-\tau}^{ss} = \frac{k_0}{K^2 V}\left[\begin{array}{l} -\left(1-e^{-KT_i}\right)+1-\left(e^{-K(\tau-T_i)}-e^{-K\tau}\right)\left(\frac{e^{-KT_i}-1}{1-e^{-K\tau}}\right) \\ -\left(1-e^{-KT_i}\right)\left(\frac{e^{-\tau K}-e^{-KT_i}}{1-e^{-K\tau}}\right) \end{array}\right]$$

$$AUC_{0-\tau}^{N} = \frac{k_0}{K^2 V_d}\left(KT_i + e^{-KT_i} - 1\right) - \left(C_{min1}F_I(e^{-KT_i}-1)\right) + \left((C_{max1}-C_{min1})F_{PI}\right)$$

$$C_{av} = \frac{k_0}{\tau K V_d}\left(T_i + \frac{e^{-KTi}}{K} - \frac{1}{K}\right) - \left(\frac{C_{min1}F_I}{\tau K}(e^{-KT_i}-1)\right) + \left(\frac{(C_{max1}-C_{min1})F_{PI}}{\tau K}\right)$$

where C_{max} and C_{min} are the respective maximum and minimum and plasma concentration attained at the end of the first infusion period and the end of the first dosing interval, F_I and F_{PI} at are the multiple dosing factor during the infusion and post infusion periods.

***PK* models for *SRDFs*:** derivation of the integral counterpart of ordinary deferential expressions (*ODE*) describing the entire *PK* behavior of *SRDF* has been done by analytic procedures. The validity of *PK* models, generated by such procedures, was ascertained by numerical solution for the same *ODE*. A sample of the models suited for drugs *PK* in the absorption domain or in the systemic circulation is provided hereunder:

Drugs plasma profile for X_{SR1}

The plasma profile associated with the first release period ($X_{SR1}(t)$) can be obtained from Eq. 2.5. A form of the $X_{SR1}(t)$ profile depends on the time periods and is different at $t \le T_{r1}$ and $t \ge T_{r1}$ because $X_{aSR1}(t)$ is included to the equation (see Eq. 2.10 and 2.14).

$$X_{SR1}(t) = \begin{cases} \frac{k_{01}}{K}(1-e^{-Kt}) + \frac{k_{01}}{K_a-K}(e^{-K_a t}-e^{-Kt}), & for\ 0 \le t \le T_r \\ \frac{k_{01}K_a}{K(K_a-K)}\left(\frac{e^{-KT_{r1}}-1}{e^{-K_a T_{r1}}}\right)e^{-K_a t} - \frac{k_{01}}{K_a-K}\left(e^{-K_a T_{r1}}-1\right)e^{-K_a t}, & for\ t \ge T_r \end{cases} \quad (2.33)$$

Drugs plasma profile for X_{SR2}

The plasma profile $X_{SR2}(t)$ can be obtained from Eq. 2.6. A form of the $X_{SR2}(t)$ profile depends on the time periods. As a result $X_{SR2}(t)$ is different at $t \le T_r$ and $t \ge T_{r2}$ because $X_{aSR2}(t)$ is included to Equation (see Eqs. 2.16, 2.19 and 2.22).

$$X_{SR2}(t) = \begin{cases} \frac{k_{02}}{K} + \frac{k_{02}}{K_a-K}e^{-K_a(t-T_{r1})}) - \frac{k_{02}K_a}{K(K_a-K)}e^{-K(t-T_{r1})}, & for\ 0 \le t \le T_r \\ \frac{k_{02}K_a}{K(K_a-K)}\left(\frac{1-e^{-KT_{r2}}}{e^{-KT_r}}\right)e^{-Kt} - \frac{k_{02}}{K_a-K}\left(\frac{1-e^{-K_a T_{r2}}}{e^{-K_a T_r}}\right)e^{-K_a t}, & for\ t \ge T_r \end{cases} \quad (2.48)$$

PKs* of missing doses:** Generalized expressions have been incorporated in all *PK* multiple dosing models used in ***PK-Works.

Intravenous infusion (with missing doses)

Unlike most other convoluted PK models with continuous time flow, the *PK* models used to predict drug levels consequent to intravenous infusion consist of discrete terms that account for infusion and post-infusion phases. This implies that for any such model two mathematical expressions will be needed to describe the entire course of plasma levels during both phases. Hence, the following expression may be used to determine the impact of missed doses(s) during the infusion phase:

$$C_{inf}^{N} = \frac{k_0}{KV}\left[\begin{array}{l}\frac{1}{(1-e^{-K\tau})}\left(1-e^{-KT_i}\left\{1-e^{-KT_{pi}}+e^{-NK\tau}(e^{KT_i}-1)\right\}-e^{-K\tau}\right)\\ -(1-e^{-KT_{Nm}})\\ -\sum_{All\ N_M}(1-e^{-KT_i})e^{-K\tau[(N_c-N_M)-(T_i+t_i)]}\end{array}\right]$$

Similarly, a plasma levels during the post-infusion phase could be estimated, in the presence of missed doses according to the following expression:

$$C_{p.inf}^{N} = \frac{k_0}{KV}\left[\begin{array}{l}\frac{(1-e^{-NK\tau})}{(1-e^{-K\tau})}(1-e^{-KT_i})e^{-Kt_{pi}}\\ -\sum_{All\ N_M}(1-e^{-KT_i})e^{-K\left[\tau(N_c-N_M)+t_{pi}\right]}\end{array}\right]$$

Targeting Ranges for *SRDFs*

Expressions for C_{min} and C_{max} in the case of *SR* forms may be provided as follows:

$$C_{\max}^{SS} = \frac{FX_{SR}}{T_rKV} + \frac{FX_{IR}}{V}\left(\frac{e^{-KT_{\max}^{ss}}}{1-e^{-K\tau}}\right), C_{\min}^{SS} = \frac{FX_{SR}}{T_rKV} + \frac{FX_{IR}}{V}\left(\frac{e^{-K\tau}}{1-e^{-K\tau}}\right)$$

These equations may be re-written in terms of the maintenance dose with the *IR* portion *(P)* represented as a fraction of such dose.

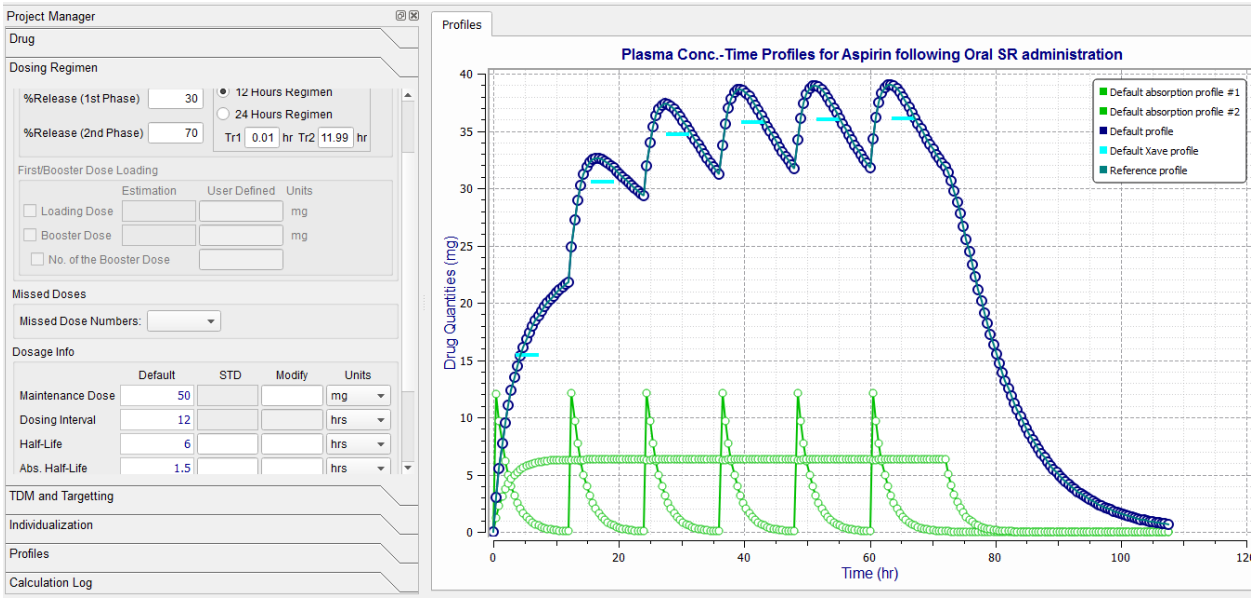
$$C_{max}^{ss} = \frac{FX_0(1-P)}{T_rKVd} + \frac{FX_0}{V}\left(\frac{e^{-KT_{max}^{SS}}}{1-e^{-K\tau}}\right),\ C_{min}^{ss} = \frac{FX_0(1-P)}{T_rKVd} + \frac{FX_0}{Vd}\left(\frac{e^{-K\tau}}{1-e^{-K\tau}}\right)$$

$$C_{max}^{ss} = \frac{FX_0}{Vd}\left[\frac{1-P}{T_rK} + \frac{Pe^{-KT_{max}^{SS}}}{1-e^{-K\tau}}\right],\ C_{min}^{ss} = \frac{FX_0}{Vd}\left[\frac{1-P}{T_rK} + \frac{Pe^{-K\tau}}{1-e^{-K\tau}}\right]$$

Dividing C_{max}^{ss} by C_{min}^{ss} and further simplification, we get the value for a new dosing interval as:

$$\tau_{new} = -\frac{1}{K}ln\left[\frac{C_{min}^{ss}\left[(1-P)+PT_rKe^{-KT_{max}^{SS}}\right]-C_{max}^{ss}(1-P)}{C_{max}^{ss}(P+PT_rK-1)+C_{min}^{ss}(1-P)}\right]$$

This equation may be solved to obtain the value of the dosing interval associated with user-defined therapeutic range. Such value may be inserted in either of the above equations for C_{min} or C_{max} to obtain the new dosing regimen that will give plasma levels contained within the desired therapeutic range.


Project Manager
Drug
Dosing Regimen
%Release (1st Phase) 30
%Release (2nd Phase) 70
12 Hours Regimen
24 Hours Regimen
Tr1 0.01 hr Tr2 11.99 hr
First/Booster Dose Loading
Estimation
User Defined
Units
Loading Dose
Booster Dose
No. of the Booster Dose
mg
Missed Doses
Missed Dose Numbers:
Dosage Info
Default
STD
Modify
Units
Maintenance Dose 50 mg
Dosing Interval 12 hrs
Half-Life 6 hrs
Abs. Half-Life 1.5 hrs
TDM and Targetting
Individualization
Profiles
Calculation Log
Profiles
Plasma Conc.-Time Profiles for Aspirin following Oral SR administration
Default absorption profile #1
Default absorption profile #2
Default profile
Default Xave profile
Reference profile
Drug Quantities (mg)
Time (hr)
0
5
10
15
20
25
30
35
40
0
20
40
60
80
100