PK-Works

(Theoretical Foundations)

Dedicated Software for

Pharmacokinetic Modeling

&

Dosing Regimen Individualization

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Disclaimer:

Although every conceivable effort has been made to insure the integrity and validity of the outputs of different functionalities of *PK-Works*, the utilization of such outputs, for whatever purpose, remains within the user's sole responsibility. Ordinary subjects, patients and/or non-healthcare individuals are discouraged, in the strongest possible terms, not to utilize any output from PK-Works to modify the dosing regimens of their medicines. Information generated by PK-Works can *NEVER* overrule the judgment of your doctor or other healthcare professionals entrusted with your well-being.

Table of Contents

Introduction

Pharmacokinetics (PK) is a fairly recent domain of science that has emerged in the fifties of the twentieth century. At that time, PK was construed as being a concern within the domain of pharmacology. From an historic perspective, the first papers addressing pure kinetic matters appeared as late as 1937 by Toresten Teorell. Also, the first textbook concerned with drug kinetics, entitled Der Blutspiegel (Blood Mirror), was published by Dost in Germany in 1953. After two decades, PK was acknowledged as an independent scientific discipline in Bethesda - Maryland in 1972. It is during this period that the entirety of the mathematical foundations of this new science has been accomplished. To this effect, many notable scholars have their prolific and pioneering contributions. These included Krüger - Theimer, J. Wagner, M. Gibaldi and E. Welson.

It is worthwhile mentioning that despite the continued advances in many aspects of the kinetic theory, PK remained mainly focused in the prediction of drugs levels in the body. This characteristic of PK made it a fundamental tool within the context of dosage regimen individualization in clinical practice.

It could be also argued that many of the existing of PK models has not been fully employed in the arena of clinical practice. This assumption is based on the realization that the utilization of these models in such practice remained mainly confined to single point estimation of drugs in the systemic circulation. Despite is relevance, profiling of drugs levels in the human body remained lacking in almost all clinical PK textbooks. This has precluded the chance of gaining a detailed view of the time course of drugs levels in the body. Notwithstanding, interest in modelling of multiple dosing is gaining increasing interest and is consequently provided in some off-the-shelf computer applications in a simplistic manner.

Although many single- and multiple-compartment PK models have been developed over the past decades, it could be demonstrated that the PK of the vast majority of drugs may be adequately described by a single-compartment linear models. This is based on the realization that the multiple compartment features become insignificant in cases where drugs are administered by intravenous infusion or via oral routes. Also, such features become less prominent upon multiple-dosing regimens where steady state condition has been attained. For these reasons, single-compartment models representing different routes of administration where used for the construction of *PK-Works*. Higher PK linear models would be contemplated in the future editions of the system if such addition is deemed necessary from user's perspective.

Intravenous Bolus Model (IVB)

For drugs that confer upon the body the characteristic of a one-compartment model, and are administered by an intravenous bolus fashion, a conceptual model could be outlined to describe the administration, and the consequent elimination, of the drug from the body:
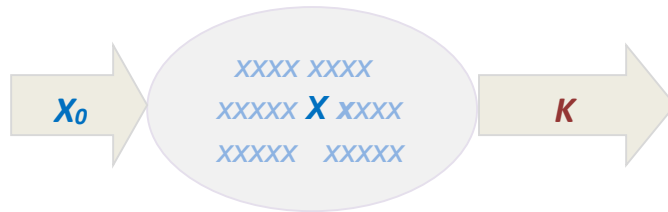
Figure 1. A schematic presentation for a one-compartment intravenous model.

According to this model, the drug is subcutaneously, intramuscularly or intravenously administered as one shot into the systemic circulation. It will be then rapidly distributed to different parts of the body in a very short period of time. Usually, this happens within few minutes after the administration of the dose. This fast distribution of the drug is associated with simultaneous clearance via different renal and hepatic elimination processes. There is ample evidence that such processes occur at a first order rate which is designated by an overall rate constant that represents the totality of the elimination processes for any drug substance.

The differential mathematical expression depicting the amount of the drug remaining in the body with time could be expressed as:

$$\frac{dX}{dt} = -KX \quad \ldots\ldots\ldots\ldots\ldots 1.0$$

This equation suggests that only a fraction amount of the drug remaining in the body gets elimination per time unit. Hence, it only depicts the ever-decreasing value of the elimination rate. The integral counterpart of Equation 1.0 may be expressed as follow:

$$X = X_0 e^{-Kt} \quad \ldots\ldots\ldots\ldots\ldots 1.1$$

Equation [1a] may be expressed in concentration terms as:

$$C_p = \frac{X_0}{V_d} e^{-Kt} \quad \ldots\ldots\ldots\ldots\ldots 1.2$$

where C_p represents the plasma concentration attained at time t, after the administration of a single dose X_0, V is volume of distribution and K is elimination rate constant.

Representation of Equation (1.2) in the logarithmic (base 10) or in the natural logarithmic form will respectively give Equations (1.3 and 1.4) as shown below,

$$\log(C_p) = \log\left(\frac{X_0}{V_d}\right) - \frac{Kt}{2.303} \quad \text{.........} \quad 1.3$$

$$\ln(C_p) = \ln\left(\frac{X_0}{V_d}\right) - Kt \quad \text{..............} \quad 1.4$$

Equation [1.4] may be also expressed in natural logarithmic terms as:

$$\ln(C_p) = \ln(C_0) - Kt \quad \text{.................} \quad 1.5$$

All the above Equation 1.5 demonstrates that the decline of the *logarithmically transformed* values of plasma levels, with respect to time, occurs in a linear fashion. This implies the representation of such value on a semi-logarithmic scale will produce a straight line with a slope equivalent to the elimination rate constant (K) and a zero-time intercept given as:

$$\ln(C_{p(0)}) = \ln(\frac{X_0}{V_d}) \quad \text{.....................} \quad 1.6a$$

$$C_{p(0)} = \frac{X_0}{V_d} \quad \text{............................} \quad 1.6b$$

The Volume of Distribution

The distribution characteristics of drugs constitute one of the major concerns in PK science. It represents a measure of the manner by which drugs get distributed in different parts of the body after its administration. It also reflects to what extent drugs get distributed in the extra-vascular space. For poorly distributed drugs, administered doses tend to remain in the system circulation. This is usually interpreted by assuming that such drugs have low volume of distribution. By contrast, drugs having higher volume of distribution tend to disappear from the circulation to various parts of the body. This may be related to the fact that such drugs possess higher affinity to proteins of the extra-vascular space compared to those circulating in the plasma.

A generalized definition to the volume of distribution may be formulated as a proportionality constant that relates the plasma concentration of the drug, at any point in time, to the total amount of the drug in the body at that particular point, i.e. $V_d = (X_t/C_t)$. According to this definition of the volume of distribution, lower plasma levels of different drugs are indicative of higher magnitude of V_d.

It should be noted that the same dose of drugs I, II and III was administered and the resulting plasma levels were measured at the same time following the drug intake. As shown above, each cylindrical shape represents the volume of distribution for one of the three drugs. The magnitude of this parameter may range from the actual size of the plasma (0.06 - 0.07 liter/kg body weight) to thousands of liters. This implies that, for neonates and infants, a volume term could be estimated at less than unity (i.e. one liter).

Reliable estimates of the volume terms are extremely important, especially within the context of dosage regimen individualization and/or the estimation of the loading dose. Erroneous volume estimates would jeopardize the ability to correctly predict the desired levels of the drug in the body.

The assessment of the distribution properties of drug is best conducted consequent to their administration via the intravenous bolus route. Drug conc.-time profiles obtained though monitoring the drug levels in the plasma are the least affected, or confounded, by other kinetic processes like absorption. The presence of such process will preclude accurate estimation of the distribution process or the volume of distribution. Different approaches have been used for the estimation of the volume terms from the plasma conc.-time data after intravenous bolus (IVB) administration. These consist either of graphic or numerical estimation procedures.

Determination of Vd Using Estimates of AUC

This method may be more reliable than the method mentioned in Equation 1.6b since it is based on the entire plasma conc.-time profile. Estimates of the area under the plasma conc.-time profile may be determined by integrating the plasma level presented in Equation 1.1c from time zero to infinity. It could be verified that such integration produces the following equality:

$$\int_0^\infty C_p dt = \frac{X_0}{KV_d}$$

Rearrangement of this expression, or solving it for V_d gives the following:

$$V_d = \frac{X_0}{K\int_0^\infty C_p dt} = \frac{X_0}{K(AUC_{0\to\infty})} \quad ....\ 1.7$$

The area under the plasma conc.-time curve from time zero to infinity ($AUC_{0\to\infty}$) could be represented by the summation of area of the plasma conc.-time profile from time zero to the last sampling point ($AUC_{0\to t}$) and the area from the last sampling point to infinity ($AUC_{t\to\infty}$)

$$AUC_{0\to\infty} = AUC_{0\to t} + AUC_{t\to\infty}$$

The first term in the above equation could be estimated as according to the linear trapezoidal rule expressed as:

$$AUC_{0 \to t} = \sum_{i=0}^{n-1} \frac{t_{i+1} - t_i}{2}(c_i + c_{i+1}) \ \ldots\ldots\ldots\ 1.8$$

The second term may be computed as:

$$AUC_{t \to \infty} = \frac{C_{p(last)}}{K}$$

Once the slope, or the elimination rate constant *(K)* has been determined on the logarithmic scale and the $AUC_{0 \to \infty}$ has been estimated on the Cartesian (rectilinear) scale, the volume of distribution could be computed as shown in Equation 1.7.

The Biological Half-life

The biological or elimination half-life ($t_{0.5}$) of drugs is an important PK metric that accounts for the duration of the sojourn of an administered dose of a drug in the body. It is also a parameter that helps in estimating the accumulation of the drugs upon repeated dosing as well as the frequency of such dosing.

The elimination half-life could be defined as the time required for any quantity available in the body, at any time, to be decreased to half its value. Using Equation 1.2, this can be exemplified by assuming that an initial quantity (X_0) equivalent to 50 mg was reduced to half its value (i.e. the quantity remaining in the body became 25 mg). It follows that:

$$X = X_0 e^{-Kt}$$
$$25 = 50 e^{-Kt_{0.5}}$$
$$0.5 = e^{-Kt} \ \ or \ \ \ln(0.5) = -Kt_{0.5}$$
$$Since \ \ \ln(0.5) = -\ln(2), \ \ then \ \ t_{0.5} = \frac{\ln(2)}{K}$$

The mathematical expression given in the above section (Equations 1.2, 1.3 and 1.4) provide basis for the computation of many useful PK metrics that have distinct clinical signification. Although drug plasma levels represent a general concern within the domain of PK science, the magnitude of drug accumulation, upon repetitive dosing, remains the most important aspect of drug therapy. In as much as accumulation of drugs in the body may be related to their therapeutic efficacy, it is also linked to its adverse effects. A so called Therapeutic Window (TW) has been established for a large number of drug entities. The concept of a TW defines a maximum level beyond which adverse may effects set in, and a minimum level below which the desired therapeutic effect will be lost. Biological half-lives of drugs vary from few minutes (4.0 - 5.0 for insulin), to several hours, days or even weeks.

In addition to the magnitude of drug accumulation consequent to repeated dosing, the degree of fluctuation in drug plasma levels may have an impact on the therapeutic outcome. The relative ratio of peak to trough plasma level represents a direct measure of the degree of fluctuation. This issue constitutes concern for clinicians as well as drug regulatory bodies at an international scale.

Multiple Dosing of IV Bolus Model

For drugs administered on repeated or multiple dosing bases, in the long run a maximum, minimum or average plasma levels will reach stable levels. Time required for such level to be reach is solely determined by the drug's elimination characteristics irrespective of the dosing frequency. As demonstrated above, the magnitude of these levels is a function of these characteristics, as well as the dosing rate (administered doses and the dosing interval). This PK model could be expressed in a generalized manner suited to construct the plasma conc.-time profiles after the administration of a single dose or under multiple dosing conditions.

$$C_p^N = \frac{X_0}{V_d}\left(\frac{1-e^{-NK\tau}}{1-e^{-K\tau}}\right)e^{-Kt} \ldots\ldots\ldots\ldots 1.9$$

The model presented in Equation 1.9 allows the estimation of plasma drugs levels, during any dosing interval, at any N number of doses. The bracketed quantity represents what could be called a multiple dosing factor (MDF) which determines the magnitude of accumulation of the drug in the body when repetitive doses are administered at regular time intervals. Equation 1.9 could be readily transformed to an expression suited for a single dose by setting N (the number of doses) to unity.

Maximum and minimum plasma levels could be estimated during multiple dosing, at any number of doses, by setting the time in the decay exponent to zero (the start of the new dose) or to τ (the end of the dosing interval). This will respectively produce Equations 1.9a and 1.9b as shown below

$$C_{p(\max)}^N = \frac{X_0}{V_d}\left(\frac{1-e^{-NK\tau}}{1-e^{-K\tau}}\right)\ldots\ldots\ldots\ldots 1.9a$$

$$C_{p(\min)}^N = \frac{X_0}{V_d}\left(\frac{1-e^{-NK\tau}}{1-e^{-K\tau}}\right)e^{-K\tau}\ldots\ldots\ldots 1.9b$$

These equations may also be transformed to account for the estimation of drug plasma levels under steady state situations. Under these conditions, the expression $e^{-NK\tau}$ oximate zero as N tends to higher values, hence,

$$C_p^{ss} = \frac{X_0}{V_d}\left(\frac{1}{1-e^{-K\tau}}\right)e^{-Kt}\ldots\ldots\ldots\ldots 1.9c$$

The maximum and minimum plasma levels at steady state could be also estimated according to equations 3a and 3b respectively,

$$C_{p(\max)}^{ss} = \frac{X_0}{V_d}\left(\frac{1}{1-e^{-K\tau}}\right)\ldots\ldots\ldots\ldots\ldots 1.9d$$

$$C_{p(\min)}^{ss} = \frac{X_0}{V_d}\left(\frac{1}{1-e^{-K\tau}}\right)e^{-K\tau}\ldots\ldots\ldots\ldots 1.9e$$

These two equations give measures of the steady state maximum and minimum plasma levels under multiple dosing conditions. While the maximum level is what is obtained immediately after the administration of a new dose, the minimum level is what is measured prior to such administration.

Attainment of Steady State (SS) Plasma Levels

It is obvious from the above multiple dosing equations that it is possible to determine drug levels in the plasma, during the dosing interval, after any number of administered doses as well as under SS condition. For the latter state to be reached the expression $e^{-NK\tau} = e^{-0.693N(\tau/t_{0.5})}$ must become very insignificant or approximates a zero value. This occurs when the number of doses (N) becomes sufficiently large. Irrespective of the number of administered doses, or the dosing interval such situation can only occur when the elapsed time, after the initiation of dosing regimen, approximate seven biological half-lives. Also, it is possible to mathematically determine the time required for a fraction of the SS (fss) to be reached. This could be done by dividing any plasma level metric attained after a certain number of doses by its corresponding SS metric. This could be mathematically expressed as:

$$f_{SS} = \frac{C_{\max}^{N}}{C_{\max}^{ss}} = \frac{X_0}{V_d}\left(\frac{1}{1-e^{-K\tau}}\right) \Big/ \frac{X_0}{V_d}\left(\frac{1-e^{-NK\tau}}{1-e^{-K\tau}}\right)$$

Cancellation of common term and simplification gives the following:

$$f_{SS} = 1 - e^{-NK\tau}, \quad or \quad 1 - f_{SS} = e^{-NK\tau}$$

In natural logarithmic terms, this expression could be re-written as:

$$-NK\tau = \ln(1 - f_{SS}), \quad or$$
$$-N\tau = 1.44 * t_{0.5} \ln(1 - f_{SS})$$

The expression $-N\tau$ in the above equation represents the length of time in terms of the number of doses and the dosing interval. It is evident that this parameter is directly proportional to the biological half-life of the drug. This situation is detailed in the following section.

The Loading Dose (X_{LD})

The therapeutic efficacy for many drugs is generally associated with certain plasma level. Accordingly, therapeutic windows have been determined for such drugs. However, when the biological half-life of a drug is relatively long, it will take a considerable time for the plasma levels to reach their therapeutic window. In general, it will take about four biological half-lives to reach 90% of the drug's steady state levels in the body.

The estimation of the loading dose should be done in a way to ensure the minimum plasma level it will produce towards the end of the first dosing interval will be identical to the predicted minimum level attained at steady state. This could be mathematically expressed, for intravenous bolus dosing as:

$$\frac{X_L}{V_d} e^{-K\tau} = \frac{X_0}{V_d}\left(\frac{e^{-K\tau}}{1-e^{-K\tau}}\right)$$

Cancellation of the common term and re-arrangement of this equation give the following:

$$\frac{X_{LD}}{X_0} = \left(\frac{1}{1-e^{-K\tau}}\right) \quad or \quad X_{LD} = X_0 * MDF$$

where MDF is defined as the multiple dosing factor, or the accumulation ratio (see next section), for a one-compartment model drug administered by an intravenous bolus mode.

Drugs Accumulation Ratio (AR)

A direct measure of the drug accumulation in the body could be estimated as a ratio between the maximum (or minimum) plasma levels attained after the administration of a single dose to their corresponding values at steady state.

$$AR = \left(\frac{1}{1-e^{-K\tau}}\right)\frac{X_0}{V_d} \Big/ \frac{X_0}{V_d}$$

Cancellation of common terms in the above equation yields the following expression that constitutes a measure of the degree of drug accumulation for a one-compartment model drug administered by an intravenous bolus mode.

$$AR = \frac{1}{1-e^{-K\tau}} = 1 \Big/ 1-e^{-0.693\frac{\tau}{t_{0.5e}}}$$

Average Plasma Concentration, $C_{p(av)}$

Although the therapeutic efficacy of certain drugs is often associated with maximum and a minimum plasma levels as mentioned above, the average plasma concentration would represent a superior PK indicator to such efficacy. A definition for this metric is usually related to the area under the plasma conc.-time curve (AUC) divided by the dosing interval. AUC could be determined by integration of Equation 1.1b from time zero to infinity after the administration of a single dose, hence

Cons $\int_0^\infty C\,dt = \frac{X_0}{}$ lasma concentration is estimated as:

$$C_p = \frac{X_0}{\tau K V_d}$$

However, under multiple dosing, Equation 1.1 must be adjusted in order to account for this situation, by multiplying it by Dost's multiple dosing factor $(1 - e^{-NK\tau} / 1 - e^{-K\tau})$:

$$C_p = \frac{X_0}{V_d}\left(\frac{1 - e^{-NK\tau}}{1 - e^{-K\tau}}\right)e^{-Kt}$$

This above equation may be integrated from time zero to end of the dosing interval. Details of this integration are provided below:

$$C_{av}^N = \frac{\int_0^\tau C_p^N}{\tau} = \frac{X_0}{\tau K V_d}(1 - e^{-NK\tau}) \ \ .... \ (1.10)$$

Equation 1.10 indicates that the average plasma levels ($C_{p(av)}^N$), as a function of the area under the plasma conc.-time curve, varies with repetitive dosing. The magnitude of $C_{p(av)}^N$ is determined by a constant quantity $(X_0 / \tau K V_d)$ for any multiple dosing situation which is multiplied by a variable quantity $(1 - e^{-NK\tau})$. This variable quantity reaches its maximum level as the exponential term $e^{-NK\tau}$ approximates zero as the number of doses (N) tends to increase. In this case Equation 1.6 reduces to the following expression:

$$C_{av}^{ss} = \frac{\int_0^\tau C_p^{ss} dt}{\tau} = \frac{X_0}{\tau K V_d} = \frac{C_0}{\tau K} = C_0 * 1.44\frac{t_{0.5}}{\tau} \ \ .....(1.13)$$

where $C_{P(0)}$ is defined as the zero-time intercept of the plasma conc.-time profile.

As implied by Equation 1.13a, the value of $C_{p(av)}^{ss}$ is a constant quantity that could be only attained at what has been conventionally called the steady state situation. The magnitude of such quantity is a function of the drug's elimination properties as well as the dosing interval. This implies that the average plasma concentration at steady state is proportional to the biological half-life if the drug and inversely proportional with the dosing interval.

Magnitude of Fluctuation (MoF)

There are different measures to assess the fluctuation of drug in the body at steady state. This can be expressed, in simplistic term as the ratio of the maximum to the minimum levels attained under SS condition as shown below,

$$MoF = \frac{C_{p(max)}^{ss}}{C_{p(min)}^{ss}} = \frac{X_0}{V_d}\left(\frac{1}{1 - e^{-K\tau}}\right)\Big/ \frac{X_0}{V_d}\left(\frac{1}{1 - e^{-K\tau}}\right)e^{-K\tau}$$

$$MoF = \frac{1}{e^{-K\tau}} = e^{K\tau}, \ \ or \ \ ln(MoF) = \ln(2)\frac{\tau}{t_{0.5}} ...... \ 1.14$$

Equation 1.14 indicates that the degree of fluctuation could be minimized by decreasing the length of the dosing interval.

The Degree of Fluctuation (DoF_swing)

Official measures have been suggested for the assessment of the degree of fluctuation. One such measure is called the swing, which relates the difference between the maximum and minimum plasma levels to the average plasma concentration at steady state in the following fashion:

$$DoS_{(SWING)} = \frac{X_0}{V_d}\left(\frac{1}{1-e^{-K\tau}}\right) - \frac{X_0}{V_d}\left(\frac{e^{-K\tau}}{1-e^{-K\tau}}\right) \Big/ \frac{X_0}{\tau K V_d}$$

Cancellation of the common and rearrangement of the above expression produces the following relationship:

$$DoS_{(SWING)} = \left(\frac{1}{1-e^{-K\tau}}\right) - \left(\frac{e^{-K\tau}}{1-e^{-K\tau}}\right) \Big/ \frac{1}{\tau K} = \frac{\tau K}{1-e^{-K\tau}}\left(1-e^{-K\tau}\right) = \tau K = 0.693\frac{\tau}{t_{0.5}}$$

This relationship suggests that the degree of fluctuation is a function of the elimination characteristics and the dosing frequency.

Targeting Therapeutic Ranges

Conventionally, clinical practioners aim at multiple dosing regimens that would guarantee a maximum plasma level is not exceeded or that plasma levels are maintained above a minimum clinically concentration.

For drugs that have a well-established therapeutic window, it is often desirable to will produce plasma drug levels that falls within such window. This implies that such levels must not exceed a maximum, or decline to less than a minimum, predefined level. Since we generally have a prior knowledge of the therapeutic window of certain drugs, the relationship between the boundaries of this window could be determined according to the elimination characteristic as well as the dosing frequency.

A new dosing interval may be defined on the basis of the desired levels of C_{max}^{SS} and C_{min}^{SS} as follows:

$$C_{min}^{ss} = C_{max}^{ss} e^{-K\tau}$$

$$\frac{C_{min}^{ss}}{C_{max}^{ss}} = e^{-K\tau} \quad and \quad \ln\left(\frac{C_{min}^{ss}}{C_{max}^{ss}}\right) = -K\tau$$

$$\tau_{New} = \frac{1}{K}\ln\left(\frac{C_{max}^{ss}}{C_{min}^{ss}}\right)$$

As demonstrated above, a dosing interval could be defined for any drug in such a way to produce a maximum and a minimum plasma level. Once such interval has been determined, it becomes possible to compute the maintenance dose that will produce these levels in accordance with the following manner.

$$C_{\min}^{ss} = \frac{X_0}{V_d}\left(\frac{e^{-K\tau_{New}}}{1-e^{-K\tau_{New}}}\right), \quad X_0 = \frac{C_{\min}^{ss}V_d(1-e^{-K\tau_{New}})}{e^{-K\tau_{New}}}$$

It is advisable to determine the dose that will ensure the attainment of the desired therapeutic window on the basis of Cmin since it is more reliable than other methods that incorporate Cmax which could confound the estimation of correct dose. This is particularly relevant in case where absorption or distribution phase is present.

Renal Clearance

Clearance may be defined, in simplified general terms, as the process(s) by which a substance gets cleared from the body through varying elimination mechanisms. Depending on the organ responsible for the elimination of these substances, clearance more strictly defined. Accordingly, it may be renal, hepatic or biliary or through the lungs. In more precise physiological terms, clearance may be defined as the organ's excretion rate ($k_r X$) divided by the plasma levels of the substance being excreted. Hence,

$$Cl_r = \frac{dX_u/dt}{C} = \frac{k_r X}{C}$$

However, since *X/C* has been earlier defined as the volume of distribution (V_d), the above expression can be restated as $Cl_r = k_r V$. This is a very important expression since it indicates a reality that is often ignored, or not emphasized, in the PK literature. It simply signifies that clearance, in PK terms, is a fraction of the volume of distribution that is cleared from the drug per unit time.

By the very fact that the PK literature has been marred with some inconsistent reporting of PK metrics, such as the biological half-lives and the volume of distribution, the equality $Cl_r = k_r V$ may be always referred to so as to verify the accuracy of the PK metrics being reported. This is not only a concern of an intellectual of scientific nature; rather, it has to do with the validity of a wide range of PK application such as the prediction of drugs levels in the body or the individualization od dosing regimens.

Taking into consideration that the urinary excretion rate is defined in terms of clearance as $dX_u/dt = Cl_r C$, then the slope of a plot of this rate versus the instantaneous plasma levels will be equated with the renal clearance. This requires that plasma levels must be taken at time points that are identical to the midpoint of urine collections.

An alternative method could be also provided to estimate renal clearance based on estimating the area under the plasma conc.-time profile between the two time point where urine has been collected. i.e.

$$\left(X_u\right)_{t1}^{t2} = Cl_r \int_{t1}^{t2} C dt$$

The later approach used for the estimation of clearance implies an approach for determining the distribution characteristics of drugs. The previous expression may be modified to estimation clearance and, consequently, the volume of distribution from the entire amount of the un-metabolized that is ultimately excreted and the total area under the plasma conc.-time profile as:

$$\left(X_u\right)_0^\infty = k_r V_d \int_0^\infty C dt, \ \& \ hence, \ V_d = \left(X_u\right)_0^\infty \Big/ k_r \int_0^\infty C dt$$

However, since the volume of distribution has been earlier estimated as: $\quad V_d = X_0 / K \int_0^\infty C dt$
It follows that,

$$\frac{\left(X_u\right)_0^\infty}{k_r \int_0^\infty C dt} = \frac{X_0}{K \int_0^\infty C dt}, \ \ or \ \ \frac{\left(X_u\right)_0^\infty}{k_r} = \frac{X_0}{K}$$

The above equation relates the urinary excretion rate constant (k_r) to the overall elimination rate constant (K). It is obvious that when the administered dose (X_0) equals the total amount of the intact form of drug excreted by the kidneys (X_u), then values of these two rate constants are identical. If this is not the case, then the urinary excretion rate constant will be given as given as fraction of the overall elimination rate constant:

$$k_r = K \left(X_u\right)_0^\infty / X_0$$

It could be concluded that estimation of the urinary excretion rate constant from urinary data per se is not feasible. This requires a prior knowledge of the overall elimination rate constant which must be derived from plasma conc.-time data obtained consequent to the administration the drug in the form of an intravenous bolus dose.

Intravenous Infusion Model

There are some situations that necessitate the administration of drugs by intravenous infusion. Drugs with very sort half-lives are often administered via this route. Also, for comatose patients, the intravenous route of administration remains the only way of administering drugs.

Unlike most other convoluted PK models with continuous flow of time, 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

The development of a PK model suited for intravenous must take into account some unique features of this kinetic situation. Unlike many other kinetic models, the intravenous infusion model may be considered as mixed-rate model. This assumption is based on the realization that most linear PK models consist of one or more than one exponential driving force, representing different simultaneous kinetic processes. The totality of these processes amounts to some sort of a continuous function. This is not the case with intravenous infusion models since they contain a zero-order input rate which concurrently proceeds with a first-order decay rate. The abrupt cessation of infusion brings the value of the input function of the model to a zero, implying the termination of a phase and resulting in a discrete quantity. Consequently, the post infusion phase will represent another distinct phase with its discrete quantities. Such considerations have not been avidly expressed in the conventional mathematical models that have been developed for the intravenous infusion dosing.

A schematic presentation for a one compartment intravenous infusion model could be described as follows:
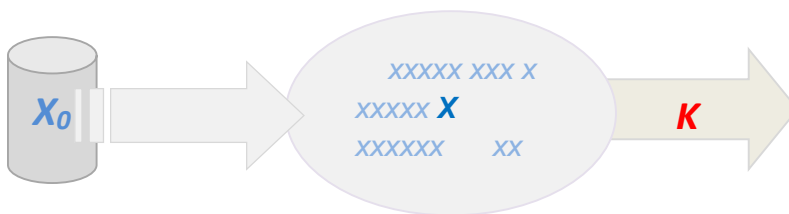
Figure 2. Schematic presentations for intravenous infusion of a drug to the systemic circulation and its consequent elimination.

A differential expression describing the input or delivery of the drug to the systemic circulation and the elimination from the body could be described as:

$$\frac{dX}{dt} = k_0 - KX$$

where k_0 is the a zero-order input rate, K is an overall elimination rate constant and X is the total amount of the drug in the body.

Solving Equation 9 for X gives the following expression which describes the buildup of drugs levels in the body during infusion:

$$X = \frac{k_0}{K}(1 - e^{-Kt_i}) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots(2.1)$$

This equation describe the change (increase) of the drug quantity during infusion

$$X = \frac{k_0}{K}(1 - e^{-KT_i})e^{-K(t-T_i)} \ldots\ldots\ldots\ldots\ldots(2.1a)$$

where t_i is the variable infusion time, T_i is a time constant representing the duration of infusion and $(t-T_i)$ is the post infusion time (t_{ni}).

$$C_P = \frac{k_0}{KV}(1 - e^{-Kt_i})e^{-Kt_{pi}} \ldots\ldots\ldots\ldots\ldots\ldots.(2.1b)$$

This model could be re-written in terms of two discrete quantities as follows:

$$C_P = \frac{k_0}{KV_d}(1 - e^{-Kt_i}) + \frac{k_0}{KV_d}(1 - e^{-KT_i})e^{-Kt_{pi}} \ldots.(2.1c)$$

where k_0 is the infusion rate, t_i is a *variable* infusion time and T_i is a constant time value representing the length of the infusion period. Other parameters where defined earlier.

After collation of terms in Equation 2.1b could be also expressed as:

$$C_P = \frac{k_0}{KV_d}(1 - e^{-Kt_i}) + \frac{k_0}{KV_d}(e^{-K(t-T_i)} - e^{-Kt}) \ldots..(2.1d)$$

It must be noted that the infusion time (t_i) varies during infusion, until it reaches a constant value (T_i) which equals the entire infusion time.

Equations 9a through to 9d could be used to generate plasma conc.-time profiles during and post-infusion periods. Plasma levels during the infusion phase could be expressed by the first discrete term of Equation (9) which given as:

$$C_P^{t_i} = \frac{k_0}{KV_d}(1 - e^{-Kt_i}), \ and \ C_P^{ss} = \frac{k_0}{KV_d} \ \ldots..(2.1e)$$

According to this expression, when the exponent within the bracketed term in this expression become insignificant as time increases, hence, the steady state level becomes equivalent to k_0/KV_d. It is obvious that the fraction of this level is determined by the value of the exponent e^{-Kt_i} in the equation that determines the plasma levels during infusion.

In order that further verification to assumption made above, the following table has been generated to demonstrate the relationship between the fraction of the C_p^{ss}, the biological half-life and the infusion time expressed in terms of the number of half-lives.

PK of Intermittent Infusion

A new approach for the development of a one-compartment multiple dosing model, for drugs administered by *IVI*, could be contemplated on the basis of Equation 2.1a provided above. It is evident that this equation represents a combination of two equations that are mathematically discrete. This is due to the fact that its first term is a mixed-order rate since it contains a zero-order input, as well as a first-order decay function; whereas second term represents a first-order decay term. Accordingly, these functions have to be treated differently from a temporal standpoint.

The second part of Equation 2.1a could be readily transformed into a multiple dosing expression that accounts for the increase in the plasma levels in the post-infusion phase upon repetitive dosing. This is done by multiplying it by the accumulation ratio $(1-e^{-NK\tau})/(1-e^{-K\tau})$. However, a different approach must be adopted for the transformation of the first term of this equation so that it accounts for the plasma profile during the infusion phase. It has been acknowledged that the ascending part of the plasma profile during intermittent infusion consists of a standard quantity produced by the term $k_0/KV(1-e^{-Kt_i})$ in addition to the plasma levels emanating from minimum plasma levels of the previous infusion up to the cessation of the current infusion. This realization has been reflected in Gibaldi's work as he and his co-workers have devised an intermittent infusion multiple-compartment model. However, since no such model for one-compartment has been given by them, the following model has been devised:

$$C_p^N = \frac{k_0}{KV}(1-e^{-Kt_i}) + \frac{k_0}{KV}(1-e^{-KT_i})e^{-K(\tau-T_i)}e^{-Kt_i}\left(\frac{1-e^{-(N-1)K\tau}}{1-e^{-K\tau}}\right) \; for \; t \le T_i$$

$$C_p^N = \frac{k_0}{KV}(1-e^{-KT_i})\left(\frac{1-e^{-NK\tau}}{1-e^{-K\tau}}\right)e^{-Kt_{pi}} \; for \; t \ge T_i \text{..............................} (2.2)$$

A simplified version of this model is also presented hereunder and will be used throughout the present study.

$$C_p^N = \frac{k_0}{KV(1-e^{-K\tau})}\left[1-e^{-Kt_i}\left\{1-e^{-KT_{pi}}+e^{-NK\tau}(e^{KT_i}-1)\right\}-e^{-K\tau}\right] \; for \; t \le T_i$$

$$C_p^N = \frac{k_0(1-e^{-NK\tau})}{KV(1-e^{-K\tau})}(1-e^{-KT_i})e^{-Kt_{pi}} \quad for \; t \ge T_i \text{..............................} (2.3)$$

The interesting characteristic of this model is its profiling capability during the entire infusion phase. This is expressed by its exponential driving force represented by the expression $1 - e^{-Kt_i}$ which causes the increase in plasma levels until a SS level $((k_0 / KV(1 - e^{-K\tau}))$ has been reached. These ascending levels are determined by the interplay of this driving force and the rest of constant values of all other exponential terms contained in the square brackets in Equation 4a. It evident that this equation may be readily transformed into an expression which account for plasma levels under SS situations through the cancelation of the term associated with the expression $NK\tau$, hence,

$$C_p^{ss} = \frac{k_0}{KV(1 - e^{-K\tau})}\left[1 - e^{-Kt_i}(1 - e^{-KT_{pi}}) - e^{-K\tau}\right] \ \ for \ t \leq T_i$$

$$C_p^{ss} = \frac{k_0}{KV(1 - e^{-K\tau})}(1 - e^{-KT_i})e^{-Kt_{pi}} \ \ for \ t \geq T_i \ .... \ (2.4)$$

Model Verification by Superposition

As explained in the PK of multiple dosing, the principle of superposition may be regarded as the most basic and rugged technique for testing the validity of profile generated by different mathematical models.

The above model has been verified against the most basic drug accumulation principle which is the superposition principle.

Mathematical Model Verification

Results obtained with this new model could be also demonstrated to be consistent with the continuous infusion model by setting the infusion time (T_i) equivalent to the dosing interval (τ). In this case the second term in the above expression will be cancelled since there will be no post infusion phase. Hence, the above expression becomes as follows:

$$C_p^{T_i = \tau} = \frac{k_0}{KV_d}(1 - e^{-K\tau}) + \frac{k_0}{KV_d}(1 - e^{-K\tau})e^{-K(\tau - \tau)}\left(\frac{1 - e^{-(N-1)K\tau}}{1 - e^{-K\tau}}\right)e^{-K\tau}$$

Further simplification of the above equation gives the following:

$$C_P = \frac{k_0}{KV_d}(1 - e^{-K\tau} + e^{-K\tau} - e^{-NK\tau}) = \frac{k_0}{KV_d}(1 - e^{-NK\tau})$$

This is a similar expression to that given in Equation 2.1a which will ultimately give the same steady state levels provided that the same PK metrics are used in either situation. However, the initial part of the plasma conc.-time profile will consist of discrete quantities until the steady level has been attained. The above expression may be re-written to account for the changes in the plasma levels during any dosing interval, hence,

$$C_P = \frac{k_0}{KV_d}(1 - e^{-NKt_{0-\tau}}), \quad and \quad C_P = \frac{k_0}{KV_d}$$

However, it should be emphasized that this relationship is meant to show that there exists a term or an entity in the full model that can generate continuous plasma levels under intermittent infusion conditions.

Another approach has been attempted to mathematically verify the validity of this model. This approach is based upon the axiomatic realization related to area estimations. It is universally accepted that the area under the plasma conc.-time curve resulting after the administration of a single dose, from time zero to infinity, is equivalent to that measure between two consecutive doses at steady state, i.e.

$$\int_0^\infty C_P^{N=1}dt = \int_0^\tau C_P^{ss}dt \Rightarrow \tau \geq T_i$$

Average Plasma Concentration (Cav)

The average plasma concentration at different dosing interval could be defined upon the integration of the first equation (C_{p1}). Due to its therapeutic efficacy, the average plasma level is more important than just defining C_{max} and C_{min}.

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

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

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

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.

Targeting Therapeutic Plasma Levels

Provided that a definition for a therapeutic window is available, it is quite possible to determine a dosing rate and frequency that will generate the desired plasma concentration range.

Different approached are provided hereunder:

Using C_{max}^{ss} and C_{min}^{ss}

One can determine a dosing rate (infusion rate and a dosing interval) if a certain plasma concentration range is to be attained. This requires a prior definition of maximum and minimum plasma levels. The mathematical considerations for this objective are provided hereunder:

$$\tau_{New} = T_i - \frac{1}{K}\left(\ln\frac{C_{min}^{ss}}{C_{max}^{ss}}\right)$$

If new maximum and minimum steady state plasma levels are to be targeted, while the infusion time is kept constant, a new dosing interval has to be estimated according as described hereunder.

The calculated dosing interval (τ_{New}) is then used to determine the infusion rate that will produce the desired targets by two ways:

$$C_{max}^{ss} = \frac{k_{0L}}{VK}(1 - e^{-KT_i})\left(\frac{1}{1 - e^{-K\tau}}\right)$$

$$k_{0T} = \frac{C_{max}^{ss} V_d K(1 - e^{-K\tau_{New}})}{(1 - e^{-KT_i})}$$

Alternatively, the similar values could be obtained for the infusion rate on the basis of the minimum plasma levels as per the following equalities:

$$C_{min}^{ss} = \frac{k_{0L}}{Vk}(1 - e^{-KT_i})\left(\frac{1}{1 - e^{-K\tau}}\right)e^{-K(\tau_{New} - T_i)}$$

$$k_{0T} = \frac{C_{min}^{ss} V_d K(1 - e^{-K\tau_{New}})}{e^{-K(\tau_{New} - T_i)}(1 - e^{-KT_i})}$$

An infusion rate estimated according to either of the above equations will exactly give the same value.

Loading Dose for Intermittent Infusion

Loading dose consideration assumes critical significance for drug with relatively long biological half-life. This is related to the fact that the attainment of steady state levels for such drugs will take a long time. It is

equally important in case of severe impairment of the drugs elimination processes. Estimates of the loading dose are generally based on drugs accumulation ratio (*AR*) expressed as: $C_{0-\tau}^{ss} / C_{0-\tau}^{N=1}$. This is based on a gross generalization with regard the estimation of area after a single infusion and that are obtained at steady state between two consecutive doses.

These area related assumptions are true in cases of intravenous and oral bolus administrations of drugs. Hence, estimates for the loading dose such as $X_L = AR * X_0$ where suggested and successfully employed. This approach has been demonstrated to be suitable for the intravenous infusion dosing and further extrapolated to the intermittent infusion. However, the administration of an intravenous bolus loading dose estimated as $X_L = C_p^{ss}V_d$ or $X_L = k_0 / K$ as suggested by the entirety of the relevant PK literature.

As an alternative approach to that suggested by Gibaldi, the loading dose could be better defined as $X_L = C_{min}^{ss}V_d$, where C_{min}^{ss} could be defined as the minimum steady state plasma level. This suggestion is based on the intuition that the administration of a bolus dose, estimated on C_{max}^{ss} or even the C_{av}^{ss} plasma levels at steady state, together with the initiation of infusion, higher levels that such steady state levels are bound to occur. It has been demonstrated that the simultaneous administration of an intravenous bolus dose with the predefined infusion regimen has produced steady state levels immediately with the initiation of infusion if the loading dose was determined as $C_{min}^{ss}V_d$.

Another intravenous infusion loading approach, similar to that attempted by Wagner, could be contemplated in situations where gradual instillation or infusion of the dose is favored. However, the direct implementation of Wagner's approach, as detailed for the continuous infusion has resulted in initial plasma levels that were higher than the predicted steady state levels. A new method could be suggested for the estimation an intravenous infusion loading dose (or rate). This method is based on the theoretical estimation of the expected maximum steady state plasma level (C_{max}^{ss}) for any infusion situation. This is generally expressed as:

$$C_p^{ss} = \frac{k_0(1-e^{-KT_i})}{KV_d(1-e^{-K\tau})}$$

where k_0 is the regular infusion rate used for the post infusion loading phase.

This quantity could be then used to estimate the infusion loading rate (k_{0L}) for any predefined infusion time (t_{iL}) that will be enough to attain this plasma levels. Once such level has been reached, after the drug has been infused at this rate (k_{0L}) for any infusion period (T_{iL}), the C_{max}^{ss} will have been reached.

$$k_{0L} = \frac{C_p^{ss}KV_d}{(1-e^{-KT_{iL}})}$$

After that the infusion rate is switched to the regular rate (k_0) which will be used throughout the intermittent dosing regimen after the cessation of the infusion loading.

The validity of this procedure could be verified for any dosing interval during the intermittent infusion. Noteworthy, it has been suggested (Milo Gibaldi) that a loading dose may be determined as:

$$X_L = \frac{k_0 T_i}{(1 - e^{-K\tau})}$$

I.V. Bolus Loading and Simultaneous Infusion

As detailed above, in instances with drug substances have a relatively long biological half-life, the attainment of a steady state concentration will take considerable length of time. This may not of benefit where the therapeutic efficacy is associated with drugs steady state plasma level. Hence, a loading dosing should be considered. This dose must be of such magnitude so that it produced the steady state plasma level at the initiation of the dosing regimen. This can only be achieved if the loading dose is administered by an intravenous bolus mode together with the initiation of infusion.

For any defined infusion criterion, the value of the steady state level could be estimated as k_0 / KV_d. Consequently, the value of the intravenous loading dose could be obtained by multiplying this quantity by the volume of distribution of the drug, i.e. $k_0 * V_d / KV_d$ or simply; k_0 / K. Under these circumstances, it could be verified that the resulting plasma level will be identical to the steady state level right from the initiation of infusion and will be maintained at this level throughout the infusion period. This could be verified as follows:

One of the prime characteristics of the PK linear model is their additive nature. This implies that if more than one dose have been simultaneously administered via different routes, such as intravenous and oral, the resulting plasma levels from one model could be summed up to those ensuing from the other model.

I.V. Infusion Loading Followed by Maintenance Infusion

The loading approach explained above may not be feasible or has its limitations. This is due to the fact that the intravenous bolus administration may cause rapid highly plasma levels that may entail the occurrence of unwarranted adverse reactions. In such cases an alternative loading approach must be contemplated. It has been suggested that the dosing regimen consists of two consecutive infusions with different infusion rates (k_{01} and k_{02}). Wagner has suggested that once the maintenance infusion criteria has been defined, the steady state plasma levels could be determined as k_{02}/KV_d. The maintenance infusion rate (k_{02}) is doubled and the drug is infused over a period of one biological half-life. Doubling the maintenance infusion rate is based on the realization that, for any drug and/or any infusion criteria, it usually takes one biological half-life to attain 50% of the steady state plasma levels. Hence, 100% of such level will be reached with the same if the infusion rate is doubled.

The above approach could be applied for drug with relatively short biological half-lives (less than 2 or 3 hours). However, for drug with much longer half-lives, or drugs with severely impaired elimination characteristics due to kidney failure or hepatic dysfunction, the Wagner's approach becomes unattractive.

As an alternative to the above approaches, it is feasible to determine the rate of the first infusion according to any chosen infusion time. Once the infusion period has been selected, the first infusion will be automatically estimated. The estimation of the infusion is lift flexible to the practitioner to decide upon according to the case at hands. This approach is better illustrated by examining the following mathematical considerations. Rearrangement of Equation 9b for the infusion phase to estimate the loading infusion rate gives the following expression:

$$k_{01} = \frac{C_p^{ss} * V_d * K}{1 - e^{-KT_{inf(01)}}}$$

where C_p^{ss} is the target plasma level associated with the maintenance infusion rate and T_{inf} is the length of the loading infusion time and

$$C_{p(01)}^{ss} = k_{01} / V_d K$$

$C_{p(01)}^{ss}$ represents the steady state level had the drugs been administered with a continuous loading infusion at k_{01} rate. Hence, plasma levels resulting from the loading could be estimated according to the following equation:

$$C_{p(01)} = C_{p(01)}^{ss} (1 - e^{-Kt_{inf(01)}})$$

This clearly signifies that the maximum plasma levels during the first infusion period will not exceed the planned or targeted steady state levels associated with the maintenance.

For PK-naïve practitioners, an infusion loading of 1400 mg/hours seems to be a huge rate if compared by the maintenance infusion rate of 40 mg/hour. However, as demonstrated in the above, the plasma levels under extremely varying scenarios remained within the controls specified for the particular dosing regimen.

Oral Bolus Model

For convenience and compliance related reasons, the vast majority of drugs are usually administered via the oral or the extra-vascular route of administration in varying dosage forms.

Consequent to the administration of an oral dosage form to gastric lumen, the drug gets absorbed and enters the systemic circulation from which it will be eliminated. These processes may be diagrammatically presented as follows:
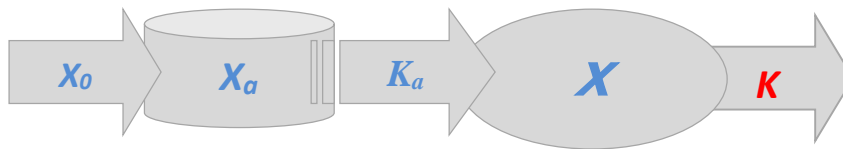

Figure 3. Schematic presentations for plasma conc.-time profiles for a one-compartment intravenous model as per Equation 1.2 (left plot) and 1.3 (right plot).

where K_a is a first order apparent absorption rate constant and X_a is the quantity of the administered dose that is actually available for absorption. Other parameters have been defined earlier.

Appreciation for the mode of administration of the oral dosage form is critical for the adequate interpretation of this model. If a drug has been administered as bolus manner (i.e. immediate release solid or liquid forms), the absorption rate will be of a first order nature. However, for sustained release form, this rate will be seriously confounded by the release pattern of the drug from the dosage form. In other words, the mode of release of the drug from the dosage form will represent the rate-limiting step in the entire absorption process. This will result in a situation that mimics the intravenous infusion model since both will have the zero input rates in the system.

Based on the above consideration, the mathematical treatment of the orally administered drugs must take into account the nature of the input rate of such drugs from their dosage form. Consequently, two distinct scenarios may be contemplated, as described hereunder.

Oral PK with first-order absorption

Considering the conceptual model as outlined above, a differential expression incorporating the absorption of the gastric and intestinal lumen may be provided as:

$$\frac{dX}{dt} = K_a X_a - KX$$

Taking the integral form of this equation will yield the following expression

$$X = \frac{K_a F X_0}{(K_a - K)}\left(e^{-Kt} - e^{-K_a t}\right)$$

26

It is noteworthy that the first order elimination does not represent a true description of the absorption process since it does not account for the fraction of that dose that has been subject to this process. This is related to the realization that parts of the administered dose may never be absorbed into the systemic circulation due to the physic-chemical nature of the drug entity. Also, other parts may be lost through various metabolic processes prior to the entry of the drug to the blood stream. For these reasons, any measurements of the absorption rate are an apparent by their very nature.

The above differential equation may be represented in an integral form to estimate the drug concentration in the plasma as a function of time

$$C_P = \frac{K_a F X_0}{V_d (K_a - K)} \left(e^{-Kt} - e^{-K_a t} \right)$$

The above mathematical model is only valid where the absorption rates are different from the elimination rates, i.e. $K_a <> K$.

This model could be used to simulate the plasma conc.-time profile under different conditions. It also represents a unique instance through which the convolution nature of the compartmental PK models could be clearly demonstrated. The concept of convolution is intimately related to most domains of the PK science. This holds true since the magnitude of drug levels in the body are determined by the number of the driving forces consisting any particular PK system. Consequently, it must be realized that the impact of such forces is decided by the magnitude of the exponential terms representing them. With the exception of the one-compartment intravenous model, the evaluation of drug's plasma conc.-time data implies the deconvolution of convoluted PK systems.

Considering the one-compartment oral model, the magnitude of the time-dependent variable (plasma levels) in this model is determined by a constant value, $K_a F X_0 / V_d (K_a - K)$, and two driving forces associated with the absorption and elimination processes. The make-up of these two forces consists of the rate constants (K_a and K) and a time variable. It is important to emphasize that since these two forces act simultaneously, the interplay of them will ultimately determine the time dependent variable C_p. This signifies that they will continue to have a significant impact on the magnitude of plasma levels in as far as they assume a significant value. Hence, the value of the exponents representing them (*i.e.* e^{-Kt} and $e^{-K_a t}$) will ultimately determine the magnitude of the plasma level. Since these two exponents consist of a variable time element and two rate constants, it follows that the relative magnitude of either of them, versus the other, will decide whether it is to have the lasting effect in the PK model. This argument provides grounds for various scenarios for the interpretation of the model.

As mentioned earlier the model consists of the absorption and elimination exponents. The magnitude of each component is determined by the time element and their respective rate constants. The rest of the model is a composite constant value incorporating the administered dose and all other PK for any specific drug. In the case of short absorption half-life, the absorption rate constant will be very high which causes a relatively fast

absorption of drugs. More pertinent to this is the fact the influence of the absorption exponent will become insignificant thus leaving the elimination exponent to drive the system.

A scenario that represents the most common PK instances for the one-compartment oral model is based on the assumption that the absorption rate constant (K_a) is relatively higher than that of the elimination rate constant (K). This assumption signifies that the exponential term associated with the absorption process in the above model will approximate zero while the exponent representing the elimination process(s) will continue to assume an infinitesimal value. Thus the model could be reduced to the following equality:

$$C_P = \frac{K_a F X_0}{V_d (K_a - K)} \left(e^{-Kt} \right), \; for \; K_a <> K \; \& \; K_a >> K$$

This model implies that the decline in the slope of the plasma conc.-time profile will be indicative of the elimination characteristic of the drug in question. Furthermore, setting the time element within the exponential term in the model to zero will produced a zero-time intercept equivalent to

$$C_{P(0)} = \frac{K_a F X_0}{V_d (K_a - K)}, \; for \; K_a <> K \; and \; K_a >> K$$

This intercept is a common term for both the absorption as well as the elimination exponent in the model. For drug with relative short biological half-lives with poor absorption characteristics from the gastro-intestinal tract (GIT), the likelihood exists for foster absorption than elimination rate. This implies that $K_a << K$. In this case the exponent associated with the elimination processes will approximate zero while that representing the absorption process will continue to assume an infinitesimal value. This means that the slope of the terminal segment of the plasma conc.-time profile will be indicative of the absorption properties of the drug. This PK instance is referred as flip-flop kinetics. In this case, the generalized one-compartment oral PK model will reduce, to the following model when the time element becomes significantly large,

$$C_P = \frac{K_a F X_0}{V_d (K_a - K)} \left(e^{-K_a t} \right), \; for \; K_a <> K \; and \; K_a << K$$

Deconvolution of the Oral Model

As mentioned earlier, one of the fundemental characteristics of many of the PK models is that they are convoluted systems. This is particularly the case with models consisting of more than one exponential term or function. Convolution signifies that although an observed plasma conc.-time data looks like a single profile, such profile represent the outcome of more than one force (or process) determining its ultimate picture. The deconvolution of these systems represent one of the prime concern of the PK science.

Noteworthy, the absorption phase comes to an end when there is no more drug available at the absorption site. This phase far exceeds the observerd maximum plasma level which representa point of time where the elimination and absorption rates are more or less identical. This realization is often overlooked in the PK literature. Irrespective of whether $K >> K_a$ or $K << K_a$ one can proceed to assess the drug's elimination as well as the absorption characteristic. This can be done though the deconvolution procedures which consist

of splitting apart the two driving forces comprising the system. This process is called the "*Method of Residual*" in the PK literature. Other synonyms are also use such as "Curve Stripping" or "Curve Feathering". The mathematical basis for this process may be outlined as follows:

For simplicity, we may assume that the zero-time intercept $K_a FX_0 / V_d (K_a - K)$ *equals* A. It follows that Equation 10 may be re-written as:

$$C_P = Ae^{-Kt} - Ae^{-K_a t}$$

Under usual circumstance, the absorption term will approximate zero which will make the terminal segment of the plasma conc.-time represent the elimination processes. This segment is then Extrapolated back to time zero. However, it must be noted that the ascending part of the plasma conc.-time profile represents both the absorption and the elimination processes. Accordingly, if we subtract such quantities from those pertaining to the extrapolated elimination values, the residuals will represent the drug's absorption characteristics. This is mathematically expressed as follows:

If the plasma levels are subtracted as mention above we get the following equalities:

$$C_{P(K)} = Ae^{-Kt}$$
$$-C_{P(K+K_a)} = -Ae^{-Kt} + Ae^{-K_a t}, \quad i.e.$$
$$C_{P(K_a)} = Ae^{-K_a t}$$

This implies that the slope of the residual exponent represents the absorption properties if, and only if, the elimination rate is relatively faster than the absorption rate. This holds true the other way round when a flip-flop situation exists. A typical presentation for a flip-flop situation is shown hereunder.

Estimation of T_{max} and C_{max}

For drug whose onset of action assumes distinct therapeutic significance, it is always desirable to determine the length of time within with the drug entity elicits its therapeutic response of efficacy. This is true for a wide variety of drugs like nitro glycerides and analgesics. On the other hand, it is often needed to assess the maximum drug levels attained in the body especially if such levels are associated with adverse drug effects. Estimation of such levels provides an important measure for the design and consequent adjustment of dosing regimen.

In order that the maximum plasma level is estimated, one needs to determine the time at which such plasma level is attained. This point of time occurs when no further increase in the drug level occurs, rather it start to decline. In other words, the slope of the ascending part of the plasma profile tends to level, or approximates a zero value. This situation could be mathematically expressed by differentiating the concentration term in

Equation [10] with respect to time and setting the resultant term equal to zero the time element set t_{max}. This is demonstrated as follows:

The natural logarithm for both side of the latter expression may be taken and further solved for T_{max} as shown hereunder:

$$T_{max} = \frac{1}{(K_a - K)} \ln\left(\frac{K_a}{K}\right)$$

Once T_{max} has been estimated, it could be substituted in Equation [10] so that an estimate for C_{max} is obtained.

PK of Oral Multiple Dosing

A mathematical model for oral multiple dosing could be formulated according to Dost's relevant generalization. This is done by multiplying each exponential term in the model for a single oral bolus mode of administration as given in Equation 3.1. Hence,

$$C_N = \frac{K_a F X_0}{V_d (K_a - K)} \left(\frac{1 - e^{-NK\tau}}{1 - e^{-K\tau}} e^{-Kt} - \frac{1 - e^{-NK_a\tau}}{1 - e^{-K_a\tau}} e^{-K_a t} \right)$$

This is a full-fledge model can be used to determine the drugs plasma level after any number (N) of doses as well as at any time point during the dosing interval (τ). It could be also rewritten to estimate specific instances such as the maximum and minimum plasma levels after any dose or once steady state has been attained according to the following equations:

$$C_{max}^{ss} = \frac{K_a F X_0}{V_d (K_a - K)} \left(\frac{e^{-Kt_{max}^{ss}}}{1 - e^{-K\tau}} - \frac{e^{-K_a t_{max}^{ss}}}{1 - e^{-K_a\tau}} \right)$$

$$C_{min}^{ss} = \frac{K_a F X_0}{V_d (K_a - K)} \left(\frac{e^{-K\tau}}{1 - e^{-K\tau}} - \frac{e^{-K_a\tau}}{1 - e^{-K_a\tau}} \right)$$

In addition to the above mentioned plasma levels estimates, the average plasma concentration after the administration of any dose, or at steady state could be also estimated. In this regard, one has to resort to a globally accepted definition of this parameter which is given as the product of the area under the plasma conc.-time curve divided by the dosing interval. It has been earlier verified that for a one-compartment intravenous bolus model the $AUC_{0-\tau}^{ss}$ is operationally equivalent to the $AUC_{0-\infty}^{N=1}$. This concept has been applied to the one-compartment oral model. However, examination of the areas estimates according to the equations provided below would invalidate such generalization.

$$AUC_{0-\tau}^{ss} = \frac{F X_0 K_a \left[(1 - e^{-K\tau}) + K(e^{-K_a\tau} - 1) \right]}{K V_d (K_a - K)(1 - e^{-K\tau})}, \; and \; AUC_{0-\infty}^{N=1} = \frac{F X_0}{K V_d}$$

Time to attain maximum plasma level (T_{max}) where $K_a <> K$

$$T_{max}^N = \frac{1}{(K_a - K)} \ln\left[\left(\frac{K_a}{K}\right)\left(\frac{1 - e^{-K\tau}}{(1 - e^{-nK\tau})}\right) / \left(\frac{1 - e^{-K_a\tau}}{(1 - e^{-nK_a\tau})}\right)\right]$$

$$T_{max}^{ss} = \frac{1}{(K_a - K)} \ln\left(\frac{K_a(1 - e^{-K\tau})}{K(1 - e^{-K_a\tau})}\right) = t_P^{ss} \ ...for \ Ka <> K$$

Once the time required to attain a maximum plasma level at steady state has been determined, the maximum plasma level could be estimated as:

$$C_{max}^{ss} = \frac{K_a F X_0}{V_d(K_a - K)}\left(\frac{e^{-Kt_{p(SS)}}}{1 - e^{-K\tau}} - \frac{e^{-K_a t_{p(SS)}}}{1 - e^{-K_a\tau}}\right)$$

$$C_{min}^{ss} = \frac{K_a F X_0}{V_d(K_a - K)}\left(\frac{e^{-K\tau}}{1 - e^{-K\tau}} - \frac{e^{-K_a\tau}}{1 - e^{-K_a\tau}}\right)$$

$$C_{max}^{ss} - C_{min}^{ss} = \frac{K_a F X_0}{V_d(K_a - K)}\left(\frac{e^{-Kt_p^{SS}} - e^{-K\tau}}{1 - e^{-K\tau}} - \frac{e^{-K_a t_p^{SS}} - e^{-K_a\tau}}{1 - e^{-K_a\tau}}\right)$$

Considering that the entity t_p^{ss} has been defined above for any dosing interval, a new dosing interval that will produce a newly defined maximum and minimum plasma levels could be estimate by numerical iteration techniques.

$$C_{max}^{SS} = \frac{K_a F X_0}{V_d(K_a - K)}\left[\left(\frac{e^{-KT_{max}^{SS}}}{1 - e^{-K\tau}}\right) - \left(\frac{e^{-K_a T_{max}^{SS}}}{1 - e^{-Ka\tau}}\right)\right]$$

$$C_{min}^{SS} = \frac{K_a F X_0}{V_d(K_a - K)}\left[\left(\frac{e^{-k\tau}}{1 - e^{-K\tau}}\right) - \left(\frac{e^{-K_a\tau}}{1 - e^{-K_a\tau}}\right)\right]$$

Magnitude of Fluctuation

As defined earlier, the degree of fluctuation may be obtained by dividing the maximum by the minimum plasma levels at steady state. Since these have been defined above, the degree of fluctuation may be given as:

$$\frac{C_{max}^{SS}}{C_{min}^{SS}} = \frac{\frac{K_a F X_0}{V_d(K_a - K)}\left(e^{-KT_{max}^{SS}} / 1 - e^{-K\tau}\right) - \left(e^{-K_a T_{max}^{SS}} / 1 - e^{-K_a\tau}\right)}{\frac{K_a F X_0}{V_d(K_a - K)}\left(e^{-K\tau} / 1 - e^{-K\tau}\right) - \left(e^{-K_a\tau} / 1 - e^{-K_a\tau}\right)}$$

This equation may be simplified as follow:

$$MoF = \frac{\left(e^{-KT_{max}^{SS}} / 1 - e^{-K\tau}\right) - \left(e^{-K_a T_{max}^{SS}} / 1 - e^{-K_a\tau}\right)}{\left(e^{-K\tau} / 1 - e^{-K\tau}\right) - \left(e^{-K_a\tau} / 1 - e^{-K_a\tau}\right)}$$

$$MoF = \frac{e^{-KT_{max}^{SS}}(1 - e^{-K_a\tau}) - e^{-K_aT_{max}^{SS}}(1 - e^{-K\tau})}{e^{-K\tau}(1 - e^{-K_a\tau}) - e^{-K_a\tau}(1 - e^{-K\tau})}$$

$$MoF = \frac{e^{-KT_{max}^{SS}} - e^{-K_aT_{max}^{SS}} + e^{-K_aT_{max}^{SS}}e^{-K\tau}}{e^{-K\tau} + e^{-K_a\tau}e^{-K\tau}}$$

If the dosing interval is set so that consecutive dosing are administered in the post absorptive phase, the above expression may approximated by the following relationship:

$$MoF = \frac{e^{-KT_{max}^{SS}} - e^{-K_aT_{max}^{SS}}(1 - e^{-K\tau})}{e^{-K\tau}}$$

$$e^{-K\tau} = \frac{e^{-KT_{max}^{SS}} - e^{-K_aT_{max}^{SS}}}{MoF - e^{-K_aT_{max}^{SS}}}$$

$$\tau_{New} = \frac{1}{K}\ln\left(\frac{MoF - e^{-K_aT_{max}^{SS}}}{e^{-KT_{max}^{SS}} - e^{-K_aT_{max}^{SS}}}\right)$$

This is due to the fact that all exponential terms associated with the expression $e^{-K_a\tau}$ will become insignificant; hence they will cancel from the previous equations.

Average Plasma Concentration ($K_a <> K$)

Estimation of the average plasma levels requires that the area under the plasma conc.-time curve (AUC) be determined. This could be done for any dose under during a dosing regimen. After a single dose, AUC from time zero to infinity may be obtained by integration the plasma levels as provided hereunder:

$$\int_0^\infty C_p dt = \frac{K_a FX_0}{V(K_a - K)}\left(\frac{1}{K} - \frac{1}{K_a}\right) = \frac{FX_0}{VK}$$

This equation clearly signifies that the AUC, or the so called total exposure of the body to the administered drug, is a function of its elimination characteristics. Assuming complete bioavailability (i.e. F equals unity), the above expression becomes identical to that obtained after intravenous bolus administration. Also, the area

under the plasma conc.-time curve during any dosing interval under multiple dosing conditions may be estimated by integration the equation representing the relevant multiple dosing model as follows:

$$\int_0^\tau C_p^N dt = \frac{K_a F X_0}{V_d(K_a - K)} \left[\begin{array}{c} \left(\dfrac{1-e^{-NK_a\tau}}{1-e^{K_a\tau}}\right)\dfrac{e^{-K_a\tau}}{K_a} - \left(\dfrac{1-e^{-NK\tau}}{1-e^{K\tau}}\right)\dfrac{e^{-K\tau}}{K} \\ + \left(\dfrac{1-e^{-NK\tau}}{1-e^{K\tau}}\right)\dfrac{1}{K} - \left(\dfrac{1-e^{-NK_a\tau}}{1-e^{K_a\tau}}\right)\dfrac{1}{K_a} \end{array} \right]$$

Simplification of the above equation produces the expression:

$$\int_0^\tau C_p^N dt = \frac{F X_0}{K V_d} \left(1 + \frac{K e^{-NK_a\tau}}{(K_a - K)} - \frac{K_a e^{-NK\tau}}{(K_a - K)} \right)$$

It is evident that the above expression could be further simplifies as the administered number of doses (N) becomes larger, or at steady state. In this case the bracketed terms associated with the exponents become very insignificant and the above equation reduces to the following:

$$\int_0^\infty C_p^N dt = \frac{F X_0}{K V_d}$$

The preceding mathematical consideration clearly demonstrate that the area under the plasma conc.-time curve, from tine zero to infinity, obtained after the administration of a single dose is identical to the area under the plasma conc.-time curve during any dosing interval at steady state.

Defining the Degree of Fluctuation (Swing)

In the of an oral bolus model, the degree of fluctuation as measured by the swing, we have the three PK metrics defining the swing. These are the maximum, minimum and average plasma levels at steady state. Their respective values are provided below:

$$C_{max}^{ss} = \frac{K_a F X_0}{V_d(K_a - K)} \left(\frac{e^{-K t_{p(SS)}}}{1-e^{-K\tau}} - \frac{e^{-K_a t_{p(SS)}}}{1-e^{-K_a\tau}} \right)$$

Hence, the degree of fluctuation may be given as:

$$C_{min}^{ss} = \frac{K_a F X_0}{V_d(K_a - K)} \left(\frac{e^{-K\tau}}{1-e^{-K\tau}} - \frac{e^{-K_a\tau}}{1-e^{-K_a\tau}} \right), \; and \; C_{av}^{ss} = \frac{F X_0}{\tau K V_d}$$

This readily rearranges after cancelation of common terms to the following expression:

$$DoF_{swing} = \frac{\tau K K_a}{(K_a - K)} \left[\left(\frac{e^{-K t_p^{ss}}}{1-e^{-K\tau}} - \frac{e^{-K_a t_p^{ss}}}{1-e^{-K_a\tau}} \right) - \left(\frac{e^{-K\tau}}{1-e^{-K\tau}} - \frac{e^{-K_a\tau}}{1-e^{-K_a\tau}} \right) \right]$$

$$DoF_{swing} = \frac{\tau K K_a}{(K_a - K)} \left(\frac{e^{-Kt_p^{ss}} - e^{-K\tau}}{1 - e^{-K\tau}} + \frac{e^{-K_a\tau} - e^{-K_a t_p^{ss}}}{1 - e^{-K_a\tau}} \right)$$

Irrespective of the relative magnitude of K or K_a, if the dosing interval is set at more than six hours, the above expression will approximate the following:

$$DoF_{swing} = \frac{\tau K K_a}{(K_a - K)} \left(e^{-Kt_p^{ss}} - e^{-K_a t_p^{ss}} \right)$$

Targeting Therapeutic Ranges

For drugs administered by the oral route a dosing regimen (a dose and dosing interval) may be theoretically determined so that a pre-defined plasma range is attained. Although the mathematical basis for determining such regimens does no differ from that adopted for other routes, the presence of an absorption phase makes it a little different. This is related to the confounding effect of the absorption rate constant to the PK definition of the targeted therapeutic range. Differences in such rate will influence the time required to attain a maximum plasma level which will further affect the estimation of the magnitude of such level. The consequent estimation if the desired therapeutic plasma range will be also affected.

This is further complicated by the realization that the time required to attain a maximum plasma level after a single dose will differ from the same at steady state. $T_{max}^{N=1}$ after the first dose is given as:

$$T_{max}^{N=1} = \frac{1}{(K_a - K)} \ln\left(\frac{K_a}{K}\right)$$

At steady state conditions T_{max}^{ss} may be given as follows:

$$T_{max}^{ss} = \frac{1}{(K_a - K)} \ln\left(\frac{K_a(1 - e^{-K\tau})}{K(1 - e^{-K_a\tau})} \right)$$

It has been demonstrated that Cmax after the first dose may be estimated according to the following equation:

$$C_{max}^{(N=1)} = \frac{FX_0}{V} e^{-KT_{max}}$$

Similarly, the maximum as well as the minimum plasma levels at steady state may be expressed as:

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

The range of peak to trough fluctuation could be accordingly estimated as:

$$\frac{C_{max}^{SS}}{C_{min}^{SS}} = \left(\frac{e^{-KT_{max}^{ss}}}{e^{-K\tau}} \right)$$

The dosing interval associated with such range is then readily determined as a function of this range:

$$e^{-KT_r} = \frac{C_{min}^{SS} e^{-KT_{max}^{ss}}}{C_{max}^{SS}}, \quad \tau = \frac{1}{K} \ln\left(\frac{C_{max}^{SS}}{C_{min}^{SS} e^{-KT_{max}^{ss}}} \right)$$

For a newly desired range a new dosing interval could be estimated as:

$$\tau_{New} = \frac{1}{K} \ln\left(\frac{C_{\max T}^{SS}}{C_{\min T}^{SS} e^{-KT_{\max}^{ss}}} \right)$$

Other less precise expression has been reported in the PK literature

$$\tau_{New} = \frac{1}{K}\left[\ln(C_{\max}) - \ln(C_{\min}) \right] + T_{\max} \quad , or$$

$$\tau_{New} = \frac{1}{K} * \ln\left(\frac{MoF - e^{-K_a T_{\max}^{ss}}}{e^{-KT_{\max}^{ss}} - e^{-K_a T_{\max}^{ss}}} \right)$$

The approximate dose needed to bring the plasma levels for the desired SS therapeutic window may be roughly estimated according to the newly defined dosing interval as provided above:

$$X_0 = \frac{C_{\min}^{ss} V_d (K_a - K)}{K_a F}\left(\frac{e^{-K\tau_{New}}}{(1 - e^{-K\tau_{New}})} - \frac{e^{-K_a \tau_{New}}}{(1 - e^{-K_a \tau_{New}})} \right)$$

Sustained Release Dosage Forms

The PK of drugs presented in controlled or sustained release forms has not received adequate attention in the scientific literature. In this regard, although enteric dosage forms represent some kind of controlled release forms, they will not be subject to the discussion in this section. This is due to the fact that they only differ from the conventional dosage form by releasing its content of the drug substance after a certain prescribed period of time. In which case, a slight modification for the time element in the one-compartment oral model should be enough to describe it PK features. This amounts to simply subtracting the time at which the dosage form starts to release its content (t_{lag}). Hence,

$$C_P = \frac{K_a FX_0}{V_d(K_a - K)}\left(e^{-K(t-t_{lag})} - e^{-K_a(t-t_{lag})}\right)$$

There are situations where there is a definitive need to instill a drug substance gradually into the systemic circulation. This is mainly encountered with drugs having relatively short half-life where desirable plasma levels could not be sustained. Also, a gradual input of the drug into the system is often preferred in drugs with rapid absorption property which may result in abrupt increase of the drugs level in the system; thus causing unwarranted adverse effect.

However, for other sustained release (SR) forms where the drug is gradually released at a predetermined rate, the situation is completely different from the enteric coated dosage forms. In this case, the native absorption characteristic of the drug will be masked or confounded by the release pattern of the drug from the dosage form. It is generally accepted that an ideal or optimal SR form must release it content in an approximate zero-order fashion. This situation may be exemplified by what has been previously discussed for the intravenous infusion mode of administration. Consequently, the release time of the drug substance from the dosage form could be conveniently considered as some kind of infusion time or period. Hence, if the release time is made available, the mathematical models introduced to account for the intravenous infusion, could be slightly modified so that the PK behavior of the SR forms is adequately catered for.

To start with the basic one-compartment intravenous infusion model may be re-written in terminology suited for the SR forms as follows:

$$C_P = \frac{FX_{SR}}{T_r KV_d}(1 - e^{-Kt_r})e^{-K(t-T_r)}$$

where $FX_{0(SR)}\big/T_R$ is the release rate if the active drug from the SR matrix, t_r is the variable release time, T_R is a time constant representing the duration of release, $(t - T_R)$ is the post release time (t_{pr}) and K is the first order overall elimination rate constant.

This model is suited for drugs that confer upon the body the characteristic of single compartments. It could be also argued that it could be also suited for multiple compartment drugs since not only the absorption, but also the distribution, characteristics will be masked by the zero order release pattern from the SR form.

It must be noted that the conventional absorption rate constant (K_a) have been completely dropped from the model since the release pattern of the drug from the dosage from has become the rate-limiting step in the entire absorption process. The above model could be expressed in terms of two discrete entities, with one accounting for the release period and the other for the post-release time. Hence,

$$C_P = \frac{FX_{SR}}{T_r KV_d}(1 - e^{-Kt_r}), \quad for \ t \leq T_r$$

$$+ \frac{FX_{SR}}{T_r KV_d}(1 - e^{-KT_r})e^{-K(t-T_r)}, \quad for \ t \geq T_r$$

This equation may be used to predict drugs plasma levels consequent to the administration of a single dose. In this case, information on the claim made about the release time must be known so that drug's input rate is inserted into them. They could be also used for the characterization of the elimination properties where experimental plasma conc.-time data are provided. However, is must be emphasized that the slope of the terminal segment of such data should be estimated after the release time has elapsed by at least three absorption half-lives. Unfortunately, this is not how plasma data obtained consequent to the administration sustained release for is presently evaluated within the context of bioequivalence studies.

For drugs with relatively long biological half-lives, a steady state plasma level will be attained after a lengthy period of time. Hence, a loading dose has to be administered together with the initiation of therapy. For the estimation of such dose, either of the equations used to estimate the maximum, minimum or the average plasma level at steady state could be employed since all these equations will give the same value. It has been always assumed that a steady state level with no fluctuation is an ideal situation which can only be observed if the drug has been administered by intravenous infusion.

Multiple Dosing of SR Forms

Like other dosage forms, the SR forms are usually administered as multiple dosing regimens. Hence, plasma levels at any number of doses as well as at steady state become of direct concern. These include the maximum, minimum and the average levels throughout the dosing regimen. To account for these levels, the above model could be adopted to account for the repeated dosing of SR drug products in a similar way to that of the intermittent infusion. This requires the incorporation of the right multiple dosing factors for the release and post release phases.

$$C_p = \frac{FX_{SR}}{T_r KV_d}(1 - e^{-Kt_r}) + \frac{X_{SR}}{T_r KV_d}(1 - e^{-KT_r})e^{-K(\tau-T_r)}e^{-Kt_r}\left(\frac{1 - e^{-(N-1)K\tau}}{1 - e^{K\tau}}\right) \ for \ t < T_r$$

$$+ \frac{FX_{SR}}{T_r KV_d}(1 - e^{-KT_r})e^{-K(\tau-T_r)}\left(\frac{1 - e^{-NK\tau}}{1 - e^{K\tau}}\right) \ for \ t \geq T_r \quad ....(11)$$

Further simplification to the above model results in the following expression:

$$C_{p(r)}^N = \frac{FX_{SR}}{T_r KV_d (1-e^{-K\tau})} \left[1-e^{-Kt_r}[1-e^{-K(\tau-T_r)}+e^{-K(N\tau-T_r)}-e^{-KN\tau}]-e^{-K\tau} \right] \ t \le T_r$$

$$C_{p(pr)}^N = \frac{FX_{SR}}{T_r KV_d (1-e^{-K\tau})} (1-e^{-KT_r})(1-e^{-NK\tau})e^{-Kt_{pr}} .... for \ t \ge T_r$$

Which could be readily modified to account for plasma level at SS condition, as provided hereunder:

$$C_p^{ss} = \frac{FX_{SR}}{T_r KV_d (1-e^{-K\tau})} \left[1-e^{-Kt_r}(1-e^{-KT_{pr}})-e^{-K\tau} \right] \ for \ t \le T_r$$

$$C_p^{ss} = \frac{FX_{SR}}{T_r KV_d (1-e^{-K\tau})} (1-e^{-KT_r})e^{-Kt_{pr}} \ for \ t \ge T_r$$

Although the analogy between this model and that used for intermittent infusion is unmistakable, its output may vary with different dosing regimens of the SR release forms. Such variability is related to compliance of these forms with the compendial requirements as well as the compliance of patients with the intake schedule as specified by the dosing regimen (DR). Accordingly, three specific scenarios for the SS conditions could be contemplated. These are outlined as follows:

In cases where the dosage form releases its contents in a period that exactly equals the claimed release time in the presence of strict compliance with the dosing schedule. This implies a continuous infusion condition, in which case the above equation reduces to the expression:

$$C_p^{ss} = \frac{FX_{SR}}{T_r KV_d} \ for \ \tau = T_r$$

$$C_p^{pr} = \frac{FX_{SR}}{T_r KV_d} e^{-Kt_{pr}}, \ upon \ the \ completion \ of \ DR$$

In another instance, doses are administered during the release period (i.e. $\tau < Tr$), which will result in positive values of the post-release time, i.e. $\tau - Tr = Tpr$ will be more than zero. This implies that higher SS average plasma level than that where the dosing interval equals the release time since the exponent associated with this parameter will serve as an input function.

Finally, in cases where consequent doses are administered after the release period (i.e. $\tau > Tr$), the post-release time (Tpr) will be less than zero. Contrary to the above instance, the SS average plasma level will be lower than that when the dosing interval equals the release time.

These two instances are operationally equivalent to other situations in the presence of patient compliance and varying release rates inconsistent with the label claim. It is evident that the value of Tpr is the critical element

that will eventually determine the magnitude of the SS plasma levels since its exponential term will be either an input or a decay function.

Average Plasma Levels for SR Forms

The above equation could be integrated from time zero to the end of the dosing interval to get an estimate for body exposure after and number of infusions throughout the dosing regimen. It could be verified that dividing such exposure by the dosing interval provides an estimate of the average plasma levels at any dosing interval:

$$C_{av}^{N} = \frac{FX_{SR}/T_r}{\tau KV_d}(T_r + \frac{e^{-KT_r}}{K} - \frac{1}{K}) - \frac{C_{min}^{N=1}F_r}{\tau K}(e^{-KT_r} - 1) + \left[\frac{C_{max}^{N=1} - C_{min}^{N=1}}{\tau K}\right]F_{pr}$$

The above equations have been developed with the aim of estimating the average plasma levels during repeated dosing of the SR forms. The multiple dosing factors *(F$_I$ and F$_{PI}$)*, as well as the plasma levels at steady state contained in this equation are defined as:

$$Assume\ that\ C_{av}^{ss} = \frac{FX_{SR}/T_r}{\tau KV_d},\ \left(\frac{1-e^{-(N-1)K\tau}}{1-e^{-K\tau}}\right) = F_r\ and\ \left(\frac{1-e^{-NK\tau}}{1-e^{-K\tau}}\right) = F_{pr}$$

Although the above model could be suited for estimating drugs plasma levels at any time during multiple dosing, a special case could be considered whereby the dosing interval is set identical to the claimed release time of the drugs from the SR matrix. This could be conceptually thought of as being a case of continuous release pattern resulting in a zero-order input rate in the system. Under such condition, and with continued dosing, either of the two multiple dosing factors, that are cited above, will be reduced to the expression $F_I = (1/1-e^{-K\tau})$.

Furthermore, considering that the post release term in Equation (11) will be irrelevant during repeated dosing where the dosing interval is considered to be identical with the release time, this equation reduces to the following:

$$C_{av}^{N} = C_{SS}\left(1 + \frac{e^{-KT_r}}{\tau K} - \frac{1}{\tau K}\right) - \frac{C_{min}^{N=1}F_r}{\tau K}(e^{-KT_r} - 1)\ ....(11)$$

Also, recalling that the minimum plasma level after the first dose ($C_{min}^{N=1}$) has been earlier defined as $C_{SS}(1-e^{-KT_R})e^{-K(\tau-T_R)}$, hence substitution for this value and the multiple dosing factor (F_I) as defined above, in Equation (11) the average concentration at any number of doses as:

$$C_{av}^{N} = C_{SS}\left(1 + \frac{e^{-KT_r}}{\tau K} - \frac{1}{\tau K}\right) - \frac{C_{SS}(1-e^{-KT_r})e^{-K(\tau-T_r)}}{\tau K}\left(\frac{1-e^{-(N-1)K\tau}}{1-e^{-K\tau}}\right)(e^{-KT_r} - 1)$$

However, for orally administered SR forms, the fluctuation of steady state plasma levels depends mainly on whether the release of the active drug material from dosage form is zero order or not. A zero order release

rate could be hardly guaranteed specially during the first few hours after the administration of the dosage form. Consequently, the guidance has set rather relaxed limits (15 - 30%) for the percent release during the first hour.

In addition, it has been a common practice by too many drug manufacturers to incorporate an immediate release component in the SR form. It has been argued (Gibaldi) that it will take less time to attain the steady state levels in the presence of such component. Although this could be true only for drugs with relatively short biological half-lives. However, such component would seriously affect the peak to trough fluctuation at steady state. Since the latter property of the dosage form represents a significant quality aspect of the SR preparation, it has been stated as a quality measure by the international guidance.

It remains imperative that either impact of usual early release of the drug substance from the SR form, or the incorporation of an IR component be accurately assessed. This could be done by the employment one of the additive characteristic of all linear PK models. Hence, a third term could be added to the standard model presented in the equation provided hereunder to represent the absorption and disposition of the IR component. This will result in the following elaborate model that could be used to precisely predict drugs plasma levels attained consequent to the administration of the combined SR/IR forms.

$$
\begin{aligned}
C_p^N &= \frac{FX_{SR}/T_r}{KV_d}\left[(1-e^{-Kt_r})+(e^{-K(\tau-T_r)}-e^{-K\tau})\ e^{-Kt_r}\left(\frac{1-e^{-(N-1)K\tau}}{1-e^{K\tau}}\right)\right],\ \ for\ t<T_r \\
&+\frac{FX_{SR}/T_r}{KV_d}(1-e^{-KT_r})\ e^{-Kt_{pr}}\left(\frac{1-e^{-NK\tau}}{1-e^{K\tau}}\right),\ \ for\ t\geq T_r=t_{pr} \\
&+\frac{K_aFX_{IR}}{V_d(K_a-K)}\left(\frac{1-e^{-NK\tau}}{1-e^{-K\tau}}e^{-Kt}-\frac{1-e^{-NK_a\tau}}{1-e^{-K_a\tau}}e^{-K_at}\right)\ for\ the\ IR\ Component
\end{aligned}
$$

The utilization of the above model requires a prior knowledge of the IR component or the amount of the dosage form that would be released within the first two hours after the administration of the dose. Aslo, the release claim related to any specific dosage form must be stated so that the release (or the input) rate of the drug is determined.

The flexibility of this model is manifested by the fact that the dosing interval does not have to be necessarily set identical to the release time of the drug from the dosage form. On the contrary, the dosing interval could be set at any value so that a desired plasma profile or a predefined theraputic window is achieved.

Plasma Levels for SR Dosage Forms

Maximum and minimum plasma levels at SS are generally employed as basis for targetting therapeutic ranges or windows. Hence, estimates of Cmin and Cmax at SS for SR formulations, in the presence of IR components, must be determined. These levels represent a summation of levels ensuing from IR and SR portions of such dosage forms at the time where maximum levels are likely to occur. For either IR or SR forms, the following equations describe the maximum and minimum plasma levels after a single dose based on the assumption that the release time from the dosage form (Tr) is equalt tp the dosing interval (tau). It may be further assumed that maximum levels will only occur at Tr. In addition, the concept of minimum and maximum concentration is irrelevant for the SR portion. Based on such assumptions, the following set of equation are devised:

For Cmin and Cmax (N = 1)

$$C_{min}^{N=1} = \frac{K_a F X_{IR}}{V_d (K_a - K)} e^{-KT_r} \ \ from \ Oral \ Part$$

$$C_{max}^{N=1} = \frac{F X_{IR}}{V_d} e^{-KT_{max}^{ss}} \ \ from \ Oral \ Part$$

$$C_p^{N=1} = \frac{F X_{SR}}{T_r K V} (1 - e^{-KT_r}) \ \ from \ SR \ Part$$

For Cmin and Cmax (N Doses)

$$C_{max}^{N} = \frac{F X_{IR}}{V_d} e^{-KT_{max}} \left(\frac{1 - e^{-NKT_r}}{1 - e^{-KT_r}} \right), \ \ C_{mim}^{N} = \frac{F X_{IR}}{V_d} e^{-KT_r} \left(\frac{1 - e^{-NKT_r}}{1 - e^{-KT_r}} \right) \ \ from \ Oral \ Part$$

$$C_p^{N} = \frac{F X_{SR}}{T_r K V} (1 - e^{-NKT_r}) \ \ from \ SR \ Part$$

All the above equations become SS by setting all exponents containing N to zero. The same applies to all absorption exponents containing tau since such exponents will approximate zero.

Considering the above equation, it becomes evident that targeting plasma levels for SR in the presence of an IR component is not a straight forward matter. This further implies that targeting can never have mathematical basis if it is to be approached though a modified tau as is the case with other dosage forms. Hence, it could be only done by estimating the difference between the newly targeted Cmax and Cmin. It should be born in mind that fluctuation in the plasma levels is strictly caused by the IR component. Accordingly the following mathematical treatment is applicable

For Cmax & Cmin (at SS)

Assuming that the dosing interval was set at exactly the release time Tr, then there will not be a maximum and minimum levels ensuing from the SS portion of the dosage form. Rather we will have a steady state level only. Hence, the following applies:

$$C_{min}^{SS} \simeq \frac{FX_{IR}}{V}\left(\frac{e^{-KT_{max}^{ss}}}{1-e^{-KT_r}}\right)e^{-K(T_r-T_{max}^{ss})} \; from \; Oral \; Part$$

$$C_{max}^{SS} = \frac{FX_{IR}}{V}\left(\frac{e^{-KT_{max}^{ss}}}{1-e^{-KT_r}}\right), \; from \; Oral \; Part$$

$$C_p^{SS} = \frac{FX_{SR}}{T_r KV} \; from \; SR \; Part$$

Accordingly, the overall maximum and minimum plasma levels may be given as follows:

$$C_{max}^{SS} = \frac{FX_{SR}}{T_r KV}+\frac{FX_{IR}}{V}\left(\frac{e^{-KT_{max}^{ss}}}{1-e^{-KT_r}}\right), \quad C_{min}^{SS} = \frac{FX_{SR}}{T_r KV}+\frac{FX_{IR}}{V}\left(\frac{e^{-KT_r}}{1-e^{-KT_r}}\right)$$

This is a paradoxical expression since it appears to contradict those cited above for the estimation of maximum and minimum plasma levels. However, it is based on the realization that the contribution of the IR component to the ascending plasma levels to the SS condition is quite different from that once SS levels have been attained. It is evident that the SR portion has the overriding impact compared to the contribution of the IR component. This will be reversed once SS has been achieved. The result obtained from this equation will be either a fraction of a multiple of unity which will be readily transformed into concentration terms by multiplying it by the value of $(X_{IR} + X_{SR})/V_d$.

Targeting Therapeutic Ranges

For the purpose of targeting plasma ranges in case of SR dosage forms, the dosing interval should not be equated with the release time of drugs from such forms since the latter ***must be assumed as a constant***, representing a definitive characteristic of the dosage form. Accordingly, the above expressions for C_{min} and C_{max} may be re-written as follows:

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

This equation may be re-written in terms of the maintenance dose with the IR portion represented as a fraction of such dose.

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

$$P = IR\ fraction$$

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

Devide C_{max}^{ss} to C_{min}^{ss} and we get

$$\frac{C_{max}^{ss}}{C_{min}^{ss}} = \frac{\frac{1-P}{T_r K} + \frac{Pe^{-KT_{max}^{ss}}}{1-e^{-K\tau}}}{\frac{1-P}{T_r K} + \frac{Pe^{-K\tau}}{1-e^{-K\tau}}} = \frac{(1-P)(1-e^{-K\tau}) + PT_r K e^{-KT_{max}^{ss}}}{(1-P)(1-e^{-K\tau}) + PT_r K e^{-K\tau}}$$

$$= \frac{(1-P) + PT_r K e^{-KT_{max}^{ss}} - (1-P)e^{-K\tau}}{(1-P) - (1-P-PT_r K)e^{-K\tau}}$$

Thus we get result expression for this fraction

$$\frac{C_{max}^{ss}}{C_{min}^{ss}} = \frac{(1-P) + PT_r K e^{-KT_{max}^{ss}} - (1-P)e^{-K\tau}}{(1-P) - (1-P-PT_r K)e^{-K\tau}}$$

Then we express term $e^{-K\tau}$

$$C_{max}^{ss}[(1-P) - (1-P-PT_r K)e^{-K\tau}] = C_{min}^{ss}\left[(1-P) + PT_r K e^{-KT_{max}^{ss}} - (1-P)e^{-K\tau}\right]$$

$$C_{max}^{ss}(1-P) + C_{max}^{ss}(P+PT_r K - 1)e^{-K\tau} = C_{min}^{ss}\left[(1-P) + PT_r K e^{-KT_{max}^{ss}}\right] - C_{min}^{ss}(1-P)e^{-K\tau}$$

$$[C_{max}^{ss}(P+PT_r K - 1) + C_{min}^{ss}(1-P)]e^{-K\tau} = C_{min}^{ss}\left[(1-P) + PT_r K e^{-KT_{max}^{ss}}\right] - C_{max}^{ss}(1-P)$$

Finally we get expression for τ.

$$\tau = -\frac{1}{K}ln\left[\frac{C_{min}^{ss}\left[(1-P) + PT_r K e^{-KT_{max}^{ss}}\right] - C_{max}^{ss}(1-P)}{C_{max}^{ss}(P+PT_r K - 1) + C_{min}^{ss}(1-P)}\right]$$

The above equation may be solved to obtain the value of the dosing interval associated with the pre-defined (or user-defined) therapeutic range.

This new tau may inserted in either of the two equations provided above for Cmin or Cmax to obtained the new maintenance dose that will ensure that plasma levels are contained within the desired plasma range.

Mathematical Aspects of Multiple Dosing

Assuming that a drug has been administered as a single dose, that maximum and minimum amount of the drug in the body, within a fixed dosing interval, could be easily determined irrespective of the model that could best describe the kinetics of the administered drug. For a one-compartment model drug, administered by intravenous route, the maximum quantity to be found in the body after the first dose will be the administered dose itself. Furthermore, the minimum quantity will be that which could be estimated at the end of the dosing interval as per the expression ($X_{min(N=1)} = X_0 e^{-K\tau}$) Likewise, the maximum quantity that will be found upon the administration of the second dose will be this dose itself plus the minimum amount that was left over from the previous dose, i.e. ($X_{nax(N=2)} = X_0 + X_0 e^{-K\tau}$). This amount will be reduced as function of the dosing interval, i.e. $X_{nin(N=2)} = X_0(1+e^{-K\tau})e^{-K\tau}$. The continuation of dosing will result in a geometric series which has been formulated by Dost as early as 1953.

$$\frac{e^{-(N-1)\lambda_i\tau} - e^{-\lambda_i\tau}}{1-e^{-\lambda_i\tau}} = \left(\frac{e^{-(N-1)}-1}{1-e^{-\lambda_i\tau}}\right)e^{-\lambda_i\tau}$$

Based on the above isotherm, it could be verified that the following expression holds true,

$$\left(\frac{e^{-(N-1)\lambda_i\tau} - e^{-\lambda_i\tau}}{1-e^{-\lambda_i\tau}}\right)e^{-\lambda_i t} = \left(\frac{1-e^{-(N-1)\lambda_i\tau}}{1-e^{-\lambda_i\tau}}\right)e^{-\lambda_i(t-(N-1)\tau)}$$

If a PK model contains what could be regarded as discrete terms or quantities, then each such quantities has to be multiplied by Dost' multiple dosing factor to transform the model into a multiple dosing model.

$$C_N = \sum_{l=1}^{n} A_l \left(\frac{1-e^{-N\lambda_i\tau}}{1-e^{-\lambda_i\tau}}\right)e^{-\lambda_l t}$$

where C_N is plasma levels after N number of doses, A_l is the zero-time intercept associated with the λ_l rate constant, τ is the dosing interval and t is the actual time.

This generalized expression could be used to quantify the plasma levels after any number of doses, during ant dosing interval. It may also be modified so that some main PK metrics be the main PK metrics ensuing from any multiple dosing situation, namely, the maximum, the minimum and the average plasma levels. The actual plasma levels during any dosing interval could also be evaluated at any dose as well as at steady state. The maximum plasma level at steady state could be determined according to the following repeated administration of intravenous bolos doses could be estimated according to the equation:

$$C_{max}^{\infty} = \sum_{l=1}^{n} A_l \left(\frac{1}{1-e^{-\lambda_i\tau}}\right) \quad and \quad C_{min}^{\infty} = \sum_{l=1}^{n} A_l \left(\frac{1}{1-e^{-\lambda_i\tau}}\right)e^{-\lambda_l\tau}$$

Dosing Regimen Individualization (DRI)

Individualization incorporates patient's specific parameters such as age, gender, body weight and height into the PK parameters employed by the system to construct plasma drug levels for any PK scenario. For healthy individuals, the following patient-related specifics or parameters have been used to individualize dosing regimens:

- Ideal or lean body wieght (IBW or LBM)
- Body surface area (BSA)
- Serum (plasma) creatine levels
- Creatinine clearance (urinary)

BSA could surve to estimate a new maintenance dose for subject of different ages and/or hight/weights. This will be of particular interest for pediatric subjects.

In cases where actual plasma levels are provided in the system PK-Database, these will be indicated as "Reported Therapeutic Range". Otherwise, the system will use the population PK metrics to construct a "Theoretical Therapeutic Range".

The above ranges could be modified by users. Such modification will be directly reflected on the graphical display of the range only. However, modifying any other default PK parameter will only affect the graphical display of the plasma profile. Reflecting such modification on the graphical display of the range band will be an option than may be selected by user. Once the new dosing interval has been determined, the maintenance dose could be estimated as described for different routes of administration.

The availability of an abundance of PK models together with PK metrics most drugs allow theoretical prediction of their plasma levels. Notwithstanding, PK metrics reported for any drug represent average values that may be associated with different levels of variability. Expressed as percent coefficient of variation around mean values, such variability may exceed 70% in some drugs. For example, the biological half-life of carbamazepine could range between 18 to 70 hours. Such variability renders any prediction of plasma level for such drug totally pointless and meaningless. In this regards, therapeutic drug monitoring bears special significance within the context of dosing regimen individualization.

It must be noted that unless a strong association exist between drugs dynamic effect and their plasma levels, predicting such levels could only bear a theoretical significance. Accordingly, users of PK-Works must be cognizant of this important realization and should offer any unfounded interpretation for drugs plasma levels provided by the system.

Age & Weight Related DRI

There are instances whereby clinical practioners prescribe drugs for individuals on the basis of their age and weight. It may be assume that regular dosing regimens of drugs are generally designed for average body surface area (*BSA*) which is estimate at $1.73m^2$ for average subjects or ideal body weight (*IBW*). It must be noted that *IBW* is referred to as lean body weight by some references. Alterations in these parameters may require a corresponding alteration in their dosing regimens. Several equations have been suggested for the estimation of these body-related metrics. The oldest of these has been suggested by DuBios (7) in 1916.

This equation is operationally equivalent to another formula suggested by Mosteller (8) in 1986. Devine (9) has also devised an equation for the estimation of IBW that takes into account weight, height and gender:

$$BSA_{(m^2)} = (W^{0.425})(H^{0.725})(0.007184)$$

$$IBW_{(kg)} = 50 + (2.3)(H_{(in)}).......(M)$$

$$IBW_{(kg)} = 45 + (2.3)(H_{(in)})........(F)$$

$$BMI = \frac{W_{(kg)}}{(H_{(m)})^2} = \frac{(W_{(lb)})(703)}{(H_{(in)})^2}$$

Estimates of *BSA* could be used as basis for *DRI*, or normalization, especially for pediatrics subjects who are administered drugs with known narrow therapeutic index. On the other hand, *IBW* is often used to normalize dosing regimens for obese individuals whose weight is 30% higher than the normal weight. This is related to the fact that the elimination of many drugs is altered with age. This is mainly caused by liver function which may be underdeveloped in children compared to adult individuals. Also, liver, as well as, kidneys function is likely to deteriorate with age.

DRI could be also undertaken when there is an established and reliable estimate of an altered *PK* metric. This applies mainly to the age- or disease-related changes in drugs accumulation properties. Clinician tend to use such officially approved information for the individualization od drugs dosing regimens In addition, drug manufacturers are often required, by the regulatory authorities, to avail information on altered PK properties in special population so that clinicians use it as basis for *DRI*.

Dosing regimen individualization could assume special importance in cases where the elimination of drugs may be influenced by patient's health condition. It is established that although the cardiac output may influence the elimination of some drug, the main two disease condition that have direct impact on drug clearance are kidneys and/or liver dysfunctions. Hence, PK-Works has been designed to account the alteration in the capacity, or the degree of impairment, of these two organs to eliminate drugs from the body. This will be detailed hereunder:

Renal Impairment

The kidneys represent an important organ in controlling body fluids and electrolytes as well as the elimination the metabolic end products of indigenous and exogenous substances. Any impairment in the kidneys function will lead to accumulation of such substances in the body. The decline in the kidney function will affects the pharmacokinetics of drugs that are partially or totally eliminated by the kidneys. Some of the more common causes of kidney failure include disease, injury, drug induced nephrotoxicity or alteration in the physiological conditions (acidity) of the kidneys. Acute or chronic diseases or of the kidneys can cause uremia, in which glomerular filtration is decrease to varying extents leading to accumulation of fluids and nitrogenous substance in the body. This may further lead to a reduction of glomerular filtration and passive or active secretion of many substances including drugs. Renal impairment may be also caused by disease conditions leading to pyelonephritis, hypertension or diabetes mellitus.

Irrespective of the underlying cause(s) for renal impairment, many test procedures have been devised to assess the degree of such impairment. All such procedures are based on the assessment of renal creatinine or inulin clearance. In this regard, Clcr is favored due to tediousness of test methods suited to measure inulin clearance. In either of these methods, their estimate clearance values if generally equated with the glomerular filtration of the kidneys.

Glomerular Filtration Rate (GFR)

Cockcroft and Gault (6) have suggested the following procedure for the assessment the kidney function:

$$GFR_{(mL/\min/1.73m^2)} = (186)(S_{cr}^{-1.154})(Age_{(yr)}^{-0.203})................(M)$$

$$GFR_{(mL/\min/1.73m^2)} = (186)(S_{cr}^{-1.154})(Age_{(yr)}^{-0.203})(0.742).....(F)$$

<u>Output of the above equation must be multiplied by 1.21 to account for African ethnicity.</u>

This method has become one of the most wildly used methods for estimating the capacity of the kidneys to eliminate substance from the body. While accounting for age, gender and ethnicity, it utilizes serum creatinine levels in estimating the glomerular filtration rate. It is well know that more than 85% is cleared by tubular secretion and minimal amounts are cleared by non-renal routes. It is also established that the production of creatinine in males and females ranges betwee 20 - 25 and 15 - 20 mg/kg IBW respectively. These value decrease with age at a rate of 2 mg/kg IBW per decade.

Estimated eGFR by Abbreviated MDRD (14) (Modified Diet Renal Disease)

$$GFR_{[mL/\min/1.73\,m2]} = 186 \times SerumCr_{[mg/dL]}^{-1.154} \times Age_{[yr]}^{-0.203} \times Sex \times Ethnicity$$

Equation parameters such as Gender, have two or more discrete values that may be used in the calculation. The numbers in the parentheses, e.g. (0.742), represent the values that will be used.

For creatinine in µmol/L:

$$eGFR = 32788 \times Serum\,Creatinine^{-1.154} \times Age^{-0.203} \times \left[1.210\,if\ Black\right] \times \left[0.742\,if\ Female\right]$$

For creatinine in mg/dl:

$$eGFR = 186 \times Serum\,Creatinine^{-1.154} \times Age^{-0.203} \times \left[1.210\,if\ Black\right] \times \left[0.742\,if\ Female\right]$$

Creatinine levels in µmol/L can be converted to mg/dL by dividing them by 88.4. The 32788 number above is equal to 186×88.41.154.

A more elaborate version of the MDRD equation also includes serum albumin and blood urea nitrogen (BUN) levels:

$$eGFR = 170 \times Serum\,Creatinine^{-0.999} \times Age^{-0.176} \times \left[0.742\,if\ Female\right] \times \left[1.180\,if\ Black\right] \times$$

$$BUN^{-0.170} \times Albumin^{+0.318}$$

Where the creatinine and blood urea nitrogen concentrations are both in mg/dL. The albumin concentration is in g/dL.

These MDRD equations are to be used only if the laboratory has NOT calibrated its serum creatinine measurements to isotope dilution mass spectrometry (IDMS). When IDMS-calibrated serum creatinine is used (which is about 6% lower), the above equations should be multiplied by 175/186 or by 0.94086.

Since these formulae do not adjust for body mass, they (relative to the Cockcroft-Gault formula) underestimate eGFR for heavy people and overestimate it for underweight people.

GFR by Schwartz (15, 16) [age less than 18]

$$GFR_{[mL/min/1.73\,m2]} = MuscleFactor \times Height_{[cm]} / SerumCr_{[mg/dL]}$$

Equation parameters such as Muscle Factor, have two or more discrete values that may be used in the calculation. The numbers in the parentheses, e.g. (0.33), represent the values that will be used.

The Muscle Factor is directly proportional to the muscle component of the body and varies with the age of the infant or child.

GFR by CKD-EPI (17, 18, 19) - Chronic Kidney Disease, Epidemiology Collaboration

$$GFR_{[mL/min/1.73m2]} = 141 \times \min\left(SerumCr_{[mg/dL]}/\kappa,1\right)^{\alpha} \times \max\left(SerumCr_{[mg/dL]}/\kappa,1\right)^{-1.209} \times$$

$$0.993^{Age_{[yr]}} \times Gender \times Ethnicity$$

Equation parameters such as Ethnicity, have two or more discrete values that may be used in the calculation. The numbers in the parentheses, e.g. (1), represent the values that will be used. GFR is estimated by an Equation developed by the Chronic Kidney Disease Epidemiology Collaboration.

For females, the following values are used: Gender = 1.018; alpha (α) = -0.329; kappa (κ) = 0.7. For males, the following values are used: Gender = 1; alpha (α) = -0.411; kappa (κ) = 0.9

GFR by MDRD (20) - Chronic Kidney Disease

$$GFR_{[mL/\min/1.73\,m2]} = 170 \times SerumCr_{[mg/dL]}^{-0.999} \times Age_{[yr]}^{-0.176} \times Gender \times Ethnicity \times$$
$$BUN_{[mg/dL]}^{-0.170} \times Albu\min_{[gm/dL]}^{0.318}$$

Equation parameters such as Gender, have two or more discrete values that may be used in the calculation. The numbers in the parentheses, e.g. (0.762), represent the values that will be used.

GFR by MDRD (21) - IDMS-Traceable SCr

(IDMS = isotope dilution mass spectrometry)

$$GFR_{[mL/\min/1.73\,m2]} = 175 \times S\tan dardized\ SerumCr_{[mg/dL]}^{-1.154} \times Age_{[yr]}^{-0.203} \times Gender \times Ethnicity$$

Equation parameters such as Gender, have two or more discrete values that may be used in the calculation. The numbers in the parentheses, e.g. (0.742), represent the values that will be used. This Equation helps estimate GFR when using IDMS-Traceable Standardized Serum Creatinine lab values.

Creatinine Clearance

Creatinine clearance (CrCl) represents the volume of blood cleared of creatinine per unit time and is used to estimate the renal glomerular filtration rate (GFR). The GFR is the sum total of filtration rates of all functioning nephrons in the kidney and is the most accurate index of renal capacity; however, it cannot be measured directly. The most accurate test currently available to determine CrCl (and therefore GFR) is the timed, 24-hour urine for creatinine along with a concurrently drawn serum creatinine. These values are inserted into an equation using patient surface area (based on patient height and weight), with the resulting value reported in mL/minute. Although tubular secretion of creatinine results in an overestimation of the true GFR by 10% to 15%, the 24-hour study remains more accurate than simple serum creatinine alone in evaluating GFR, as serum creatinine is affected by muscle mass, age, gender, and tubular secretion (NKF, 2011).

An alternative to the cumbersome and inconvenient urine collection method is to estimate CrCl based on serum creatinine-based formulas. These formulas take into consideration gender, weight, and ethnicity to determine an estimated GFR (eGFR). While not as precise as the 24-hour urine method, eGFR equations improve upon the limitations of serum creatinine alone. Of the several formulas validated and endorsed by national renal groups to estimate GFR, the CockCroft-Gault equation is the one most often used to determine the need for medication adjustments in the clinical setting.

As oulied earlier in this text, the physiologic definition of ceatinine relates its serum or plasma level at any time to its urinary excretion rate at that point in time. This could be mathematically expressed as follows:

$$Cl_{cr} = \frac{U_{cr(mg/dL)} * V_{urine(mL)}}{S_{cr(mg/dL)} * \Delta t_{(min)}}$$

GFR has invariably been equated with Cl_{cr} since its estimation makes use of serum creatinine level and it accounts for all other patien's age and gender. Cockcroft-Gault (6) have devised alternative procedures that account for other physical characteristic of patiens such as weight and height.

$$Cl_{cr} = \left[\frac{(140 - Age_{(yr)})(Wt_{(kg)})}{(72)(S_{cr(ss)})}\right]..............(M)$$

$$Cl_{cr} = 0.85\left[\frac{(140 - Age_{(yr)})(Wt_{(kg)})}{(72)(S_{cr(ss)})}\right]......(F)$$

Since Cl_{cr} estimated by the above equation has been based on ideal body surface area (BSA = 1.73m^2), its output must be normalized according to the specific BSA of the patient by a factor of 1.73m^2/BSA.

Further adjustemnt is deemed necessay for obese subjects by inserting an adjusted IBW in the above equation according to the following formula:

An $Adj.\ IBW_{(kg)} = IBW + 0.4(TBW - IBW)$ ə estimation of Cl_{cr} in obese subjects whose weight is equivalent to 125% the IBW, in which case the following formula has been suggested:

$$Cl_{cr} = \left[\frac{(137 - Age_{(yr)})(0.285)(Wt_{(kg)}) + (12.1)(H^2)}{(60)(S_{cr})}\right]......(M)$$

$$Cl_{cr} = \left[\frac{(146 - Age_{(yr)})(0.287)(Wt_{(kg)}) + (9.74)(H^2)}{(60)(S_{cr})}\right]......(F)$$

The above formula has been subject to criticism due to its failure to accurately account for creatinine clearance in obese individuals. Many clinicians prefer a 40% adjustment for the more robust Cochcroft-Gault equation.

In situations where the production of creatinine is unstable, Jellife & Choiu suggested two different procedures to estimate its clearance based on average levels of serum creatinine. It has been assumed that such levels would approximate SS creatinine levels which could be associated by its SS excretion (E_{SS}).

By the early 1970s, Jellife and Jellife have suggested a formula to estimate creatinine clearance based on age, gender and serum creatinine levels. The following is depiction of this formula that has been cited by many sources. However, its direct implementation did not give reasonable values for creatinine clearance.

$$Cl_{cr} = \frac{(98-16)*(Age-20)/20}{S_{cr}}, \quad mL/min/1.73m^2$$

Other sources have cited different equations which produced comparable values to other more recent equations. Notwithstanding, this method works reasonable for adults with normal muscle mas and has been superceeded by more efficient fulmulas.

$$Cl_{cr} = \frac{98*0.8*(Age-20)}{S_{cr}}, \quad ....(M)$$

$$Cl_{cr} = \frac{88*0.7*(Age-20)}{S_{cr}}, \quad ....(F) \quad (mL/min/1.73m^2)$$

All equation used for the estimation of creatinine clearance were based on the assumption that the human body produces creatinine at a constant rate with time. However, when such condition is doubtful, new procedures have been independently suggested Jellife and Chiou. Both procedures take into account age IBM, age, gender and average serum creatinine over a spicified period of time. Jelliffe & Jelliffe (11) have provided the following equations which have been used to estimate a SS serum level of creatinine which is corrected for IBW.

$$E_{(SS)} = IBW_{kg}[29.3-(0.203 \ x \ Age_{(yr)}).....(M)$$
$$E_{(SS)} = IBW_{kg}[25.1-(0.175 \ x \ Age_{(yr)}).....(F)$$

$$E_{ss(corrected)} = E_{(ss)} [1.035-(0.0337 \ x \ S_{cr(av)})]$$

$$E = E_{ss(corrected)} - \frac{[4*IBW_{(kg)}(S_{cr2}-S_{cr1})]}{\Delta T(days)}$$

$$Cl_{cr(ss)} = \frac{E}{(14.4*S_{cr(av)})}, \quad mL/min/1.73m^2$$

Measured Creatinine Clearance (CrCl)

$$CrCl_{[mL/min]} = Urine\ Cr_{[mg/dL]} \times Day'sUrineVolume_{[mL]} / SerumCr_{[mg/dL]} / 1440$$

Many clinicians think that the procedure suggested by Chiou and his co-worker (12) for the estimation of creatinine clearalce in cases were creatinine production is not stable is more realaible. These equations are provided as follows:

It must be noted that Jellife procedure has been deprecated in favor of the Chiou method.

Estimation of Cl$_{cr}$ in Pediatrics

Some empirical formulae (13) have been suggest for the estimation of creatinine clearance in pediatric population. The most commonly used procedure may be expressed as follows:

$$Cl_{cr} = \frac{0.45 * Height_{(cm)}}{S_{cr}}, \ Infants\ up\ to\ 1\ year\ of\ age,\ (mL/\min/1.73m^2)$$

$$Cl_{cr} = \frac{0.55 * Height_{(cm)}}{S_{cr}}, \ Children\ up\ 1\ to\ 10\ year\ of\ age,\ (mL/\min/1.73m^2)$$

CrCl by Jelliffe (22) - Obese Individuals

$$CrCl\ Normalized_{[mL/min/1.73m2]} = Sex \times \left(98 - \left(0.8 \times \left(Age_{[Years\ old]} - 20\right)\right)\right) / SerumCr_{[mg/dL]}$$

Equation parameters such as Sex, have two or more discrete values that may be used in the calculation. The numbers in the parentheses, e.g. (0.9), represent the values that will be used.

The Jelliffe formula represents a way to estimate CrCl. Because it is not weight-based, it may be preferred for use in obese subjects.

CrCl by Sanaka (23)

This author suggested an equation for elderly subject with aged between 60 - 92 years, with body mass between 24 and 61 kg

$$CrCl_{[mL/min]} = \frac{\left(Weight_{[kg]} \times \left(\left(MultiFactor \times PlasmaAlbumin_{[gm/dL]}\right) + AddFactor\right)\right)}{\left(100 \times SerumCr_{[mg/dL]}\right)}$$

For females the Multi Factor is 13 and the Add Factor is 29. For *males*, the Multi Factor is 19 and the Add Factor is 32. However, its estimates may not be appropriate in patients with protein wasting states such as nephrotic syndrome.

Normal Values

Refer to testing laboratory for lab-specific normal values. Typical values

Pediatrics: 70-140 mL/minute/1.73 m2

Adult male: 85-125 mL/minute/1.73 m2

Adult female: 75-115 mL/minute/1.73 m2

Note: CrCl values generally decrease by 6.5 mL/min/1.73 m2 per every 10 years after age 40.

Critical Values

Severe renal impairment: 15-29 mL/minute/1.73 m2

End-stage renal impairment: <15 mL/minute/1.73 m2

For drug dosing in the majority of patients, the difference in estimated GFR (eGFR) based on the two most widely used formulas, the Cockcroft-Gault equation and the MDRD Study equation, will not lead to a difference in drug dosages. Recent recommendations from the National Kidney Disease Education Program suggest that either value can be used to determine drug dosages (NKF, 2011).

CrCl by Cockcroft-Gault

$$CrCl_{[mL/\min]} = Gender \times \left(\left(140 - Age_{[yr]} \right) / \left(SerumCr_{[mg/dL]} \right) \right) \times \left(Weight_{[kg]} / 72 \right)$$

Equation parameters such as Sex, have two or more discrete values that may be used in the calculation. The numbers in the parentheses, e.g. (0.85), represent the values that will be used.

The default unit of measure for weight is kilograms. Please verify that the correct unit of measure has been selected.

This Equation provides an estimate of the creatinine clearance (Cr Clear) if the plasma creatinine concentration is stable. Weight is the estimated lean body weight.

CrCl by Cockcroft-Gault with IBW (24) - Obese Subjects

$$CrCl_{[mL/\min]} = \left(\left(140 - Age_{[yr]} \right) \times \left(Weight_{[kg]} CrCl_{[mL/\min]} / \left(SerumCr_{[mg/dL]} \times 72 \right) \right) \right) \times CrCl_{[mL/\min]} Sex$$

This calculator is not appropriate for dialysis patients or for pediatric patients. (IBW represents the

calculated ideal body weight).

The Cockcroft-Gault Equation estimates creatinine clearance and uses IBW unless the actual weight is less than the IBW in which case, the actual weight is used.

The CrCl Sex term is 0.85 for females and 1 for males.

Advantages and Limitation of Different Methods

It is evident that the above given methods for estimating creatinine clearance have advantages and limitation. Accordingly. It is the sole respoissibility of users to determine the best method suited to the clinical situation being dealt with. Merits and shortcomings of these methods are summerised in the table provided hereunder:

Formula	Advantages	Limitations
MRDR Study: Modification of Diet in Renal Disease Study equation CKD-EPI: The Chronic Kidney Disease Epidemiology Collaboration equation Formula calculators available at:www.kidney.org/professionals/kdoqi/gfr_calculator.cfm		
Cockcroft-Gault	• Extensively reviewed in the drug study literature and widely used for drug dosage recommendations • Easily calculated • {[(140-age) x weight] / (72 x Scr)} x 0.85 if female	• Does not take into consideration body surface area in an era of increasing obesity • Overestimates CrCl by 10% to15% • Does not correct for ethnicity • Only for > 18 years old
MDRD Study	• Normalized to body surface area • Includes consideration due to ethnicity • Updated in 2005 for use with standardized serum creatinine assays • Superior when renal function is moderate to severely reduced	• Complicated formula requiring access to computer-based applications • Tends to underestimate GFR in healthy individuals • Less accurate for eGFR > 60 mL/min/1.73m2 • Has not been validated for < 18, > 85 years old, pregnancy
CKE-EPI	• Normalized to body surface area • Includes consideration due to ethnicity • Superior when GFR is normal or only mildly reduced • Only for use with standardized creatinine assays	• Complicated formula requiring access to computer-based applications • Has not been validated for <18 years old, pregnancy, and certain ethnic subgroups (Hispanics)
Schwartz	• For use in those <18 years old • Includes consideration for child's height and muscle mass, which varies by age • Updated in 2009 for use with standardized serum creatinine assays	

Hepatic Dysfunction

The liver represents the main organ that rids the body from the indigenous metabolic waste as well as exogenous substance introduced to the human body. Recent decades witness the identification of about 60 liver enzymes that are responssible for most of the so-called phase-I metabolism. The clearance of more than 75% of drugs administered to the human body is determined by the activity of these enzymes. In situations where such activity is affected by liver dosease, dosing regimen must be modified to ensure that drugs plasma levels remain within safe and effective ranges.

High-Pugh score (CPS) is used as a measure of the decline in the activity or capacity of the liver enzymes to elimainate drugs from the body. Hence, user must provide a measured CPS, or details of such score so that the system estimates it. In either of the above cases, the main concern for the system will be the estimation of the change on overall value of K. This could be achieved by splitting the overall value of K to its representative components, i.e, K_r and K_h according to the precent of drug eliminated by either organ (Q_0).

Example: A dose of 1 mg/kg (body weight) is given to a patient every 8 hours

Patient's specifics (data entry): Age (52 yr), Weight (75 kg), S_{cr} (2.4 mg/dL)

Hereunder is the solution for estimating the Cl_{cr} for this patient:

$$Cl_{cr} = \frac{(140 - 52) \times (75)}{72(2.4)} = 38.19 \ {}_{(mL/\min)}$$

This means the kidneys have lost 61.8% of its capacity or Kr has decreased by 61.8%. Hence, if Qo is 0.00 (i.e. the drug is completely eliminated by the kidneys), the dose has to be reduced by this ratio. One may recall that K = Kr + Knr. Hence, if Qo is 0.5, the decrease in the overall K will be 30.9%. The same applies if the liver has lost part of its capacity.

Child Pugh Score

Bilirubin (mg/dL) :	□ < 2	□ 2 - 3	□ > 3
Albumin (g/dL):	□ > 3.5	□ 3.5 - 2.8	□ < 2.8
PT (INR):	□ < 4 (< 1.7)	□ 4 - 6 (1.7 - 2.3)	□ > 6 (> 2.3)
Ascites:	□ Absent	□ Mild - Moderate	□ Severe
Encephalopathy:	□ Absent	□ Mild	□ Severe
Display score:	99		

Pharmacokinetics of Missed Doses

Although missed doses represents a concern for patients and clinical practioners alike, its PK considerations have not been fully dealt with in the entirety of PK literature. Interestingly, both regulatory authorities and drug manufacturers provide the same recommendation if a single dose has been missed irrespective of the very characteristics of the drug in question. Such recommendation is not based on any PK or scientific grounds. Needless to say that no answer is provided where more than one dose went missing!

Lack of compliance may be encountered in some occasions. This is manifested by patients not taking the doses at the recommended times or failing to take some doses altogether. The former case is not expected to have drastic impact on plasma levels, whereas the latter may disrupt such levels significantly, depending on the PK nature of the drug in question. To examine the impact of lack of compliance, the missing quantities must be estimated in mathematical terms. In the first place, one has to revert to the mathematical model that is suited to describe the drug's PK properties. It is appreciated that such model must contain a multiple dosing function of the sort of $(1-e^{-nK\tau})/(1-e^{-K\tau})$ that will determine the magnitude of accumulation of the drug in the body. This function is basically determined by some constant elements, such as the number of doses and the rate constants, and a time element which represents a continuous quantity. These are in turn multiplied by similar quantities representing the exponential decay terms, like $e^{-K\tau}$, in the model. According, assessment of the impact of missing doses should be interpreted in terms of the effect of such event (a missed dose) on these quantities. The mathematical treatment for this situation should focus on the impact of the missed dose on whatever Pk metric of interest consequent to such missing dose. The two models shown hereunder are used for the assessment of missing a dose in the case of a one-compartment intravenous bolus model drug,

$$C_n = \frac{X_0}{V_d}\left[\left(\frac{1-e^{-NK\tau}}{1-e^{-K\tau}}e^{-Kt}\right)-e^{-Kt_{miss}}\right]$$

$$C_\infty = \frac{X_0}{V_d}\left[\left(\frac{e^{-Kt}}{1-e^{-K\tau}}\right)-e^{-Kt_{miss}}\right]$$

These two equations have been transformed into the right equation to determine the impact of a missing dose on any consequent dose by subtracting the value of $e^{-Kt_{miss}}$ from the multiple dosing factor at any time during a dosing interval. The time element in this exponential term (t_{miss}) is equated with the number of elapsed doses prior to a particular dose of interest plus at any time point with its interval. Similar treatment could be contemplated for orally administered drugs that confer upon the body the characteristics of a one compartment model.

$$C_n = \frac{K_a F X_0}{V_d (K_a - K)} \left[\left(\frac{1 - e^{-nK\tau}}{1 - e^{-K\tau}} e^{-Kt} \right) - e^{-Kt_{miss}} - \left(\frac{1 - e^{-nK_a\tau}}{1 - e^{-K_a\tau}} e^{-K_a t} \right) - e^{-K_a t_{miss}} \right]$$

$$C_\infty = \frac{K_a F X_0}{V_d (K_a - K)} \left[\left(\frac{e^{-Kt}}{1 - e^{-K\tau}} \right) - e^{-Kt_{miss}} - \left(\frac{e^{-K_a t}}{1 - e^{-K_a\tau}} \right) - e^{-K_a t_{miss}} \right] \quad ......(5.2)$$

The impact is not significant for drug with relatively short half-lives and requires no intervention by a booster dose. By contrast, for drugs with relatively long half-lives, the impact is significant which may necessitate the administration of booster dose to restore the disrupted steady state condition.

PK Generalization of Missed Doses

PK models may be generally described as consisting of constant quantities that are associated with some driving force that causes their accumulation or regression. Accordingly, the temporal element in such model assumes critical significance since it will drive these constant quantities in up- or down-ward direction. Close examination of Equation 5.2 reveals this basic characteristic of any PK model that tends to account for missed doses. This model consists of the accumulation function $(1 - e^{-NK\tau}) / (1 - e^{-K\tau})$ as well as the decay functions e^{-Kt_τ} and $e^{-Kt_{miss}}$. With the exception of intravenous infusion; the presence of exponential terms in these models transforms them into typical geometric series which allows the prediction of the time dependent variable they estimate, i.e., the plasma levels. Whereas the exponential term e^{-Kt_τ} accounts for the decay of plasma level during any dosing interval of a multiple dosing regimen, the other term $(e^{-Kt_{miss}})$ determines the amount of the drug that could have been contributed to the plasma level if the missed dose were not lost. This term may be considered as an intruder on the well-established PK models that are routinely used to predict plasma levels. Hence, it will be the only element to be subject to generalization within the context of devising PK model that account for missed doses.

For all purposes, questions regarding missed doses are usually posed in conjunction with a certain point in time where the effect of such missing is to be determined. This time point may be regarded as the point where the patient has informed the healthcare profession or has asked for advice on the matter. The current doses number (N_C) may be considered as the point of time to be used for the estimation of the

elapsed time for one or more than one dose(s) that might have been missed. Thus a generalized expression for this elapsed time may be provided as follows:

$$t_M = \tau(N_C - N_M) + t_\tau$$

where t_M is the elapsed time since a dose(s) was missed, N_{CD} and N_{MD} are the respective numbers of the current and missed dose(s) and t_τ is the time within any dosing interval.

According to this definition of the elapsed time, Equation 5.1 may be re-written according to this definition of the elapsed time for a multiple dosing condition, where a single dose was missed, as follows:

$$C_P^{N_C} = \frac{X_0}{V_d}\left[\left(\frac{1-e^{-N_C K\tau}}{1-e^{-K\tau}}e^{-Kt_\tau}\right) - e^{-K\tau(N_C-N_M)+t_\tau}\right] \quad ...... (5.3)$$

In cases where more than one doses has been missed, their contribution to the decay in any plasma level will correspond to the sum of the individual exponential decay terms associated with the respective elapsed times of these doses. Hence, a generalized expression for summing up the values of all exponential terms of missed dose(s) may be provided as:

$$\sum_{l=1}^{n} e^{-\lambda_l\left[\tau(N_C-N_M)+t_\tau\right]}$$

Intravenous Bolus

A model could be suggested to determine the impact of missed doses for drugs administered by intravenous bolus mode as follows:

$$C_P^{N_C} = \frac{X_0}{V_d}\left[\left(\frac{1-e^{-N_C K\tau}}{1-e^{-K\tau}}e^{-Kt_\tau}\right) - \left(\sum_{All\ N_M} e^{-K\tau(N_C-N_M)+t_\tau}\right)\right]$$

This equation could be used to determine the plasma level(s) at any time prior to the administration of the current dose after the most recent missed dose. It could be also used for predicting the plasma level for any consequently administered doses. In the latter case the term N_C will assume the number of the future dose(s) at which plasma levels need to be predicted.

First-order absorption

The conventional 1-compartment oral model could be readily transformed into a model that accounts for missed doses as follows:

$$C_n = \frac{K_a F X_0}{V_d(K_a-K)}\left\{\left[\left(\frac{1-e^{-NK\tau}}{1-e^{-K\tau}}\right)e^{-Kt_\tau} - \left(\sum_{All\ N_M} e^{-K\left[\tau(N_C-N_M)+t_\tau\right]}\right)\right] - \left[\left(\frac{1-e^{-NK_a\tau}}{1-e^{-K_a\tau}}\right)e^{-K_a t_\tau} - \left(\sum_{All\ N_M} e^{-K_a\left[\tau(N_C-N_M)+t_\tau\right]}\right)\right]\right\}$$

Intravenous infusion

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:

$$C_{p(Inf)}^{N} = \frac{k_0}{KV_d} \left[\begin{array}{l} \frac{1}{(1-e^{-K\tau})}\left(1-e^{-Kt_i}\left\{1-e^{-KT_{pi}}+e^{-NK\tau}(e^{KT_i}-1)\right\}-e^{-K\tau}\right) \\ -(1-e^{-Kt_{iNm}}) \\ -\sum_{All\ N_M}(1-e^{-KT_i})e^{-K\tau[(N_C-N_M)-(T_i+t_i)]} \end{array} \right]$$

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

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

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