PHARMACODYNAMIC PARAMETERS: INFLUENCE ON DOSE-RESPONSE RELATIONSHIP AND ESTIMATION

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PHARMACODYNAMIC PARAMETERS: INFLUENCE ON DOSE-RESPONSE RELATIONSHIP AND ESTIMATION.

BY

SUZETTE F. RASHED

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN APPLIED PHARMACEUTICAL SCIENCES

UNIVERSITY OF RHODE ISLAND

1999
DOCTOR OF PHILOSOPHY DISSERTATION

OF

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APPROVED:

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ABSTRACT

Overall drug response is controlled by pharmacodynamic (PD) phase and pharmacokinetic (PK) phase. Over the last twenty years, much greater emphasis has been placed in PK phase because its outcome is much easier to measure and model compared to that of PD. In fact, PD and its parameters play an important role in controlling drug response. This document consists of three studies. The first study demonstrates through computer simulations using STELLA (High Performance System) the manner in which the main PD parameters influence the dose response relationship. A one compartment PK model linked to a sigmoid $E_{\text{max}}$ model through an effect compartment was used. The results show that as the sigmoidicity constant increases the duration of effect gets shorter. This parameter also impacts the magnitude of the response where its effect depends on the drug concentration and its ratio to the concentration at 50% of the maximum effect (EC$_{50}$). Also, it was found that as the EC$_{50}$ increases, the response from a given concentration gets smaller and the duration of effect gets shorter. When an effect compartment is necessary to model drug action, the effect compartment characteristics become more prominent as $k_{e0}$ decreases. Thus the delay in response gets larger, the magnitude of response from a given dose gets smaller and the duration of action gets longer as $k_{e0}$ decreases.

The second study was designed to investigate the effect of different sources of variability, dose, PK and PD parameters, on drug response through computer simulations using STELLA. The different sources of variability were studied separately and in combination.
using a one-compartment PK model linked to sigmoid $E_{\text{max}}$ and linear PD models. The results show that in presence of similar amount of variability, the response is much more sensitive to variability in PD parameters than variability in PK parameters. It is concluded that variability in PD parameters are clinically important and must be taken into account in order to use the drug effectively and safely.

The third study was designed to investigate the optimum sampling design for a PD modeling study through computer simulation using an inhibitory Sigmoid $E_{\text{max}}$ model in NONMEM (Non-linear Mixed Effect Modeling). The bias and precision of parameter estimates were used to judge the performance of various studied designs. The effects of population size and level of inter-individual variability were further studied using the most optimum design. The experimental design for the determination of the equilibrium rate constant associated with an effect compartment was also studied. The most optimum design for determination of PD parameters in the absence of an effect compartment was found to be the one with the following sampling windows: 0.1-0.5, 0.5-1 and 1-2 $EC_{50}$ units. However, in the presence of high inter-individual variability (60%) estimates of variability parameters, using the most optimum design, were biased and imprecise. More precise estimates of the parameters were obtained with a larger population. The most optimum design for the equilibrium rate constant was found to be the one in which two samples were taken per individual, but it gave poor estimates of the variability parameter.
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Finally, I would like to dedicate this work to The Lord, Jesus Christ, for he has the kingdom, the power and the glory forever.
PREFACE

This document was prepared in the format of the manuscript plan in accordance to section 11-3 of the Graduate School Manual at the University of Rhode Island.

This dissertation consists of three manuscripts followed by appendices that include additional tables and figures related to the work in the manuscripts. At the end of the dissertation, there is a bibliography in which all sources used as references in this document are cited.
### TABLE OF CONTENTS

ABSTRACT ................................................................................................................. ii

ACKNOWLEDGEMENTS ............................................................................................ v

PREFACE ...................................................................................................................... vi

TABLE OF CONTENTS ............................................................................................... vii

LIST OF TABLES .......................................................................................................... xi

LIST OF FIGURES ........................................................................................................ xiv

MANUSCRIPT I: THE EFFECT OF PHARMACODYNAMIC PARAMETERS ON
DRUG RESPONSE ........................................................................................................ 1

I.1. ABSTRACT ............................................................................................................. 1

I.2. BACKGROUND: HISTORICAL AND LITERATURE REVIEW ON
PHARMACODYNAMICS .......................................................................................... 3

I.2.2. Pharmacodynamic models used clinically: ..................................................... 5

I.2.2.1. Fixed effect model: ..................................................................................... 5

I.2.2.2. Logarithmic model: .................................................................................... 6

I.2.2.3. E_{max} model: .......................................................................................... 7

I.2.2.4. Sigmoid E_{max} model: .............................................................................. 8

I.2.3. Linking the pharmacodynamic model to the pharmacokinetic model: .......... 11

I.2.3.1. Linking the effect to the peripheral compartment of multi-compartment PK
model: ...................................................................................................................... 12

I.2.3.2. Effect compartment method: ..................................................................... 12

I.2.3.3. Indirect PD model: .................................................................................... 14

I.3. CLINICAL RELEVANCE OF PHARMACODYNAMIC PARAMETERS: .......... 16
1.3.1. Introduction: .................................................................
1.3.2. Methods: .................................................................
1.3.2.1. Pharmacokinetic Model: ........................................
1.3.2.2. Pharmacodynamic Model: ........................................
1.3.2.3. Effect Compartment Model: ...................................
1.3.3. Results: .................................................................
1.3.3.1. Single IV Dose: .....................................................
1.3.3.1.1. Single IV dose with no effect compartment: ..........
1.3.3.1.1.1. Effect of n on the response: ..............................
1.3.3.1.1.2. Effect of EC50 on the drug response: ..................
1.3.3.1.2. Single IV dose with an effect compartment: ...........
1.3.3.1.2.1. Effect of k0 on the drug response: ......................
1.3.3.1.2.2. Effect of n on the response in presence of an effect compartment: ........
1.3.3.1.2.3. Effect of EC50 on the response in presence of an effect compartment: ........
1.3.3.2. Multiple IV Doses: ...............................................  
1.3.3.2.1. Multiple IV doses with no effect compartment: .......
1.3.3.2.1.1. Effect of n on the response: ..............................
1.3.3.2.1.2. Effect of EC50 on the response: ..........................
1.3.3.2.2. Multiple IV dosing with an effect compartment: .....  
1.3.3.2.2.1. Effect of k0 on response: .................................
1.3.3.2.2.2. Effect of n on the response in presence of an effect compartment: ....
1.3.3.2.2.2.2. Effect of EC50 on the response in presence of an effect compartment: ..
1.3.4. DISCUSSION: ....................................................
1.3.5. Conclusion: ................................................................................... 31

1.4. REFERENCES: .................................................................................... 32

MANUSCRIPT II: THE EFFECT OF DIFFERENT SOURCES OF VARIABILITY ON THEOPHYLLINE RESPONSE ........................................................................... 66

II.1. ABSTRACT: .......................................................................................... 66

II.2 INTRODUCTION: .................................................................................. 68

II.3 METHODS: .............................................................................................. 73

II.3.1. Structural Model: .............................................................................. 74

II.3.1.1. Pharmacokinetic Model: ................................................................. 74

II.3.1.2. Pharmacodynamic Model: .............................................................. 74

A. The linear model: .................................................................................... 74

B. The sigmoid $E_{\text{max}}$ model: ............................................................... 75

II.3.2. Variability Model: .............................................................................. 75

II.4. RESULTS: .............................................................................................. 77

II.4.1. Variability in the Dose: ..................................................................... 77

II.4.2. Variability in PK parameters: ........................................................... 78

II.4.3. Variability in PD parameters: .............................................................. 79

A. Variability in the PD parameters of the linear model: ............................. 79

B. Variability in the PD parameters of the sigmoid $E_{\text{max}}$ model: ............ 79

II.4.4. Combined PK-PD Variability: .......................................................... 80

II.5. DISCUSSION: ..................................................................................... 81

II.6. CONCLUSION: ..................................................................................... 88

II.7. REFERENCES: ..................................................................................... 90
LIST OF TABLES

Table I.1. Effect of n on drug response using a single IV dose .........................41
Table I.2. Effect of EC_{50} on drug response using a single IV dose ...................42
Table I.3. Effect of k_e0 on drug response using a single IV dose .......................43
Table I.4. Effect of n on drug response using a single IV dose with an effect compartment of k_e0 of 0.2 \text{ et}_{1/2}^{-1} .................................................................44
Table I.5. Effect of n on drug response using a single IV dose with an effect compartment of k_e0 of 1 \text{ et}_{1/2}^{-1} .................................................................45
Table I.6. Effect of EC_{50} on drug response using a single IV dose with an effect compartment of k_e0 of 0.2 \text{ et}_{1/2}^{-1} .................................................................46
Table I.7. Effect of n on drug response using a single IV dose with an effect compartment of k_e0 of 1 \text{ et}_{1/2}^{-1} .................................................................47
Table I.8. Effect of n on drug response using multiple IV doses .........................48
Table I.9. Effect of EC_{50} on drug response using multiple IV doses ...................49
Table I.10. Effect of k_e0 on drug response using multiple IV doses ......................50
Table I.11. Effect of n on drug response using multiple IV doses in presence of an effect compartment of k_e0 of 0.2 \text{ et}_{1/2}^{-1} .................................................................51
Table I.12. Effect of n on drug response using multiple IV doses in presence of an effect compartment of k_e0 of 1 \text{ et}_{1/2}^{-1} .................................................................52
Table I.13. Effect of EC_{50} on drug response using multiple IV doses in presence of an effect compartment of k_e0 of 0.2 \text{ et}_{1/2}^{-1} .................................................................53
Table I.14. Effect of EC$_{50}$ on drug response using multiple IV doses in presence of an
effect compartment of k$_{e0}$ of 1 et$_{1/2}$ .......................... 54

Table II.1. Variability (%CV) in dose and its influence on plasma concentration (Cp) and
drug response using linear [E(L)] and sigmoid E$_{max}$ [E(S)] models......................97

Table II.2. Variability (%CV) in PK parameters and its influence on plasma concentration
(Cp) and drug response using linear [E(L)] and sigmoid E$_{max}$ [E(S)] models............98

Table II.3. Variability (%CV) in PD parameters of the linear model and its influence on
drug response...........................................................................................................99

Table II.4. Variability (%CV) in PD parameters of the sigmoid E$_{max}$ model and its
influence on drug response......................................................................................100

Table II.5. Variability (%CV) in PK and parameters and their influences on plasma
concentration (Cp) and drug response using linear [E(L)] and sigmoid E$_{max}$ [E(S)]
models......................................................................................................................101

Table II.6. Variability (%CV) in dose, PK and PD parameters and their influences on
plasma concentration (Cp) and drug response using linear [E(L)] and sigmoid E$_{max}$ [E(S)]
models......................................................................................................................102

Table III.1. Sampling windows for the four basic designs..........................146

Table III.2. Sampling windows for designs A & B...........................................147

Table III.3. Percent bias of parameter estimates using the four basic designs........148

Table III.4. Percent precision of parameter estimates using the four basic designs.....149

Table III.5. Bias and precision of parameter estimates using the four basic designs....150

Table III.6. Effect of total sample size on percent bias of parameter estimates........151

Table III.7. Effect of total sample size on percent precision of parameter estimates....152
Table III.8. Effect of increasing inter-individual variability (IIV) on percent bias of parameter estimates.................................................................153

Table III.9. Effect of increasing inter-individual variability (IIV) on percent precision of parameter estimates................................................................................154

Table III.10. Percent bias of equilibrium rate constant ($k_{e0}$) and variability parameter estimates using Designs A & B..........................................................................................155

Table III.11. Percent precision of equilibrium rate constant ($k_{e0}$) and variability parameter estimates using Designs A & B..........................................................................................156
### LIST OF FIGURES

| Figure | Description                                                                 | Page |
|--------|-----------------------------------------------------------------------------|------|
| I.1    | The concentration-effect relationship of the $E_{\text{max}}$ model          | 55   |
| I.2    | The concentration-effect relationship of the sigmoid $E_{\text{max}}$ model  | 56   |
| I.3    | Schematic representation of a PK model linked to an effect compartment       | 57   |
| I.4    | Four basic indirect response models                                          | 58   |
| I.5    | The fall in plasma concentration ($C_p$) and Response ($E$) with time in absence and presence of effect compartment of $k_{eo}$ of 0.2 and 1 using single IV dose | 59   |
| I.6    | The concentration-effect relationship of the sigmoid $E_{\text{max}}$ model with different $n$ | 60   |
| I.7    | Effect of $n$ on drug response using single IV dose                         | 61   |
| I.8    | The concentration-effect relationship of the sigmoid $E_{\text{max}}$ model with different $EC_{50}$ | 62   |
| I.9    | Effect of $EC_{50}$ on drug response using single IV dose                   | 63   |
| I.10   | Effect of the equilibrium rate constant ($k_{eo}$) on drug response using single IV dose | 64   |
| I.11   | The fall in plasma concentration ($C_p$) and Response ($E$) with time in absence and presence of effect compartment of $k_{eo}$ of 0.2 and 1 using multiple IV doses | 65   |
| II.1   | Effect of variability in PK parameters on plasma concentration ($C_p$)       | 103  |
| II.2   | Effect of variability in PK and PD parameters on drug response using linear model (separate) | 104  |
| II.3   | Effect of variability in PK and PD parameters on drug response using sigmoid $E_{\text{max}}$ model (separate) | 105  |
Figure II.4. Effect of variability in PK and PD parameters on drug response using linear model (combined)...........................................................................................................106

Figure II.5. Effect of variability in PK and PD parameters on drug response using sigmoid $E_{\text{max}}$ model (combined)...........................................................................................................107

Figure III.1. Percent bias of parameter estimates using the four basic designs.........157

Figure III.2. Percent precision of parameter estimates using the four basic designs.....158

Figure III.3. Percent bias and precision of parameter estimates using Design 1........159

Figure III.4. Effect of total sample size on percent bias of parameter estimates........160

Figure III.5. Effect of total sample size on percent precision of parameter estimates....161

Figure III.6. Effect of increasing inter-individual variability on percent bias of parameter estimates...........................................................................................................162

Figure III.7. Effect of increasing inter-individual variability on percent precision of parameter estimates...........................................................................................................163

Figure III.8. Percent bias of $k_{e0}$ and variability parameter estimates using Designs A and B.....................................................................................................................164

Figure III.9. Percent precision of $k_{e0}$ and variability parameter estimates using Designs A and B.............................................................................................................165

Figure III.10. Percent bias and precision of parameter estimates using Designs A and B......................................................................................................................166

Figure A.1. Effect of n on drug response using single IV dose in presence of an effect compartment of $k_{e0} = 0.2$...........................................................................................................168

Figure A.2. Effect of n on drug response using single IV dose in presence of an effect compartment of $k_{e0} = 1$...........................................................................................................169
Figure A.3. Effect of EC$_{50}$ on drug response using single IV dose in presence of an effect compartment of $k_{e0} = 0.2$.................................170

Figure A.4. Effect of EC$_{50}$ on drug response using single IV dose in presence of an effect compartment of $k_{e0} = 1$.................................................................171

Figure A.5. Drug response vs time with different multiple IV doses at n and EC$_{50}$ of 1.................................................................172

Figure A.6. Drug concentration vs time with different multiple IV doses at n and EC$_{50}$ of 1.................................................................173

Figure A.7. Concentration-effect relationship using the linear model..................174

Figure A.8. Steady state plasma concentrations at different theophylline doses........175

Figure A.9. NONMEM control file of the pharmacodynamic model (PRED model)....176

Figure A.10. NONMEM control file of the effect compartment model (ADVAN 3)....177
THE EFFECT OF PHARMACODYNAMIC PARAMETERS ON DRUG RESPONSE

I.1. ABSTRACT

Pharmacodynamics (PD) describes the relationship between drug concentration at the site of action and the response. Mathematical models have been used to describe this process. One of the most widely used models is the sigmoid $E_{\text{max}}$ model, which incorporates the PD parameters of efficacy ($E_{\text{max}}$), potency ($EC_{50}$) and sigmoidicity constant ($n$). For the study of the dose response relationship in vivo a PD model may be linked to a pharmacokinetic (PK) model, which describes the dose-plasma concentration time relationship. Often, because of delays between the rise and fall in plasma concentration and the rise and fall in response, a special effect compartment is necessary to link the PK and PD models.

Despite PD's important role in the dose-response relationship, the application of PD parameters to therapeutic drug use is fairly new. This study demonstrates through a series of computer simulations the manner in which the main PD parameters ($EC_{50}$, $n$ and equilibrium rate constant ($k_{\text{eq}}$)) influence the dose response relationship. Simulations were conducted using a one compartment PK model with intravenous input linked to a sigmoid $E_{\text{max}}$ model in the presence and absence of an effect compartment. Response was assessed in terms of maximum observed effect and duration of effect half-life. The
response data were simulated using STELLA (High Performance System) with single and multiple doses.

The results show the manner in which the various PD parameters affect the magnitude and duration of drug response. As $n$ increases the duration of effect gets shorter. Thus the effect dissipates faster at higher values of $n$. This parameter also impacts the magnitude of the response but the effect of $n$ depends on the drug concentration and its ratio to the EC$_{50}$. If this ratio is greater than one, the drug response gets larger as $n$ increases, but if this ratio is less than one, the drug response gets smaller as $n$ increases. When this ratio equals one, i.e. when the concentration equals to EC$_{50}$, the response is 50% $E_{\text{max}}$ and independent of the value of $n$. As predicted, as the EC$_{50}$, which reflects the potency of drug, increases, the potency or sensitivity to the drug decreases and the response from a given concentration gets smaller. Also the effect of the drug decays more rapidly when drug concentrations are low relative to the EC$_{50}$. Thus as the EC$_{50}$ increases, the effect decays more rapidly and the duration of effect associated with a given effect gets shorter.

When an effect compartment is necessary to model drug action, the effect compartment characteristics become more prominent as $k_c$ decreases. Thus the delay in response gets larger, the magnitude of response from a given dose gets smaller and the duration of action gets longer as $k_c$ decreases. The study demonstrates that the design of rational dosing regimens for clinical therapeutics cannot be performed with knowledge of PK alone. The true optimization of dosage regimens must also take into consideration the PD parameters of the drug.
1.2. BACKGROUND: HISTORICAL AND LITERATURE REVIEW ON PHARMACODYNAMICS

1.2.1. Introduction:

Pharmacodynamics (PD) is defined as the study of the biological effects resulting from the interaction between drugs and biological systems \(^1\). Models are used to provide a simplified quantitative description of the concentration-response observations in an experiment and possibly make predictions for future experiments. Models have been developed, based on clinical observations to relate drug concentrations at the site of action to the pharmacological response. Although, the concentration at site of action drives the response, clinically it is usually impossible to measure this concentration. Thus, pharmacological response is usually related to plasma concentration (Cp). This approach appears satisfactory when the drug response is direct, receptor site rapidly equilibrates with plasma and the receptor interaction and response occurs rapidly. However, in some situations, there is a delay between rise and fall in Cp and rise and fall in response possibly due to a distribution delay. This may necessitate the link between the pharmacokinetic (PK) model and the PD model, using for example an effect compartment.

As early as 1878, Langley suggested that the law of mass action probably governed the drug action and Clark extensively developed this theory in the 1920s \(^2\). According to classical receptor theory, it is assumed that the drug action is proportional to the fraction
of receptors occupied. And that maximum effect results when all receptors are occupied 
(3,4). Using this assumption, the relationship between the drug effect and its concentration 
is hyperbolic in shape. This hyperbolic function is used to describe the concentration- 
effect relationship for many drugs and is now known as the $E_{\text{max}}$ model. The model was 
expanded to incorporate the possibility that more than one drug molecule may bind to 
each receptor. This expanded model is known as the sigmoid $E_{\text{max}}$ model and will be 
discussed in detail later. Clark also used the advantage of the logarithmic transformation 
of the sigmoid $E_{\text{max}}$ model equation to determine the PD parameters by linear regression 
method, which is later, modified to the logarithmic model (4).

The PK of most drugs are described as linear. Thus drug distribution and elimination are 
generally first order processes, and under the influence of elimination, $C_p$ falls mono- 
exponentially and the half-life is constant. As dictated by receptor theory, the PD of most 
Drugs however are most often non-linear and as discussed above the concentration-effect 
relationship may be hyperbolic or sigmoid. Thus, as $C_p$ decays, the effect will not 
necessarily fall in parallel. Thus, the time for the effect to fall by 50% will not necessarily 
be equal to the PK half-life. In consequence, clinically useful dosing guidelines cannot be 
based on PK models alone but must incorporate a PD model in order to consider non- 
linearity in concentration-effect relationship. A delay caused by the time for the drug to 
distribute from the plasma to its site of action may further limit the value of using PK to 
develop dosing guidelines (5).
In recognition of the importance of PD in controlling drug response, the Food and Drug Administration (FDA) recently called for PD modeling of clinical data as a component of new drug application \(^{(6)}\). The objective of this study is to demonstrate through computer simulations the manner in which the PD parameters affect drug response. The results of the simulations have been integrated with published reports from literature.

1.2.2. Pharmacodynamic models used clinically:

Several PD models have been used clinically to relate drug concentration at the effect site to the pharmacological response such as fixed effect model, logarithmic model, \(E_{\text{max}}\) model and sigmoid \(E_{\text{max}}\) model. A brief description of the characteristics of these models is as follows:

1.2.2.1. Fixed effect model:

The fixed effect model is the simplest PD model. The effect is considered as a categorical not a continuous variable. Thus the effect is either present or absent. The degree of the effect is immaterial, what is important is whether or not it occurs. For example, Bellar et al \(^{(7)}\) collected observations on a series of patients receiving digoxin. The effect was defined as the presence or absence of digitalis toxicity. The cumulative response rate for therapeutic effect can be compared to the cumulative rate of toxicity or adverse effect of a drug in order to obtain a measure of the therapeutic index and therapeutic range of the drug. This model has many limitations such as it suggests that all people respond to the
drug in the same way. Thus at a specific concentration in the therapeutic range, all people are assumed to respond optimally to the drug (8). Additionally, the model does not incorporate a graded drug response.

1.2.2.2. Logarithmic model:

The logarithmic model relates the drug response (E) to the logarithmic function of drug concentration at the site of action (C).

\[ E = S \log(C) + A \]

Where: S is a slope parameter, and A is the intercept. This model has the advantage that it linearizes the concentration effect relationship predicted by the more complex E\text{max} model (4). Nagashima et al (9) used this model to describe the time course of anticoagulation effect of warfarin. However, the logarithmic model has some limitations. The pharmacological effect cannot be predicted when the concentration is zero because of the logarithmic function. Also, it does not predict a maximum effect. Platzer et al (10) studied the PD of beta-blocking actions of bopindolol using the logarithmic model. They found that observations were likely to deviate from the predictions of this model at concentrations well below or well above the concentration at 50% of the maximum effect and resulted in errors in predicting the time course of pharmacological effect. Consequently, the E\text{max} or sigmoid E\text{max} model, which can describe the whole concentration-effect relationship, should be used whenever possible.
1.2.2.3. $E_{\text{max}}$ model:

The $E_{\text{max}}$ model is based on receptor theory where the effect is assumed to be proportional to the concentration or the fraction of receptors occupied \(^{(4)}\). The $E_{\text{max}}$ model equation is as follows:

$$E = \frac{E_{\text{max}} C}{EC_{50} + C}$$ \hspace{1cm} 1.2

Where: $E_{\text{max}}$ is the maximum effect (efficacy) and $EC_{50}$ is the potency, which reflects the sensitivity of organ or tissue to the drug \(^{(11)}\). The $EC_{50}$ is the concentration at 50% of the maximum effect.

This model predicts a hyperbolic concentration-effect relationship (Figure I.1). At low concentrations, well below the $EC_{50}$, the receptors are less saturated and the pharmacological action approximates a first order process and the concentration-effect relationship is linear. At higher drug concentrations, as receptor saturation is approached this relationship starts to be non-linear and the law of diminishing returns is observed. This model has many advantages such as: it incorporates a maximum effect and incorporates no effect at zero concentration. Additionally, it can be modified to incorporate the situation where more than one drug molecule binds to each receptor (the sigmoid $E_{\text{max}}$ model).
Oosterhuis et al (12) used the \( E_{\text{max}} \) model to study the PD of terbutaline. They studied the effect of terbutaline on lung function in 10 asthmatic patients after subcutaneous dosing with 0.75 mg terbutaline where a hyperbolic concentration-effect relation was found. Holford et al 1995 (11) used the \( E_{\text{max}} \) model to study the population PD of romazarit (a disease modifying anti-rheumatoid agent) to describe the time course of disease progress in 164 patients with rheumatoid arthritis.

When the drug effect is measured as inhibition of a biological phenomenon, the \( EC_{50} \) may be referred as \( IC_{50} \) (concentration producing 50% of maximum inhibition). Holford (14) used inhibitory \( E_{\text{max}} \) model to study the PD of warfarin. When this model was applied to the effect of warfarin the value of \( E_{\text{max}} \) was assumed to be 100% (i.e. complete inhibition of clotting factors synthesis) leaving only one parameter to be estimated (\( IC_{50} \)). Also, Lalonade et al (15) used the \( E_{\text{max}} \) model to study the PD of propranolol as % inhibition of exercise heart rate in 9 subjects. They found that at concentration well below the \( EC_{50} \), there was a linear relationship between effect and concentrations.

### 1.2.2.4. Sigmoid \( E_{\text{max}} \) model:

The sigmoid \( E_{\text{max}} \) model is a modification of the \( E_{\text{max}} \) model, which accounts for the probability that more than one drug molecule binds to each receptor, using the term \( n \), sigmoidicity. The sigmoid \( E_{\text{max}} \) model is derived from the Hill equation (14). It has been proposed as a useful model to describe the in-vivo relationship between dose/concentration and continuous pharmacological effect for many drugs (15). The
sigmoid $E_{\text{max}}$ is the most widely used today because it solves all the limitations of previous described models. This model predicts a sigmoidal concentration-effect relationship (Figure 1.2). The sigmoid $E_{\text{max}}$ model equation is as follows:

$$E = \frac{E_{\text{max}} C^n}{EC_{50}^n + C^n}$$  \hspace{2cm} (1.3)

The sigmoid $E_{\text{max}}$ model has three PD parameters that control the drug response. These parameters are the efficacy ($E_{\text{max}}$), the potency ($EC_{50}$) and the sigmoidicity constant ($n$). As with $E_{\text{max}}$ model, the efficacy and potency are the same as $E_{\text{max}}$ model parameters. The efficacy represents the maximum effect that occurs when all the receptors are occupied. Sometimes the efficacy is assigned a value of 100%. The $EC_{50}$ is the concentration at 50% of the maximum effect and $n$ is the number of drug molecules bound to each receptor and it determines the sigmoid shape of the concentration-effect relationship. For example if $n = 1$, concentration-effect relationship will be hyperbolic (the $E_{\text{max}}$ model), but when $n$ is greater than 1 the curve becomes sigmoid with a steeper slope in its central region as shown in Figure 1.2. If $n$ is less than 1, the slope is steeper at low concentration and shallower at high concentration ($^1$).

Although this model is based on receptor theory it cannot be assumed, even if the concentration-effect data fits the model, that the underlying pharmacological process is truly described by the model. It must be kept in mind that data drive the model. For example, sigmoidicity has been found to be a non-integer in some cases even though the
receptor theory would predict it to be always an integer \(^{(18,21)}\). When Meffin et al\(^{(15)}\) used this model to describe the response of patients to tocainide administered for suppression of ventricular ectopic depolarizations, non-integer values of \(n\) ranging from 2.3 to 20 were found. These values are unlikely to reflect receptor structure, but do emphasize the steepness of the curves. Braat et al\(^{(19)}\) used this model to study the side effects of theophylline (eosinopenia and hypokalemia) where \(n\) was found to be 6.22 for eosinopenic effect and 6.78 for hypokalemic effect. Minto et al\(^{(20)}\) used the sigmoid \(E_{\text{max}}\) model \((n = 2.51)\) to study the influence of age and gender on the PD of remifentanil, a short-acting opioid. Anderson et al\(^{(21)}\) studied the preoperative PD of acetaminophen analgesia in children where they found that the PD of acetaminophen could be described using a fractional sigmoid \(E_{\text{max}}\) model that is with \(n\) is less than 1 \((0.54)\).

In some cases (for example, heart rate and blood pressure), a baseline response is incorporated in the model. The modeled response may be added or subtracted from the baseline effect depending upon whether the response is stimulatory or inhibitory. If the drug has an inhibitory effect on a physiologic response, such as lowering of the exercise heart rate with a beta-blocker, the response is subtracted from the baseline effect. The baseline effect \((E_0)\) is the response at zero drug concentration and it is measured in absence of drug or during placebo administration. It is added to or subtracted from the model equation as follows:

\[
E = E_0 \pm \frac{E_{\text{max}} C^n}{EC_{50}^n + C^n}
\]
The $E_0$ can be estimated during modeling process or if it is known it can be substituted directly. In the latter case it would be subtracted from the response. Corey et al (22) studied PD of azimilide in 119 healthy volunteers where they found that the $E_{\text{max}}$ ranged from 24 to 28% change in QTc interval, a measure of the ventricular myocardial repolarization, from the baseline. Dias et al (23) studied the PD of intravenous diltiazem, a calcium channel blocker, in 32 patients with atrial fibrillation or atrial flutter using a sigmoid $E_{\text{max}}$ model with a baseline response. A strong relation ($R^2 = 0.78$) was observed between plasma diltiazem concentration and percent reduction in heart rate from the baseline. Anderson et al (21) studied the analgesic effect of acetaminophen in 120 children undergoing outpatient tonsillectomy using the sigmoid $E_{\text{max}}$ model with a baseline response where $E_0$ was fixed at 10(maximum pain score).

1.2.3. Linking the pharmacodynamic model to the pharmacokinetic model:

When the plasma concentration is substituted for concentration in PD equations, the underlying assumption is that the concentration at the site of action is in equilibrium with plasma. It should be emphasized that it is not necessary to assume that plasma concentrations are equivalent to effect site concentrations. This former assumption may be valid, if the drug effect is direct, receptor site rapidly equilibrates with plasma and the receptor interaction and response occurs rapidly. However, sometimes a delay between the pharmacological effect and the plasma concentration occurs which manifests itself by hysteresis. This delay may be due to the formation of an active metabolite, increased
receptor sensitivity, adaptation of some autoregulatory process that initially tries to compensate for the drug action, a close relation of the response to the drug concentration in peripheral compartment of multi-compartment PK model\(^{(24, 25)}\), distributional delay\(^{(12, 20, 21, 26, 27)}\) or a cascade of events to produce the response\(^{(14, 28-40)}\).

I.2.3.1. Linking the effect to the peripheral compartment of multi-compartment PK model:

The pharmacological effect could be related to the concentrations in the peripheral compartment if the drug exhibits multi-compartment characteristics for its disposition. Wagner et al\(^{(24)}\) demonstrated that the effects of lysergic acid diethylamide on mental performance were more closely related to the predicted peripheral compartment concentrations than to plasma concentrations. Reuning et al\(^{(25)}\) showed that the inotropic effect of digoxin related more closely to concentrations in the peripheral compartment than to those in plasma. However, the use of the peripheral compartment concentrations to describe concentration effect relationships has the limitation that the concentration in peripheral compartment represents the average concentration among the group of tissues that comprise the peripheral compartment and does not necessarily represent the concentration at the effect site.

I.2.3.2. Effect compartment method:
Sheiner et al (26) developed a method to deal with hysteresis caused by an equilibrium delay between the concentration of drug in plasma and its concentration at the effect site. They developed a method to estimate the half time for effect equilibration when plasma concentrations are not constant. These investigators proposed a model to describe the time course of muscle paralysis with d-tubocurarine where they linked the central compartment of the PK model with a hypothetical effect compartment by a rate constant $k_{1e}$ (Figure I.3). It was assumed that $k_{1e}$ was very small relative to any other rate constant in the PK model and consequently a negligible amount of drug entered the effect compartment relative to the amount of drug in the other compartments. Because the amount of drug that entered the effect compartment was negligible, the amount returning to the central compartment from the effect compartment was negligible and could be considered as eliminated directly from the effect compartment. Thus the effect compartment did not alter the plasma concentration-time curve. Under these assumptions, the specific value of $k_{1e}$ was unimportant, whereas the rate constant for drug loss from the effect compartment, $k_{e0}$, (Figure I.3) determined the time for the equilibration process between central and effect compartments and characterized the equilibration time between plasma concentrations and pharmacological effect. The major advantage of the effect compartment method was that non-steady state data could be used in conditions where a delay existed between plasma concentration and effect.

Tfelt & Paalzow (27) studied the effect of ergotamine on peripheral arteries, measured as a decrease in toe-arm systolic gradients, after intramuscular injection of ergotamine tartarate in 10 subjects with migraine. A delay existed between plasma concentration and
the effect. A hypothetical effect compartment model was used, the rate constant for equilibration of the drug between plasma and effect site was found to be 0.07 hr⁻¹. Thus, it took 9.9 hr for the drug to appear at the effect site. Oosterhuis et al \(^{(12)}\) studied the effect of terbutaline on bronchodilation in asthmatic patients. They found that fitting the time course of the effects required an effect compartment in the integrated PK/PD model. The equilibration half time was found to be 11.5 minutes. Minto et al \(^{(20)}\) used 3-compartment PK model linked to sigmoid E⁰ model through an effect compartment \((k_c = 0.516 \text{ min}^{-1})\) to study the influence of age and gender on the PK and PD of remifentanil. They found that volume of distribution and clearance decreased by approximately 25% and 33%, respectively while both EC₅₀ and Kₐ decreased by approximately 50% over the age range of 20 to 85 years while gender had no influence on any PK or PD parameters. So based on this study, remifentanil dose should be reduced for elderly people. Anderson et al \(^{(19)}\) used a one compartment PK model linked to sigmoid E⁰ model through an effect compartment to study the PD of acetaminophen in children where they found that the time for acetaminophen to reach the site of action was 1.6 hr.

### 1.2.3.3. Indirect PD model:

Some drugs exhibit an indirect relationship between their concentrations and their pharmacological response. Four indirect, mechanism based models have been proposed to model this type of response (Figure 1.4) \(^{(28)}\). Each of these models assumes that the drug either inhibits or stimulates the production \((K_{in})\) or dissipation \((K_{out})\) of factors controlling the measured effect \(^{(29)}\). Thus, in model I the drug inhibits \(K_{in}\). The action of
warfarin is an example of this category of response. Warfarin blocks the synthesis of vitamin K dependent clotting factors but has no effect on the degradation of these same factors. Thus, warfarin concentration may be related to the clotting factors synthesis but only indirectly related to the ultimate therapeutic effect (anticoagulation) (14, 28, 30-34).

Another example of model I is the cell trafficking effect of the corticosteroid, methylprednisolone. This drug causes changes in the cellular trafficking pattern of leucocytes, which results in a net movement of the cells from blood to extra vascular sites. It appears that the drug inhibits cells returning to the blood without affecting the egress of cells from the blood (35-38). Also, Sun et al (39) used the indirect PD model (I) to elucidate the relationships between the events in the molecular cascade that result in muscle wasting and fat deposition by methylprednisolone in rats. They found that this model was useful for describing the characteristics of time delay in the pharmacological action.

The second indirect response model deals with inhibition of $K_{\text{out}}$ by a drug. An example of this model is the effect of pyridostigmine (a cholinesterase inhibitor) on muscular response following intravenous injection. Pyridostigmine inhibits the degradation and increases acetylcholine concentrations at the neuromuscular junction thus improving muscular response (15). Another example of model II is the diuretic effect of furosemide following intravenous injection, where it inhibits water reabsorption.

Model III indirect response deals with stimulation of $K_{\text{in}}$ by a drug. An example of the application of model III is the effect of terbutaline on bronchodilation. Terbutaline
increases cyclic adenosine monophosphate (cAMP) in bronchial smooth muscle thus increasing bronchodilation as a function of plasma concentrations\(^{(35)}\).

Model IV indirect response deals with drug mediated stimulation of \(K_{\text{out}}\). An example of this model is terbutaline-induced hypokalemia. Terbutaline stimulates the \(\beta_2\)-adrenergic receptors leading to an increase in the formation of cAMP, and thereby activates the cellular membrane sodium-potassium adenosine triphosphate (ATP) pump. The hydrolysis of ATP is directly coupled to the transport of sodium ions out of cells and influx of potassium ions, resulting in the temporary reduction of plasma potassium levels\(^{(40)}\).

**1.3. CLINICAL RELEVANCE OF PHARMACODYNAMIC PARAMETERS:**

**1.3.1. Introduction:**

The magnitude and duration of response produced by a given dose of a drug is a function of the sequential PK and PD phases. Consequently the parameters used to model each of the phases are critical in controlling overall drug response and the design of suitable dosage regimens to produce optimum outcomes. Over the last 25 years PK principles have been universally applied to target specific concentrations or concentration ranges. However, owing to the paucity of information on the PD characteristics of drugs, this phase has been simplified and condensed down to the concept of the therapeutic range. The limitations of this approach combined with the increase in number of sophisticated
PD models published in literature are now permitting alternative, more thorough approaches to the consideration of PD phase in dose optimization (8).

As these models and their associated parameters become more integrated in clinical practice, it becomes critical that practitioners fully appreciate the manner in which PD parameters impact response and thus dosage optimization in much the same way that the importance of the PK parameters, clearance, volume of distribution and half-life, are known.

This study was designed to demonstrate through computer simulations the impact of the major PD parameters, EC$_{50}$, n and $k_{e0}$ on the magnitude and duration of drug response. The magnitude of response was evaluated by comparing the maximum observed effect (MOE) from a series of doses. The duration of effect was assessed by measuring the time for the effect to fall by 50% (effect half-life) at different concentrations. Simulations were performed using a one-compartment PK model linked to a sigmoid E$_{max}$ model with and without an effect compartment. The goal of the study was to provide practitioners and pharmaceutical scientists with information about the PD parameters comparable to that of major PK parameters of clearance, volume of distribution and half-life.

1.3.2. Methods:

An integrated PK-PD model was constructed in STELLA (High Performance Systems, Inc, Hanover, NH).

17
I.3.2.1. Pharmacokinetic Model:

A one-compartment PK model with a first order elimination rate constant was used. Units of time were the half-life (t$_{1/2}$). The drug was assumed to have a volume of distribution (VD) of 20 L. Thus the drug's clearance would be equal to, VD$\times$0.693/t$_{1/2}$, 13.9 L/t$_{1/2}$. Simulations were performed using intravenous (IV) single dose and IV multiple doses in presence and absence of the effect compartment. Concentration was measured in units of EC$_{50}$. Single IV doses were selected to produce MOE of 25, 50 or 90 % respectively when n = 1 and EC$_{50}$ = 1 in absence of the effect compartment. Multiple IV doses were given every elimination half-life to produce MOE at steady state of 25, 50 and 90 % respectively when n=1 and EC$_{50}$ =1 in absence of the effect compartment.

I.3.2.2. Pharmacodynamic Model:

Response data were generated using the sigmoid E$_{max}$ model. Simulations using different values of n (0.5, 1, 2, 3 & 5) and EC$_{50}$ (0.5, 1, 2, 3 & 5) were performed in order to evaluate the influence of these parameters on the magnitude and duration of response. The response data were generated by numerical integration every 0.01 hr.

I.3.2.3. Effect Compartment Model:
In addition to a direct link, the PD model was also linked to the PK model through an effect compartment. Illustration of the hypothetical effect compartment is shown in Figure 1.3, as mentioned previously. The effect of different equilibrium rate constant, \( k_{e0} \), (0.2, 0.4, 0.6, 0.8 & 1) on MOE and on the duration of effect half-life was studied [(\( k_{te} \) was kept constant at 0.01 elimination half-life\(^{-1} \) (et\( _{1/2}^{-1} \))]. The effects of the values of \( n \) and EC\(_{50} \) on drug response in presence of the effect compartment were studied.

I.3.3. Results:

The time for the plasma concentration to fall by 50% (PK half-life) is constant while the time for the effect to fall by 50% (PD half-life) varies on the curve and is much longer than the PK half-life as shown in Figure 1.5. Moreover, the fall in response gets longer in presence of an effect compartment than that in absence of it.

I.3.3.1. Single IV Dose:

I.3.3.1.1 Single IV dose with no effect compartment:

I.3.3.1.1.1 Effect of \( n \) on the response:

The effect of different values of \( n \) on the response is shown in Table I.1, Figures 1.6 and 1.7. As \( n \) increases, the slope of the concentration-response curve gets steeper (Figure 1.6). The parameter \( n \) is often referred to as the steepness parameter. As \( n \) increases the
concentration-response curve becomes steeper. The impact of this on the MOE from a specific dose depends on the ratio of the concentration to the EC$_{50}$. If this ratio is less than one i.e. at low drug concentration, the MOE from a given dose gets smaller as n increases. In contrast, at ratio greater than one, the MOE gets larger with increase in n. Note in Figure 1.6, when n is small, very large concentration would be necessary to achieve maximum response. When the ratio is equal to one, i.e. when concentration = EC$_{50}$, the effect is 50% $E_{max}$ irrespective of the value of n. The effect of n on the duration of effect is shown in Figure 1.7, where again it can be seen that as n increases, the slope of the effect-time curve gets steeper. Thus, as n increases the response dissipates faster and the duration of response decreases. Thus, n affects both the magnitude and duration of response from a given dose.

1.3.3.1.1.2. Effect of EC$_{50}$ on the drug response:

The manner in which the values of the EC$_{50}$ influences drug response is shown in Table 1.2 and Figures 1.8 and 1.9. Changes in the potency or EC$_{50}$ shift the effect-concentration curve along the x-axis (Figure 1.8). As EC$_{50}$ increases, the curve is shifted to the right. Thus as EC$_{50}$ increases, the response from a given concentration decreases. The effect-time relationship after a standard single dose is also considered (Figure 1.9), it can be seen that as EC$_{50}$ increases, the MOE from a given dose gets smaller and the rate of fall of effect is more rapid with higher values of EC$_{50}$. As mentioned earlier, at low concentration relative to EC$_{50}$, the fall in effect with time approximates first order process. At high concentration relative to EC$_{50}$ however, when the receptors display a
greater degree of saturation the rate of fall of effect with time is less than for a linear first order process.

I.3.3.1.2. Single IV dose with an effect compartment:

The influences of \( k_{eo} \), \( n \) and \( EC_{50} \) on drug response were studied when the integrated PK/PD model incorporated an effect compartment. The effects of \( n \) and \( EC_{50} \) were studied at two values of the \( k_{eo} \) (0.2 and 1 \( \text{et}_1/2^{-1} \)).

I.3.3.1.2.1. Effect of \( k_{eo} \) on the drug response:

The equilibrium rate constant \( (k_{eo}) \) quantifies the delay between plasma concentrations and pharmacological response caused by the time required for drug distribution to its site of action. Compared to models where the distribution process proceeds essentially instantaneously, the MOE from a given dose is less but the duration of action is longer (Figure I.10). The more significant the delay (i.e. the small the value of the \( k_{eo} \)), the smaller the MOE and the longer the duration of effect. The effect of different \( k_{eo} \) on the MOE and on duration of effect half-life is shown in Table I.3 and Figure I.10 using the same doses that gave 25, 50 or 90 % response in absence of the effect compartment when \( n=1 \) and \( EC_{50} =1 \). As expected, there is a delay in the response after dose administration. The time for the peak effect gets longer as \( k_{eo} \) decreases.
1.3.3.1.2.2. Effect of \( n \) on the response in presence of an effect compartment:

The effect of \( n \) on drug response in presence of an effect compartment is shown in Tables 1.4 and 1.5 for \( k_{e0} \) of 0.2 and 1 \( \text{et}_{1/2}^{-1} \), respectively. The effect of \( n \) on the maximum response and duration of action is similar to that in absence of the effect compartment. Additionally, however \( n \) influences the delay for the initial response. The delay in the initial response observed in the presence of an effect compartment gets longer as \( n \) increases. For a given \( k_{e0} \), the time to reach MOE is almost the same irrespective of changing \( n \) and the dose because it depends only on the value of \( k_{e0} \).

1.3.3.1.2.3. Effect of EC\(_{50}\) on the response in presence of an effect compartment:

The effect of EC\(_{50}\) on drug response in presence of an effect compartment is shown in Tables 1.6 and 1.7 for \( k_{e0} \) of 0.2 and 1 \( \text{et}_{1/2}^{-1} \), respectively. The delay in the response and time to reach MOE are essentially independent of EC\(_{50}\). As expected, the response gets smaller and the duration of effect gets shorter as EC\(_{50}\) increases.

1.3.3.2. Multiple IV Doses:

Multiple IV doses were given every PK half-life to produce MOE at steady state (7-PK half lives) of 25, 50 and 90\% respectively when \( n=1 \) and EC\(_{50}=1 \) in absence of the effect
compartment. The duration of effect half-life could not be studied with multiple dosing because at the concentration used the response never fell by 50% during a steady state condition. At steady state condition, the maximum $C_p$ fell by half while the drug response was only slightly affected by that fall in $C_p$. In presence of the effect compartment, the fall in drug response got much longer than that in absence of the effect compartment as shown in Figure I.11.

1.3.3.2.1. Multiple IV doses with no effect compartment:

The effects of $n$ and $EC_{50}$ on drug response in case of multiple dosing were studied in terms of MOE. The drug response at initiation of therapy is less than that at steady state, because of the accumulation of drug that occurs during the build up to steady state.

1.3.3.2.1.1. Effect of $n$ on the response:

The effect of $n$ on drug response using multiple IV doses is shown in Table I.8. The manner in which the drug response is affected by $n$ using multiple doses is similar to that of single dose where the effect of $n$ depends mainly on drug concentration and its relation to $EC_{50}$.

1.3.3.2.1.2. Effect of $EC_{50}$ on the response:
The effect of EC\textsubscript{50} on the drug response using multiple IV doses is shown in Table I.9. As with single IV dose, the MOE gets smaller as EC\textsubscript{50} increases for all doses studied.

1.3.3.2.2. Multiple IV dosing with an effect compartment:

1.3.3.2.2.1. Effect of k\textsubscript{e0} on response:

The effect of different k\textsubscript{e0} on the drug response is shown in Table I.10. The EC\textsubscript{50} and \( n \) were kept at 1 and k\textsubscript{1e} was kept at 0.01 \( \text{et}_{1/2}^{-1} \).

As expected, there was no initial response after dose administration. The delay gets longer as k\textsubscript{e0} decreases. Compared to single dose, the magnitude of maximum response is slightly affected by the decrease in k\textsubscript{e0}. The fall in drug response is much longer than that in absence of the effect compartment as shown in figure I.11, where the slope of the time-response relationship in presence of the effect compartment is much shallower than that in absence of the effect compartment.

1.3.3.2.2.2. Effect of \( n \) on the response in presence of an effect compartment:

The effect of \( n \) on the response in presence of the effect compartment is shown in Tables I.11 and I.12 for k\textsubscript{e0} of 0.2 and 1 \( \text{et}_{1/2}^{-1} \), respectively. As with single dose, the delay gets
longer as n increases and the effect of n on drug response depends on drug concentration and its relation to $EC_{50}$.

### I.3.3.2.2. Effect of $EC_{50}$ on the response in presence of an effect compartment:

The effect of different values of $EC_{50}$ on drug response in presence of an effect compartment is shown in Tables I.13 and I.14 for $k_{e0}$ of 0.2 and 1 $et_{1/2}^{-1}$, respectively. As with single dose, the MOE from given doses gets larger as $EC_{50}$ decreases with all doses studied. The influence of the effect compartment appeared to be more prominent on the impact of $EC_{50}$ on drug response than that of n.

### I.3.4. DISCUSSION:

In recognition of the importance of PD in determining the response achieved by a given dose of a drug and by extension, the determination of optimum dosage regimen to achieve a desired response, PD studies are receiving increased emphasis in various branches of pharmaceutical science. The importance of these studies in optimizing drug dosage during drug development was recognized and stressed by Reigner et al (41). Recently PD have been used together with PK studies to optimize clinical trial design.

More recently, the use of integrated PK/PD models has been proposed as a superior method of individualizing doses of drugs in clinical use to achieve the desired therapeutic
effect. Traditionally the process of therapeutic drug monitoring aims to have the Cp within the therapeutic range, which is an empirically chosen range in which the average person would experience optimum response. However, therapeutic drug monitoring uses the passive concept of monitoring and fails to explicitly take drug effects into account.

As PD models and their associated parameters become more integrated in clinical practice, it becomes increasingly important that practitioners fully appreciate and understand the relevance of the various PD parameters to drug response in the same way that PK parameters are well related to Cp. For example, it is generally accepted that clearance determines the steady state plasma concentration and the value of a maintenance dose and that volume of distribution controls the early plasma concentration and the value of a loading dose.

These simulations have demonstrated the clinical importance of the PD parameters, n, EC_{50} and k_{e0} in determining the magnitude and duration of the drug response. It is important to understand how the drug response declines with time in the sigmoid E_{max} model as shown in Tables I.1 & I.2 and Figures I.7 & I.9. As a result of the non linear relationship, the half-life for the decay of response varies and depends on the initial response. Also, it is very important to consider the influence of the effect compartment in terms of k_{e0}, on the MOE, achieved from a given dose, and on the duration of effect half-life as shown in Tables I.3 and I.10.
The study of the effect of $n$ on the drug response shows that the effect depends on the ratio between drug concentration and $E_{50}$. If this ratio is more than 1, the drug response from a given dose gets larger as $n$ increases as shown with single and multiple doses that give MOE of 90% at $n = 1$ in Tables 1.1 and 1.8 respectively. At concentrations less than $E_{50}$, the response from a given dose gets lower as $n$ increases as shown with single dose and multiple doses that give MOE of 25% at $n = 1$ in Table 1.1 and Table 1.8, respectively. When this ratio equals 1, i.e. at 50% effect, the MOE is not influenced by $n$, because the effect is independent of $n$ when the concentration at the site of action (C) is equal to $E_{50}$. The independence of the effect on $n$ at this concentration can be proven below:

At 50% effect, drug concentration = $E_{50}$.

Thus $E = \frac{E_{\text{max}} \cdot C^n}{C^n + C^n}$

$E = \frac{E_{\text{max}} \cdot C^n}{C^n (1+1)}$

$E = 100 / 2 = 50\%$ regardless of the value of $n$.

The value of $n$ varies from drug to drug and from individual to individual. It was found that $n$ for tocainide varied from 2.3 to 20 (18). The study of the effect of theophylline on eosinopenia and hypokalemia showed that $n$ varied from 3.9 to 8.5 for the eosinopenic effect and 4.2 to 9.4 for the hypokalemic effect (19). Also, the study of the PD of remifentanil (20) showed that $n$ varied from 1.2 to 3.9. In addition, the study of preoperative PD of acetaminophen analgesia in children showed that $n$ varied from 0.31 to 0.77 (21). Individuals with low $n$ values will experience a greater effect and longer
duration of action, at low concentration than individuals with higher n values. Conversely, at higher concentration, when the receptors are approaching saturation, individuals with low n values will experience lesser response but still experience longer duration of action than those with higher n values.

The study of the effect of EC\textsubscript{50} on the drug response shows that EC\textsubscript{50} or potency shifts the concentration-response relationship up and down the x-axis as shown in Figure I.8. As EC\textsubscript{50} increases, the drug gets less potent and a smaller response is achieved from a given dose as shown in Table I.2 and Table I.9 with single and multiple doses, respectively. Likewise as the potency decreases, the EC\textsubscript{50} increases and the duration of action of the drug gets shorter. This is very important clinically, because when EC\textsubscript{50} increases or decreases it will result in a lower or higher drug response respectively.

Jonkers et al\textsuperscript{(42)} studied the changes over time in the concentration-effect relationship of the beta 2-adrenoceptor-agonist, terbutaline. A sigmoid E\textsubscript{max} model was used to relate drug concentrations to the response. After one week on oral terbutaline the concentration-effect relationship was shifted to the right with a higher EC\textsubscript{50} of terbutaline, which resulted in a higher drug concentration to produce a given response. Minto et al\textsuperscript{(20)} studied the influence of age on the PD of remifentanil where they found that age was a significant covariate of EC\textsubscript{50}. The EC\textsubscript{50} decreased by approximately 50% for the age range studied (20-85 years) as the individual gets older, which resulted in less drug concentration was required to produce the drug response in elderly people who were more sensitive to the effect of the drug.
The equilibrium rate constant ($k_{e0}$) is associated with effect compartment, which often added to account for a delay between the rise and fall in $C_p$ and the rise and fall in response. As the value of $k_{e0}$ gets smaller, the time to reach the equilibrium between the drug concentration in plasma and its concentration at the site of action gets longer and the influence of the effect compartment becomes more prominent as the time to reach the equilibrium is very long. This study demonstrated that as $k_{e0}$ decreases the MOE from a given dose gets smaller and the duration of response gets longer. This is because the smaller the value of $k_{e0}$, the slower the drug distribution to the effect site and the lower the concentration at the site of action from a given dose which results in a lower MOE. The duration of action gets longer which may be due to the slower redistribution of the drug. For example, a single dose that gives MOE of 90% and duration of effect half life of 3.4 elimination half-life ($et_{1/2}$) at $n = 1$ and $EC_{50} =1$ in the absence of an effect compartment, gives MOE of 80% and duration of effect half life of 3.9 $et_{1/2}$ in presence of $k_{e0}$ of 1 $et_{1/2}^{-1}$ and MOE of 61% and duration of effect half life of 8 $et_{1/2}$ in presence of $k_{e0}$ of 0.2 $et_{1/2}^{-1}$. The time to reach MOE gets longer as $k_{e0}$ increases. For example, a single dose that gives MOE of 90% at $n = 1$ and $EC_{50} = 1$ in absence of the effect compartment reaches the MOE at 2.44 $et_{1/2}$ and 1.15 $et_{1/2}$ in presence of $k_{e0}$ of 0.2 and 1 $et_{1/2}^{-1}$, respectively. The time to reach MOE is almost the same for a particular $k_{e0}$ irrespective of the dose as shown in Tables I.3, I.4, I.5, I.6 & I.7.

Using multiple IV doses, the MOE gets slightly smaller as $k_{e0}$ decreases. For example, multiple doses that give MOE of 90% at $n = 1$ and $EC_{50} = 1$ in absence of the effect
compartment, gives MOE of 82% and 86% in presence of an effect compartment of $k_{e0}$ of 0.2 and 1 respectively. Contin et al. (43) studied the time course of levodopa Cp and pharmacological effect (on finger tapping rate as a measure of motor response) in a patient with Parkinson's disease over 4 years of disease progression. There was essentially no effect on the drug PK but the onset of drug effect occurred earlier and the duration of effect became shorter over the years. This is because $k_{e0}$ gradually increased and hysteresis became less pronounced. The half-life of the apparent equilibration process decreased from 173 minutes to about 43 minutes (44).

Stanski et al. (45) studied the effect of halothane on d-tubocurarine response and found that halothane decreased the $k_{e0}$ for d-tubocurarine muscle paralysis and thus delayed the onset of muscle paralysis. This was due to halothane-induced reduction in muscle perfusion. The magnitude of $k_{e0}$ depends on many factors such as perfusion of the effect site, rate of drug diffusion from capillaries to the effect site, blood tissue partition coefficient of the drug, rate of drug-receptor association and dissociation, time course of subsequent pharmacological response and age (20).

The manner in which the values of n and EC$_{50}$ affect drug response in presence of an effect compartment are similar to that as in absence of the effect compartment with single and multiple doses.
I.3.5. **Conclusion:**

The PD parameters namely sigmoidicity constant, potency and equilibrium rate constant, influence the magnitude and duration of drug response. It has to be born in mind that the overall drug action consists of two phases, PK phase and PD phase. Thus, PD parameters should be taken into consideration in evaluating the drug response. Prospective implementation of large-scale population PD evaluation is feasible in early drug development and this approach generates clinically relevant findings\(^{(46)}\). The expanded use of PK/PD-modeling is found to be highly beneficial for drug development as well as applied pharmacotherapy and will most likely improve the current state of applied therapeutics\(^{(47)}\).
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Table I.1. Effect of n on drug response using a single IV dose:

| n  | MOE (%) | T<sub>1/2</sub> (et<sub>1/2</sub>) | MOE (%) | T<sub>1/2</sub> (et<sub>1/2</sub>) | MOE (%) | T<sub>1/2</sub> (et<sub>1/2</sub>) |
|----|---------|-------------------------------|---------|-------------------------------|---------|-------------------------------|
| 0.5| 75.0    | 4.61                         | 50.0    | 3.15                         | 36.6    | 2.71                         |
| 1  | 90.0    | 3.44                         | 50.0    | 1.58                         | 25.0    | 1.22                         |
| 2  | 98.8    | 3.17                         | 50.0    | 0.79                         | 10.0    | 0.54                         |
| 3  | 99.9    | 3.15                         | 50.0    | 0.53                         | 3.58    | 0.34                         |
| 5  | 100.0   | 3.15                         | 50.0    | 0.32                         | 0.41    | 0.19                         |

MOE: maximum observed effect.

<sup>1</sup>, <sup>2</sup>, <sup>3</sup> means that the dose used, gives MOE of 90%, 50% or 25% respectively when n and EC<sub>50</sub> = 1, in absence of the effect compartment.

T<sub>1/2</sub>: duration of effect half-life and et<sub>1/2</sub>: is the elimination half-life.
Table 1.2. Effect of EC$_{50}$ on drug response using a single IV dose:

| EC$_{50}$ | $1^{st}$ MOE (%) | T$_{1/2}$ (et$_{1/2}$) | $2^{nd}$ MOE (%) | T$_{1/2}$ (et$_{1/2}$) | $3^{rd}$ MOE (%) | T$_{1/2}$ (et$_{1/2}$) |
|-----------|------------------|-----------------------|------------------|-----------------------|------------------|-----------------------|
| EC$_{50}$=0.5 | 94.7             | 4.30                  | 66.7             | 1.99                  | 40               | 1.41                  |
| EC$_{50}$=1  | 90               | 3.44                  | 50               | 1.58                  | 25               | 1.22                  |
| EC$_{50}$=2  | 81.8             | 2.68                  | 33.3             | 1.31                  | 14.3             | 1.11                  |
| EC$_{50}$=3  | 75               | 2.31                  | 25               | 1.21                  | 10               | 1.07                  |
| EC$_{50}$=5  | 64.3             | 1.91                  | 16.7             | 1.13                  | 6.25             | 1.04                  |

MOE: maximum observed effect.
$1^{st}$, $2^{nd}$, $3^{rd}$ means that the dose used, gives MOE of 90%, 50% or 25% respectively when EC$_{50}$ = 1, in absence of the effect compartment.
T$_{1/2}$: duration of effect half-life and et$_{1/2}$: is the elimination half-life.
Table I.3. Effect of $k_{e0}$ on drug response using a single IV dose:

| $k_{e0}$ | $^{1}\text{MOE}$ (%) | $T_{1/2}$ (et) | $^{2}\text{MOE}$ (%) | $T_{1/2}$ (et) | $^{3}\text{MOE}$ (%) | $T_{1/2}$ (et) |
|----------|----------------------|----------------|----------------------|----------------|----------------------|----------------|
| $k_{e0}=0.2$ | 60.8                | 8.02           | 14.7                 | 5.46           | 5.44                 | 5.29           |
| $k_{e0}=0.4$ | 70.9                | 5.54           | 21.3                 | 3.67           | 8.28                 | 3.38           |
| $k_{e0}=0.6$ | 75.4                | 4.58           | 25.4                 | 2.98           | 10.2                 | 2.74           |
| $k_{e0}=0.8$ | 78.0                | 4.2            | 28.2                 | 2.63           | 11.6                 | 2.41           |
| $k_{e0}=1$   | 79.7                | 3.91           | 30.3                 | 2.40           | 12.7                 | 2.18           |

MOE: maximum observed effect.

$^{1,2,3}$ means that the dose used, gives MOE of 90%, 50% or 25% respectively when $n$ and $EC_{50}=1$, in absence of the effect compartment.

$T_{1/2}$: duration of effect half-life and $et_{1/2}$: is the elimination half-life.
Table 1.4. Effect of n on drug response using a single IV dose with an effect compartment of k_{e0} of 0.2 et_{1/2}^{-1}:

| n  | E_{init} (%) | MOE (%) | Time at MOE (et_{1/2}) | E_{init} (%) | MOE (%) | Time at MOE (et_{1/2}) | E_{init} (%) | MOE (%) | Time at MOE (et_{1/2}) |
|----|--------------|---------|-------------------------|--------------|---------|-------------------------|--------------|---------|-------------------------|
|    |              |         |                         |              |         |                         |              |         |                         |
|    | Dose 1       | Dose 2  | Dose 3                  | Dose 1       | Dose 2  | Dose 3                  | Dose 1       | Dose 2  | Dose 3                  |
| n=0.5 | 11.8 | 55.5 | 2.42 | 13.5 | 4.28 | 29.4 | 2.43 | 10.5 | 2.52 | 19.4 | 2.43 | 9.76 |
| n=2 | 0.03 | 70.7 | 2.46 | 7.76 | 0 | 2.89 | 2.37 | 3.24 | 0 | 0.33 | 2.18 | 3.4 |
| n=3 | 0 | 78.9 | 2.48 | 6.91 | 0 | 0.51 | 2.26 | 2.53 | 0 | 0.02 | N/A | N/A |
| n=5 | 0 | 90.0 | 2.45 | 6.34 | 0 | 0.02 | 2.27 | 0.47 | 0 | 0 | N/A | N/A |

E_{init}: effect (%) at 0.01 et_{1/2}.

T_{1/2}: duration of effect half-life and et_{1/2} is the elimination half-life.

1,2,3 means that the dose used, gives MOE of 90%, 50% or 25% respectively when n and EC_{50} = 1, in absence of the effect compartment.

N/A: not applicable.
Table 1.5. Effect of n on drug response using a single IV dose with an effect compartment of $k_{e0}$ of 1.0 $et_{1/2}^{-1}$:

| n    | $E_{\text{init}}$ (%) | 1$\text{MOE}$ (%) | Time at MOE ($et_{1/2}$) | 2$\text{MOE}$ (%) | Time at MOE ($et_{1/2}$) | $T_{1/2}$ ($et_{1/2}$) | 3$\text{MOE}$ (%) | Time at MOE ($et_{1/2}$) | $T_{1/2}$ ($et_{1/2}$) |
|------|----------------------|-------------------|---------------------------|-------------------|---------------------------|-----------------------|-------------------|---------------------------|-----------------------|
|      | Dose 1               | Dose 2            | Dose 3                    |                   |                           |                       |                   |                           |                       |
| n=0.5 | 23.1                | 66.4              | 1.15                      | 5.44              | 9.09                      | 39.8                  | 1.16              | 4.18                      | 5.46                  | 27.6                  | 1.13              | 3.86              |
| n=1   | 8.26                 | 79.7              | 1.15                      | 3.91              | 0.99                      | 30.3                  | 1.16              | 2.4                       | 0.33                  | 12.7                  | 1.14              | 2.18              |
| n=2   | 0.8                  | 93.9              | 1.15                      | 3.33              | 0.01                      | 15.9                  | 1.15              | 1.42                      | 0                     | 2.07                  | 1.16              | 1.31              |
| n=3   | 0.07                 | 98.4              | 1.15                      | 3.25              | 0                         | 7.63                  | 1.16              | 1.06                      | 0                     | 0.31                  | 1.15              | 1.02              |
| n=5   | 0                    | 99.9              | 1.01                      | 3.37              | 0                         | 1.54                  | 1.13              | 0.8                       | 0                     | 0.01                  | N/A               | N/A               |

$E_{\text{init}}$: effect (%) at 0.01 $et_{1/2}$.

$T_{1/2}$: duration of effect half-life and $et_{1/2}$ is the elimination half-life.

$1, 2, 3$ means that the dose used, gives MOE of 90%, 50% or 25% respectively when n and EC$_{50}$ =1, in absence of the effect compartment.

N/A: not applicable.
Table I.6. Effect of EC\textsubscript{50} on drug response using a single IV dose with an effect compartment of $k_e$ of 0.2 et\textsubscript{1/2}:

| EC\textsubscript{50} | $E_{\text{init}}$ (%) | 1 MOE (%) | Time at MOE (et\textsubscript{1/2}) | T\textsubscript{1/2} (et\textsubscript{1/2}) | $E_{\text{init}}$ (%) | 2 MOE (%) | Time at MOE (et\textsubscript{1/2}) | T\textsubscript{1/2} (et\textsubscript{1/2}) | $E_{\text{init}}$ (%) | 3 MOE (%) | Time at MOE (et\textsubscript{1/2}) | T\textsubscript{1/2} (et\textsubscript{1/2}) |
|----------------------|------------------------|-----------|-----------------------------|-------------------|------------------------|-----------|-----------------------------|-------------------|------------------------|-----------|-----------------------------|-------------------|
| Dose 1               | Dose 2                 | Dose 3    |
| EC\textsubscript{50}=0.5 | 3.47 | 75.6  | 2.41 | 9.87 | 0.4 | 25.7 | 2.47 | 5.86 | 0.13 | 10.3 | 2.4 | 5.4 |
| EC\textsubscript{50}=1 | 1.77 | 60.8  | 2.44 | 8.02 | 0.2 | 14.7 | 2.47 | 5.46 | 0.07 | 5.44 | 2.36 | 5.29 |
| EC\textsubscript{50}=2 | 0.89 | 43.7  | 2.45 | 6.75 | 0.1 | 7.94 | 2.38 | 5.34 | 0.03 | 2.8 | 2.4 | 5.16 |
| EC\textsubscript{50}=3 | 0.60 | 34.1  | 2.45 | 6.25 | 0.07 | 5.44 | 2.39 | 5.25 | 0.02 | 1.88 | 2.27 | 5.26 |
| EC\textsubscript{50}=5 | 0.36 | 23.7  | 2.44 | 5.81 | 0.04 | 3.34 | 2.43 | 5.14 | 0.01 | 1.14 | 2.31 | 5.17 |

$E_{\text{init}}$: effect (%) at 0.01 et\textsubscript{1/2}.
T\textsubscript{1/2}: duration of effect half-life and et\textsubscript{1/2} is the elimination half-life.
1, 2, 3 means that the dose used, gives MOE of 90%, 50% or 25% respectively when n and EC\textsubscript{50}=1, in absence of the effect compartment.
N/A: not applicable.
Table I.7. Effect of EC$_{50}$ on drug response using a single IV dose with an effect compartment of $k_e$ of 1 et$_{1/2}^{-1}$:

| EC$_{50}$ | $E_{init}$ (%) | $^1$MOE (%) | Time at MOE (et$_{1/2}$) | $T_{1/2}$ (et$_{1/2}$) | $E_{init}$ (%) | $^2$MOE (%) | Time at MOE (et$_{1/2}$) | $T_{1/2}$ (et$_{1/2}$) | $E_{init}$ (%) | $^3$MOE (%) | Time at MOE (et$_{1/2}$) | $T_{1/2}$ (et$_{1/2}$) |
|-----------|----------------|--------------|--------------------------|----------------------|----------------|--------------|--------------------------|----------------------|----------------|--------------|--------------------------|----------------------|
|           | Dose 1         | Dose 2       |                          | Dose 3               |                |              |                          |                      |                |              |                          |                      |
| EC$_{50}$=0.5 | 15.3           | 88.7         | 1.16                     | 4.7                  | 1.96           | 46.6         | 1.15                     | 3.85                 | 0.66           | 22.5         | 1.15                     | 2.29                 |
| EC$_{50}$=1  | 8.26           | 79.7         | 1.15                     | 3.91                 | 0.99           | 30.3         | 1.16                     | 3.56                 | 0.33           | 12.7         | 1.14                     | 2.18                 |
| EC$_{50}$=2  | 4.31           | 66.2         | 1.18                     | 3.22                 | 0.50           | 17.9         | 1.15                     | 3.38                 | 0.17           | 6.77         | 1.13                     | 2.13                 |
| EC$_{50}$=3  | 2.91           | 56.7         | 1.17                     | 2.92                 | 0.33           | 12.7         | 1.16                     | 3.32                 | 0.11           | 4.62         | 1.14                     | 2.09                 |
| EC$_{50}$=5  | 1.77           | 43.9         | 1.15                     | 2.65                 | 0.20           | 8.01         | 1.13                     | 3.27                 | 0.07           | 2.82         | 1.1                      | 2.12                 |

$E_{init}$: effect (%) at 0.01 et$_{1/2}$.

$T_{1/2}$: duration of effect half-life and et$_{1/2}$ is the elimination half-life.

$^1$, $^2$, $^3$ means that the dose used, gives MOE of 90%, 50 % or 25 % respectively when $n$ and EC$_{50}$ =1, in absence of the effect compartment.

N/A: not applicable.
Table I.8. Effect of n on drug response using multiple IV doses:

| n   | ¹MOE (%) | ²MOE (%) | ³MOE (%) |
|-----|---------|---------|---------|
| n=0.5 | 75      | 50      | 36.6    |
| n=1   | 90      | 50      | 25      |
| n=2   | 98.8    | 50      | 10      |
| n=3   | 99.9    | 50      | 3.6     |
| n=5   | 100     | 50      | 0.41    |

MOE: maximum observed effect.
¹, ², ³ means that the multiple doses used, give MOE of 90%, 50 % or 25 % respectively at steady state when n and EC₅₀ =1, in absence of the effect compartment.
Table 1.9. Effect of EC\textsubscript{50} on drug response using multiple IV doses:

| EC\textsubscript{50} | \(^1\)MOE (\%) | \(^2\)MOE (\%) | \(^3\)MOE (\%) |
|----------------------|----------------|----------------|----------------|
| EC\textsubscript{50}=0.5 | 94.8           | 66.7           | 40             |
| EC\textsubscript{50}=1  | 90             | 50             | 25             |
| EC\textsubscript{50}=2  | 81.6           | 33.3           | 14.3           |
| EC\textsubscript{50}=3  | 75             | 25             | 10             |
| EC\textsubscript{50}=5  | 64.3           | 16.7           | 6.25           |

MOE: maximum observed effect.

\(^1\), \(^2\), \(^3\) means that the multiple doses used, give MOE of 90\%, 50\% or 25\% respectively at steady state when n and EC\textsubscript{50} =1, in absence of the effect compartment.
Table 1.10. Effect of $k_{e0}$ on drug response using multiple IV doses:

| $k_{e0}$   | 1 MOE (%) | 2 MOE (%) | 3 MOE (%) |
|-----------|-----------|-----------|-----------|
| $k_{e0}=0.2$ | 81.6      | 33        | 14.1      |
| $k_{e0}=0.4$ | 85        | 38.6      | 17.3      |
| $k_{e0}=0.6$ | 85.7      | 40        | 18.2      |
| $k_{e0}=0.8$ | 85.8      | 40.2      | 18.3      |
| $k_{e0}=1$  | 85.9      | 40.2      | 18.3      |

MOE: maximum observed effect.

1, 2, 3 means that the multiple doses used, give MOE of 90%, 50% or 25% respectively at steady state when $n$ and $EC_{50}=1$, in absence of the effect compartment.
Table 1.11. Effect of n on drug response using multiple IV doses in presence of an effect compartment of $k_{ae}$ of 0.2 et_{1/2}^{-1}:

| n   | $E_{init}$ (%) | $M_{OE}$(%) | $E_{init}$ (%) | $M_{OE}$(%) | $E_{init}$ (%) | $M_{OE}$(%) |
|-----|----------------|-------------|----------------|-------------|----------------|-------------|
| n=0.5 | 8.75          | 67.8        | 3.09           | 41.2        | 1.81           | 28.8        |
| n=1  | 0.91           | 81.6        | 0.1            | 33          | 0.03           | 14.1        |
| n=2  | 0.01           | 95.2        | 0              | 19.5        | 0              | 2.62        |
| n=3  | 0              | 98.9        | 0              | 10.6        | 0              | 0.44        |
| n=5  | 0              | 99.9        | 0              | 2.8         | 0              | 0.01        |

$E_{init}$: effect (%) at 0.01 et_{1/2}.
$M_{OE}$: maximum observed effect at steady state.
1, 2, 3 mean that the multiple doses used, give MOE of 90%, 50% or 25% respectively at steady state when n and EC_{50} =1, in absence of the effect compartment.
Table 1.12. Effect of \( n \) on drug response using multiple IV doses in presence of an effect compartment of \( k_{e0} \) of 1 et_{1/2}^{-1}:

| \( n \) | \( E_{\text{init}} \) (%) | \( ^1\text{MOE} \) (%) | \( E_{\text{init}} \) (%) | \( ^2\text{MOE} \) (%) | \( E_{\text{init}} \) (%) | \( ^3\text{MOE} \) (%) |
|--------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| 0.5    | 17.7                        | 71.1                        | 6.67                        | 45                          | 3.96                        | 32.1                        |
| 1      | 4.4                         | 85.8                        | 0.51                        | 40.2                        | 0.17                        | 18.3                        |
| 2      | 0.21                        | 97.3                        | 0                           | 31.1                        | 0                           | 4.76                        |
| 3      | 0.01                        | 99.6                        | 0                           | 23.2                        | 0                           | 1.11                        |
| 5      | 0                           | 100                         | 0                           | 12                          | 0                           | 0.06                        |

\( E_{\text{init}} \): effect (%) at 0.01 et_{1/2}.

MOE: maximum observed effect at steady state.

\(^{1,2,3}\) means that the multiple doses used, give MOE of 90%, 50% or 25% respectively at steady state when \( n \) and EC_{50} = 1, in absence of the effect compartment.
Table 1.13. Effect of EC$_{50}$ on drug response using multiple IV doses in presence of an effect compartment of k$_{eo}$ of 0.2 et$_{1/2}$:

| EC$_{50}$ | E$_{init}$ (%) | 1MOE (%) | E$_{init}$ (%) | 2MOE (%) | E$_{init}$ (%) | 3MOE (%) |
|---------|----------------|---------|----------------|---------|----------------|---------|
| EC$_{50}$=0.5 | 1.81 | 89.9 | 0.2 | 49.6 | 0.07 | 24.7 |
| EC$_{50}$=1 | 0.91 | 81.6 | 0.1 | 33 | 0.03 | 14.1 |
| EC$_{50}$=2 | 0.46 | 68.9 | 0.05 | 19.7 | 0.02 | 7.58 |
| EC$_{50}$=3 | 0.31 | 59.7 | 0.03 | 14.1 | 0.01 | 5.18 |
| EC$_{50}$=5 | 0.18 | 47 | 0.02 | 9 | 0.01 | 3.17 |

E$_{init}$: effect (%) at 0.01 et$_{1/2}$.
MOE: maximum observed effect at steady state.

1, 2, 3 means that the multiple doses used, give MOE of 90%, 50% or 25% respectively at steady state when n and EC$_{50}$ = 1, in absence of the effect compartment.
Table I.14. Effect of EC₅₀ on drug response using multiple IV doses in presence of an effect compartment of kₑ₀ of 1 eₗ/₂⁻¹:

| EC₅₀  | Eᵢₐₖᵢ (%) | ¹MOE (%) | Eᵢₐₖᵢ (%) | ²MOE (%) | Eᵢₐₖᵢ (%) | ³MOE (%) |
|-------|------------|----------|------------|----------|------------|----------|
| EC₅₀=0.5  | 8.42       | 92.4     | 1.01       | 57.3     | 0.34       | 30.9     |
| EC₅₀=1    | 4.4        | 85.8     | 0.51       | 40.2     | 0.17       | 18.3     |
| EC₅₀=2    | 2.25       | 75.2     | 0.25       | 25.1     | 0.08       | 10.1     |
| EC₅₀=3    | 1.51       | 66.9     | 0.17       | 18.3     | 0.06       | 6.94     |
| EC₅₀=5    | 0.91       | 54.8     | 0.1        | 11.8     | 0.03       | 4.28     |

Eᵢₐₖᵢ: effect (%) at 0.01 eₗ/₂.  
MOE: maximum observed effect at steady state.  
¹, ², ³ means that the multiple doses used, give MOE of 90%, 50% or 25% respectively at steady state when n and EC₅₀ =1, in absence of the effect compartment.
Figure 1.1. The concentration-effect relationship of the Emax model
Figure 1.2. The concentration-effect relationship of the sigmoid Emax model.
Figure 1.3 Schematic representation of a PK model linked to an effect compartment.
I. Inhibition ($K_{in}$)

II. Inhibition ($K_{out}$)

III. Stimulation ($K_{in}$)

IV. Stimulation ($K_{out}$)

Figure I.4. Four basic indirect response models (28)
Figure 1.5. The fall in plasma concentration (Cp) and Response (E) with time in absence and presence of effect compartment of $ke_0$ of 0.2 and 1 using single IV dose.

The single dose used gave MOE of 90% at n and EC50 of 1 in absence of the effect compartment.
Figure 1.6. The concentration-effect relationship of the sigmoid Emax model with different n.
Figure I.7. Effect of sigmoidicity constant (n) on drug response using single IV Dose*.

*: this dose gave MOE of 90% at n and EC50 of 1 in absence of the effect compartment.
Figure I.8. The concentration-effect relationship of the sigmoid Emax model with different EC50 (n=2)
Figure 1.9. Effect of EC50 on the Drug Response Using Single IV Dose.

*: this dose gave MOE of 90% at n and EC50 of 1 in absence of the effect compartment.
Figure 1.10. Effect of the equilibrium rate constant (ke0) on drug response using single IV dose:

*: this dose gave MOE of 90% at nand EC50 of 1 in absence of the effect compartment.
Figure I.11. The fall in plasma concentration (Cp) and Response (E) with time in absence and presence of effect compartment of ke0 of 0.2 and 1 using multiple IV doses.

The multiple doses used gave MOE of 90% at steady state at n and EC50 of 1 in absence of the effect compartment.
MANUSCRIPT II

THE EFFECT OF DIFFERENT SOURCES OF VARIABILITY ON
THEOPHYLLINE RESPONSE

II.1. ABSTRACT:

Theophylline is widely used in treatment of bronchial asthma. It has a narrow therapeutic range and displays wide variability in its pharmacokinetic (PK) and pharmacodynamic (PD) parameters. As a result, the PK and PD of theophylline have been extensively studied and published in the literature.

In this study, simulated data were used to investigate the effect of variability arising from the dose and the intra-individual variability in PK parameters (rate of absorption and clearance) and several PD parameters on theophylline plasma concentration and response. A one compartment PK model with zero-input linked to linear and sigmoid E\textsubscript{max} models was used to simulate data. For each set of model parameters, the response was measured every 12 hours over a 10-day period. Hundred replications were performed giving a total of 2000 responses. The influence of PK/PD variability on theophylline response was studied at low, moderate and high levels of intra-individual variability. The effect of variability in dose, PK and PD parameters was studied separately and in combination and their impacts on theophylline response were assessed by estimating the % coefficient of variation in the response using Excel 2000.
The drug response was found to be more sensitive to variability in PD parameters than to variability in PK parameters or dose. The drug response was more sensitive to the changes in the dose and PK parameters when the sigmoid $E_{\text{max}}$ model was used compared to when the linear model was used. In conclusion, variability in PD parameters is clinically important and must be taken into account in order to use the drug effectively and safely.
II.2 INTRODUCTION:

Pharmacokinetics (PK) is the study of the relationship between the dose of a drug and the manner in which its plasma concentrations change over time. Models for PK are used to provide a mathematical representation of this relationship and relate the independent variables of time and dose to the dependent variable, plasma concentration. In a one compartment model the value of plasma concentration is controlled by three PK parameters, clearance (CL), volume of distribution and bioavailability factor. Pharmacodynamics (PD) is the study of the biological effects resulting from the interaction between drugs and biological systems. Models for PD are used to provide a simplified description of the drug action and relate the independent variable of drug concentration at site of action to the dependent variable of drug response.

A thorough understanding of PK and PD is the scientific foundation of clinical therapeutics (1). Variability in the PK and PD parameters may be small, moderate or large depending on the drug and the pathological state of the patient. Variability in PK and PD parameters will lead to a variation in the drug response. Drugs used for chronic diseases with a proven PK-PD relationship, a small therapeutic range, large PK/PD variability and severe adverse effects are likely to be good candidates to study the impact of different sources of variability on drug response. An example of this category is theophylline, which has been widely used in the treatment of bronchial asthma.
Theophylline has a wide variability in its CL, which controls the steady state plasma concentration and is critical for determining the maintenance dose. Theophylline's CL is affected by many factors such as diet, disease state and smoking. The resulting variation in CL may lead to substantial variation in plasma concentration and drug response. Theophylline is mainly eliminated by hepatic metabolism, mediated by cytochrome P450 liver enzymes (CYP1A2 and 3A4). Diet influences the metabolism of theophylline for example; high-protein, low carbohydrate diets generally metabolize theophylline more rapidly, presumably because the diet induces hepatic enzymes (3). Charcoal broiling induces CYP1A2, so it increases theophylline's CL (4). Cigarette smoking increases theophylline's CL by 1.5 to 2 times that of non-smokers (5,6). It was found that the effect of smoking appear to last several months after the cigarettes have been discontinued (7). Also some diseases affect theophylline's CL. Congestive heart failure reduces theophylline's CL to about 40% of normal (8). Hepatic cirrhosis can significantly reduce theophylline's CL. Also severe pulmonary disease significantly reduces theophylline's CL (6). It has been found that CL displays 20% (9), 25% (10), 30% (10) coefficient of variation (% CV) in patients with respiratory diseases. There is not much variability in theophylline's volume of distribution and it is usually kept at a constant value of 0.5 L/Kg (6).

The rate of drug absorption differs among various slow-release formulations (11,12) and occasionally between lots (11) of the same brand. Differences in rates of absorption may be clinically important (13). Also, dose to dose variation in plasma concentration have been observed for some theophylline products, probably as a result of intra-individual
variability in gastrointestinal function. Food may decrease the rate of absorption of theophylline from many sustained release products. This is probably a result of delayed gastric emptying rate where the drug is held in the stomach for longer time before entering the alkaline medium of small intestine where dissolution is more rapid. Food also may cause dumping of large amounts of theophylline from some sustained release products. This may be due to dissolution of the sustained release film coat rapidly at the pH of small intestine after a meal (pH 7.4).

Theophylline is an example of drug that has a narrow therapeutic range. Traditionally a range of 10-20 mg/L has been used. However, more recently concentrations at the lower end of the range have been advocated since there is significant and serious adverse effects are more common at higher theophylline concentrations and recent studies indicate that 10 mg/L is as effective as 20 mg/L. The effect of theophylline on bronchodilation can be measured in terms of forced vital capacity (FVC) and peak expiratory flow rate (PEFR). However, the FVC is usually used because it assesses ventilatory response as it closely reflects the patency of small airways and it represents the spirometric index, which is the most reproducible measure. A linear model has been used to describe the effect of theophylline on FVC. A sigmoid Emax model has been used to describe theophylline's effect on PEFR.

The linear model is derived from the Emax model, since when concentrations are small relative to the potency (EC50), the Emax model will collapse into a linear model in which the effect [E (L)] is proportional to steady state plasma concentration (Cpss). The linear
model, will predict no effect when concentrations are zero but its major limitation is that it cannot predict a maximum response. This model can be modified to evaluate data with baseline ($E_0$) as follows:

$$E (L) = (m) (C_{p_{50}}) + E_0$$  \hspace{1cm} \text{II.1}$$

Where $m$ is the slope parameter, which will approach the value of the ratio of efficacy to potency ($E_{\text{max}}/EC_{50}$). The baseline effect is the response at zero drug concentration and it is measured in absence of the drug or during placebo administration. The concentration-effect relationship using this model is linear. The advantage of linear model is that it can be used for some relatively toxic drugs when the $E_{\text{max}}$ cannot be approached \textsuperscript{(21,23)}. If the $E_{\text{max}}$ can be achieved at concentration that do not cause toxicity, the $E_{\text{max}}$ or the sigmoid $E_{\text{max}}$ model would be considered superior models. Examples of the use of the linear model in the literature are the study of PD of theophylline on bronchodilation in term of forced vital capacity (FVC) \textsuperscript{(21)} and the study of the PD of clonidine on pain threshold, blood pressure and salivary flow\textsuperscript{(23)}.

The sigmoid $E_{\text{max}}$ model is a modification of the $E_{\text{max}}$ model that accommodates the probability that more than one drug molecule, binds to each receptor by using the term sigmoidicity. According to sigmoid $E_{\text{max}}$ model, the effect is related to drug concentration ($C$) in the following manner:

$$E = \frac{E_{\text{max}} C^7}{EC_{50}^7 + C^7}$$  \hspace{1cm} \text{II.2}$$

71
Where $E_{max}$ is the efficacy, $EC_{50}$ is the potency, which reflects the sensitivity of organ or tissue to the drug, and $\gamma$ is the sigmoidicity constant, which is the number of drug molecules bound to each receptor. Using this model, the concentration-effect relationship is sigmoidal in shape. Although this model is based on receptor theory it cannot be assumed that it is the basis of drug action. Sigmoidicity has been found to be a non-integer in some cases even though the receptor theory would predict it to be always an integer $^{9,22,24-26}$. Also, this model can incorporate a baseline response ($E_0$). Examples of the use of the sigmoid $E_{max}$ model in the literature include the study of PD of theophylline side effects (eosinopenia and hypokalemia) $^{9}$, the study of PD of theophylline bronchodilation in asthmatic patients $^{22}$, the study of the PD of tocainide on suppression of ventricular ectopic depolarizations in patients $^{24}$, the study of the influence of age and gender on the PD of remifentanil $^{25}$, the study of the preoperative PD of acetaminophen analgesia in children $^{26}$ and the study of the PD of intravenous diltiazem in patients with atrial fibrillation or atrial flutter $^{27}$.

It has been found that individuals can vary with respect to the baseline, maximum response, potency and the slope of the concentration-effect relationship. These are the main determinants of PD variability $^{28}$. In the past, it was assumed that PK variability is primarily responsible for quantitative differences in drug response $^{29}$. This is probably because PD studies in human were rare until the last couple of decades $^{30}$. Recently, several studies have demonstrated that PD variability in humans is large, reproducible and usually more pronounced than PK variability $^{30-34}$. Because of the importance of PD,
the Food and Drug Administration (FDA) has recently encouraged the modeling of clinical PD data as a component of new drug applications.

There is a large inter-individual variability in theophylline's PD parameters. The parameters associated with the linear model, the baseline and the slope parameter have been found to display a 50% and 30% CV, respectively in a population of 56 patients with chronic bronchitis \(^{(21)}\). The % CV for the parameters associated with theophylline's sigmoid \(E_{\text{max}}\) model have been found to be 78%, 22%, 38% for potency, maximum attainable response (MAE) and the baseline, respectively in a population of 174 asthmatic patients \(^{(22)}\). Looking at the magnitude of theophylline PD variability, it is clear that the inter-individual PD variability \(^{(21,22)}\) is larger than that of PK \(^{(1,10)}\).

In this work, theophylline was used as a model drug to study the impact of different sources of variability, namely dose in term of content uniformity, PK parameters and PD parameters, on its response. The relative impact of different sources of variability on theophylline response using published models for the linear \(^{(21)}\) and the sigmoid \(E_{\text{max}}\) \(^{(22)}\) models was compared.

### II.3 METHODS:

An integrated PK-PD model of theophylline was constructed in STELLA (High Performance Systems, Inc, Hanover, NH) \(^{(35)}\).
11.3.1. Structural Model:

11.3.1.1. Pharmacokinetic Model:

Initially, a one-compartment PK model, with first order gastrointestinal absorption \( (k_a = 0.09 \text{ hr}^{-1}) \) \(^{36}\) was used. Subsequently, a zero order absorption in which the dose was assumed to be absorbed at a constant rate over 12 hours was used. For the study of rate of drug absorption, a zero order input with an infusion rate was used in which the infusion time was 7.7 hours.

The model was based on an average 70 Kg individual. The volume of distribution was 35 L based on 0.5 L/Kg \(^6\), CL was 2.8 L/hr, based on 0.04 L/kg/hr \(^9,10\). The drug was assumed to undergo first order elimination; thus its elimination rate constant \( (k_e) = 0.08 \text{ hr}^{-1} \) and its half-life was 8.7 hours. Simulation was based on a 400 mg oral dose of theophylline administered every 12 hours. This dosage regimen gave steady state plasma concentration of 11.9 mg/L.

11.3.1.2. Pharmacodynamic Model:

A. The linear model:

The effect of theophylline on FVC \([E \text{ (L)}]\), was described as a linear function of the steady state plasma concentration \( (C_{pss}) \) as in Equation II.1 where the slope, m,
represents the sensitivity of an individual to theophylline and the intercept, $E_0$, is the untreated (baseline) FVC. The population values for the PD parameters of this model were $0.04 \text{ L} \cdot \mu g^{-1} \text{ ml}$ for $m$ and $1.58 \text{ L}$ for $E_0$.\(^{(21)}\)

B. The sigmoid $E_{\text{max}}$ model:

The effect of theophylline on PEFR $[E(S)]$ was described using the sigmoid $E_{\text{max}}$ model\(^{(22)}\) as follows:

$$E(S) = \frac{(\text{MAE} - E_0) \cdot C^\gamma}{EC_{50}^\gamma + C^\gamma}$$

The $E_{\text{max}}$ in this model is the difference between MAE and $E_0$. The population mean values for the $EC_{50}$, MAE, $E_0$ and $\gamma$ were 11 mg/L, 477 L/min, 133 L/min and 2.13, respectively.

II.3.2. Variability Model:

Using the first order absorption model, there were fluctuations in the plasma concentration and drug response while the zero input model did not produce fluctuations in plasma concentration and response within a dosing interval. Consequently, the zero-input model was used to show more clearly the impacts of different sources of variability on drug concentration and response. The effect of variability in the dose, intra-individual PK variability and intra-individual PD variability were studied at steady state condition.
Thus, all drug levels and responses were constant. The different sources of variability were studied separately and in combination.

The proportional error (constant coefficient of variation) model was used to describe the variability in the dose, PK and PD parameters as follows:

\[ P_j = P_m * (1 + \varepsilon_{pj}) \]

Where \( P_j \) is the dose or PK or PD parameter at time \( j \), \( P_m \) is the mean dose or population mean value of the PK or PD parameter and \( \varepsilon_{pj} \) is a normally distributed random variable with an average value of 0. The standard deviation of \( \varepsilon_{pj} \) represents the CV for variability in the dose, PK or PD parameter.

For the dose, the % CV was set at 3, 6 or 10%. For intra-individual PK variability, % CV in CL was set at 5, 10, 15, 20 \(^{(9)}\), 25 \(^{(10)}\), 30 \(^{(10)}\) or 45% and % CV in the rate of absorption was set at 5, 10, 15, 30 or 45%. For the intra-individual PD variability, % CV for the linear model parameters was set at 5, 10, 15, 30 \(^{(21)}\) or 45% for \( m \) and 5, 10, 15, 50, 45 or 50% \(^{(21)}\) for \( E_0 \). Using the sigmoid \( E_{max} \) model, the % CV for the inter-individual PD parameters was set at 5, 10, 15, 30, 45 or 75% \(^{(22)}\) for \( EC_{50} \), 5, 10, 15, 20 \(^{(22)}\), 30 or 45% for MAE, 5, 10, 15, 30, 40 \(^{(22)}\) or 45% for \( E_0 \) and 5, 10, 15, 30 or 45% for \( \gamma \).

The response was measured every 12 hours over a 10-day period. Hundred replications were performed giving a total of 2000 responses. The plasma concentration and drug
response just before the administration of a dose were tabulated and the coefficient of variation of the 2000 values was determined.

II.4. RESULTS:

A One compartment PK model with first order absorption, in absence of the variability model was used to study theophylline's steady state plasma concentrations at different doses (250, 300, 350, 400, 450, 500 mg) every 12 hours. A dose of 400 mg of sustained release theophylline every 12 hours was selected for the study since in the model used, it gave a steady state plasma concentration of 11.9 mg/L, which is near the lower end of the therapeutic range (10-20 mg/L) and is a common therapeutic target. Using the zero input model, a dosage regimen of 400 mg of theophylline every 12 hours gave the same plasma concentration and drug response as that of the first order absorption model.

The variability in dose, PK and PD parameters was translated to theophylline response in terms of E (L) for FVC and E (S) for PEFR with the linear and sigmoid E_{max} models, respectively.

II.4.1. Variability in the Dose:

Variability in the dose resulted in essentially equivalent amounts of variability in plasma concentration and E (S), but E (L) was less affected. For example, 6% variability in the dose gave 5.78% and 5.48% CV in plasma concentration and E (S), respectively, while %
CV in E (L) was 1.29. The effect of variability in dose on plasma concentration and drug response is shown in Table II.1.

II.4.2. Variability in PK parameters:

Variability in CL resulted in essentially equivalent amounts of variability in plasma concentration and E (S), but E (L) was less affected. For example, 45% variability in the CL gave 46% and 40.2% CV in plasma concentration and E (S), respectively, while % CV in E (L) was 10.65. The effect of variability in CL on plasma concentration and drug response is shown in Table II.2 and Figures II.1, II.2 and II.3 for plasma concentration and drug response using linear model [E (L)] and sigmoid E\text{max} model [E (S)], respectively. Study of the values reported in literature for the variability in theophylline's CL showed that 20% \textsuperscript{[9]}, 25% \textsuperscript{[10]} or 30% \textsuperscript{[10]} CV in CL resulted in 18.37%, 24.11%, 28.12% respectively, in plasma concentration, 4.25%, 5.56% or 6.49% respectively, in drug response using linear model and 18.16%, 24.47% or 28.62% CV respectively, in drug response using sigmoid E\text{max} model.

Variability in the rate of drug absorption (R\text{abs}) resulted in slight changes in plasma concentration and E (S) and negligible change in E (L). However, high level of variability (45%) in the rate of drug absorption resulted in high variation in plasma concentration (35.6%). The effect of variability in rate of drug absorption on plasma concentration and drug response is shown in Table II.2 and Figures II.1, II.2 and II.3 for plasma
concentration and drug response using linear model [E (L)] and sigmoid E_{max} model [E (S)], respectively.

II.4.3. Variability in PD parameters:

A. Variability in the PD parameters of the linear model:

Variability in drug response increased dramatically by increasing % CV in the intercept. On the other hand, increasing the % CV in the slope (m) resulted in a slight increase in % CV in the drug response. Of course plasma concentration was not affected at all by the changes in any of the PD parameters. The effect of variability in PD parameters on drug response using the linear model is shown in Table II.3 and Figure II.2. Study of the values reported in literature for the variability in theophylline PD parameters of the linear model \(^{(21)}\) showed that 50% CV in E_0 or 30% in m resulted in 37.6% or 6.89% CV in drug response, respectively.

B. Variability in the PD parameters of the sigmoid E_{max} model:

Changes in the EC_{50} resulted in almost equivalent amounts of variability in the drug response. Variations in the maximum attainable effect (MAE) produced a large amount of variability in the drug response. For example 30% CV in MAE produced 41.6% CV in
drug response. Changes in the baseline \((E_0)\) resulted in slight changes in the \% CV in drug response. Changes in the sigmoidicity constant resulted in a very small change in drug response. The effect of variability in PD parameters on drug response using sigmoid \(E_{\text{max}}\) model is shown in Table II.4 and Figure II.3. Study of the values reported in literature for the variability in theophylline PD parameters of the sigmoid \(E_{\text{max}}\) model (22) showed that 20\% CV in MAE, 40\% CV in \(E_0\) or 75\% in \(E_{50}\) resulted in 27.17\%, 15.59\% or 49.78\% CV in drug response, respectively.

II.4.4. Combined PK-PD Variability:

After the effect of variability of each parameter was studied separately, combinations of PK and PD variability were studied. The effect of combined PK/PD variability on plasma concentration and drug response is shown in Table II.5 and Figures II.1, II.4 and II.5 for plasma concentration and drug response using linear model \([E (L)]\) and sigmoid \(E_{\text{max}}\) model \([E (S)]\), respectively.

Variability in PK parameters resulted in almost same \% CV in plasma concentration, which was not affected at all by any changes in PD parameters. High level of intra-individual variability (45\% CV) in the rate of drug absorption could not be studied with large variability in CL/PD because the simulation was unsuccessfully terminated possibly due to division by zero or a value that has become too large to represent (35). Using the sigmoid \(E_{\text{max}}\) model, drug response was much more sensitive to the changes in the PK.
and PD parameters than that of the linear model. The drug response from the two models was much more affected by the changes in PD parameters than that of PK parameters.

II.4.5. Combination of all sources of variability (Dose, PK & PD):

Finally, a combination of all sources of variability (dose, PK and PD) was studied. The effect of combined variability in dose PK and PD parameters on plasma concentration and drug response is shown in Table II.6.

The addition of variability in the dose to the combined PK/PD variability had very small and negligible effects on the variability in plasma concentration and drug response, respectively.

II.5. DISCUSSION:

Computer simulations have been successfully applied in support of clinical drug development for predicting clinical outcomes of planned trials (37). The use of PK/PD models has been found to be useful in analyzing and integrating data from clinical trials (38). In this study, computer simulations were used to investigate the effect of different sources of variability, dose, PK and PD parameters, on drug response.

A dose regimen of 400 mg of sustained release theophylline every 12 hours was chosen for this study because it gave a steady state plasma concentration of 11.9 mg/L, which is
at the lower end of the therapeutic range. It is clinically important to keep theophylline concentration near the lower end of the therapeutic range to avoid its side effects. These side effects may occur at concentration of 13 mg/L \(^{39}\). In addition, this dose gave comparable effects to those in literature for the FVC \(^{(21)}\) and PEFR \(^{(22)}\).

The drug input used was designed to mimic a sustained release theophylline preparation where the drug was slowly released and absorbed. The half-life of theophylline in this study was 8.7 hours, and the dosing interval was 12 hours i.e. the half-life was shorter than the dosing interval. Thus, the drug experienced only modest accumulation and under these circumstances the effect of variability in dose would be more pronounced. The United States pharmacopoeia (USP) \(^{(40)}\) allows 6% variability in the dose. Based on this fact, the values for the variability in the dose were chosen for this study where a lower value than 6% (3%), a higher value than 6% (10%) and 6%CV were used. Variability in the dose may result from mixing or weight variation or any other process in the tablet formulation. Variability in the dose resulted in almost same amount of variability in plasma concentration and drug response, estimated from the sigmoid \(E_{\text{max}}\) model, but only very slight change in %CV in drug response estimated from the linear model. Thus, the linear model appears less sensitive to changes in plasma concentration than the sigmoid \(E_{\text{max}}\) model. For example, 10% CV in dose resulted in only 2.2% CV in drug response, using the linear model but 9.5% CV in drug response using the sigmoid \(E_{\text{max}}\) model.
Whiting et al. \textsuperscript{(21)} found that variability in both theophylline PK and PD must be taken into account if the drug is to be used to its best advantage. When looking at the PK parameters, the volume of distribution was kept constant because it had no effect on steady state plasma concentration in this model and only a small degree of variability in theophylline's volume of distribution is reported in the literature \textsuperscript{(6)}. As mentioned earlier in section II.2, theophylline's CL is influenced by many factors. Any drug, disease or other factor that can affect the liver enzymes that are responsible for theophylline metabolism (Cytochrome P450 1A2 and 3A4) will affect the CL of theophylline. In literature, the variability in theophylline CL is in the range of 20-30\% \textsuperscript{(9,10)} for asthmatic patients. Based on that, different values for the variability in CL, from 5\% to 45\%, were studied. Variability in CL, resulted in almost same amount of variability in plasma concentration and drug response, using sigmoid E\textsubscript{max} model, but drug response from the linear model was only very slightly affected. For example, 5\% and 45\% CV in CL gave only 1.1\% and 10.7\% CV, respectively in drug response using the linear model.

The rate of drug absorption from sustained release theophylline product is clinically important \textsuperscript{(13)} since it differs among various theophylline products \textsuperscript{(11,12)} and among the lots \textsuperscript{(11)} of the same brand. In addition, the rate of theophylline release from many sustained release preparation is dramatically affected by food, which may cause dose dumping \textsuperscript{(18,19)} and results in theophylline toxicity. Also, for other preparations food may decrease the rate of theophylline absorption \textsuperscript{(15,16)} by holding the drug for longer time in the stomach before going to the intestine where it rapidly dissolves at the alkaline pH of the intestinal fluid. In this study, small and moderate intra-individual variability in the
rate of drug absorption resulted in slight changes in plasma concentration and drug response. However, high level of variability (45% CV) in the rate of drug absorption resulted in high variation in the plasma concentrations (36% CV) but the drug response estimated from sigmoid $E_{max}$ model was less affected (16% CV). The drug response estimated from the linear model was very slightly affected by the changes in the rate of drug absorption.

The intra-individual variability in PD parameters were chosen based on the values reported in the literature for these parameters, keeping in mind that intra-individual variability is smaller than inter-individual variability. Thus the value of 45% CV was considered a high level of variability for this study. Low levels of intra-individual variability were also studied such as 5% and 10%. In other words, low, moderate and high levels of intra-individual PD variability were studied to show their impacts on the drug response.

Variability in PD parameters of the linear model, namely the baseline FVC ($E_0$) and the sensitivity of individual to theophylline (slope) are very important factors to be taken into account in studying drug response. Variability in $E_0$ resulted in a high variability in drug response. For example, 5% and 50% CV in $E_0$ gave 4% and 37.6% CV, respectively in drug response. It was found that the drug response estimated from the linear model was much more sensitive to the changes in the baseline than any other parameter. Variability in the slope ($m$) resulted in a less variability in drug response than that of $E_0$. For example, 5% and 45% CV in $m$ gave 1.1% and 10.2% CV respectively in drug response.
Variability in PD parameters of the sigmoid $E_{\text{max}}$ model, namely maximum attainable effect (MAE), potency ($EC_{50}$), baseline ($E_0$), sigmoidicity constant ($\gamma$) were found to be important determinants of drug response. The drug response estimated from the sigmoid $E_{\text{max}}$ model was most sensitive to the variability in MAE, for example 45% CV in MAE resulted in 63.03% CV in drug response. Variability in $EC_{50}$ also affected the drug response significantly, but to less extent than that of the MAE, for example 45% CV in $EC_{50}$ resulted in 36.63% CV in drug response. Variability in the baseline affected the drug response slightly, for example 45% CV in $E_0$ resulted in 16.85% CV in drug response. This is in contrast to the effect of baseline on the drug response using linear model where 45% CV in the baseline resulted in 34.27% CV in drug response. Variability in $\gamma$ had a negligible effect on drug response, for example 45% CV in $\gamma$ resulted in 3.47% CV in drug response. Of course, none of the PD parameters in sigmoid $E_{\text{max}}$ model and linear model had an effect on plasma concentration. By conducting analysis of variance test\(^{(41)}\) on the PK/PD parameters that affected drug response, it was found that there was a significant difference between these parameters namely $CL$, rate of drug absorption, $E_0$ and $m$ for the linear model and $CL$, rate of drug absorption, $EC_{50}$, $E_0$, MAE and $\gamma$ for the sigmoid $E_{\text{max}}$ model at level of significance of 0.05.

Variability in PD parameters may result from many factors. These factors include receptor density and affinity, post-receptor transduction processes, the kinetic characteristics of transporters involved in drug transfer between fluids of distribution and the biophase\(^{(30)}\) and variation in the baseline response\(^{(21,22)}\).
Combined variability in CL and rate of drug absorption resulted in slight increase in %CV in plasma concentration achieved from variability in CL alone. The drug response was much more sensitive to the changes in PD parameters than that of PK parameters. For example 30% CV in all PD parameters resulted in 23.8 and 53.7% CV in drug response from linear and sigmoid E\textsubscript{max} models, respectively while same amount of variability in PK parameters resulted in 7.74 and 27.2% CV in drug response from linear and sigmoid E\textsubscript{max} models, respectively. Addition of PK variability to PD variability did not cause much difference in % CV in drug response resulted from PD variability alone. By looking at the combined PK/PD variability, PD variability was found to be the main contributing factor to the changes in the drug response.

The addition of tablet-to-tablet content variability to the combined PK/PD variability resulted in negligible variations in plasma concentration and drug response obtained from PK/PD variability alone. For example, 30% CV in PK/PD resulted in 30.8% CV in plasma concentration and 24.7 and 56.8% CV in drug response with linear and sigmoid E\textsubscript{max} model, respectively while addition of 6% variability in dose to this PK/PD variability resulted in 31.6% CV in plasma concentration and 25.4 and 57.8% CV in drug response with linear and sigmoid E\textsubscript{max} model, respectively.

The drug response estimated using the sigmoid E\textsubscript{max} model was much more sensitive to the different sources of variability than that of the linear model at all levels of variability studied. For example, at low (3% CV in dose and 10% CV in PK/PD) and high (10% CV
in dose and 45% CV in PK/PD) levels of variability in dose, PK and PD parameters, %
CV in drug response was 8.26% & 37.32% for the linear model and 19% & 85.4% for the
sigmoid E_{max} model, respectively.

The linear model was used to study theophylline effect on bronchodilation in terms of
forced vital capacity. This model was very useful in studying the impact of different
sources of variability on theophylline response. However, it has some limitations such as
it cannot define the maximum effect. In practice, it may not be possible to achieve
concentrations that produce effects approaching the maximum; and therefore the
maximum effect cannot be known \(^{(42)}\). Using the linear model, the influence of plasma
concentration on drug response was much reduced, for example plasma concentrations of
10 and 20 mg/L resulted in FVC of 1.98 and 2.38 L, respectively. In other words, 200%
change in plasma concentration resulted in 120% change in drug response, i.e. plasma
concentration slightly affected the drug response. Consequently the impact of PK
variability was less pronounced on the drug response. This was not the case with the
sigmoid E_{max} model, which was used to study theophylline effect on bronchodilation in
term of peak expiratory flow rate. Using plasma concentrations of 10 and 20 mg/L
resulted in drug response of 154.6 to 268.8 L/min, i.e. 200% change in plasma
concentration resulted in 174% change in drug response. Consequently, the drug response
estimated from the sigmoid E_{max} model was much more sensitive to the variation in
plasma concentration. Thus, drug response estimated from the sigmoid E_{max} model was
more affected by the variability in the dose and PK parameters, than that of the linear
model.
II.6. CONCLUSION:

Simulation study can reveal the effect of different sources of variability on the plasma concentration and drug response. This is very important to be considered in designing a PK/PD study.

From this study, the following conclusions can be drawn:

1- The impact of the variability in dose and PK parameters on the drug response was less when the linear model rather than the sigmoid $E_{\text{max}}$ model was used.

2- Drug response was more sensitive to the PD variability rather than the PK variability.

3- In the linear model, drug response was most sensitive to variability in baseline FVC.

4- In the sigmoid $E_{\text{max}}$ model, drug response was most sensitive to variability in the maximum attainable effect.

5- Variability in the tablet content resulted in a negligible variability in the response when added to the combined PK/PD variability.
6- Drug response estimated from the sigmoid $E_{\text{max}}$ model was much more sensitive to different sources of variability, dose, PK and PD parameters, than that of the linear model.

In summary, variability in PD of a drug is clinically important and must be taken into account in order to use the drug effectively and safely.
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Table II.1. Variability (% CV) in dose and its influence on plasma concentration (Cp) and drug response using linear [E (L)] and sigmoid E\textsubscript{max} [E (S)] models:

| % CV in Dose | % CV in Cp | % CV in E (L) | % CV in E (S) |
|--------------|------------|---------------|---------------|
| 3            | 2.76       | 0.65          | 2.76          |
| 6            | 5.78       | 1.29          | 5.48          |
| 10           | 9.28       | 2.22          | 9.25          |

The response was measured every 12 hours over a 10-day period. Hundred replications were performed giving a total of 2000 responses.
Table II.2. Variability (% CV) in PK parameters (clearance (CL) and rate of drug absorption (R_{abs})) and its influence on plasma concentration (Cp) and drug response using linear [E (L)] and sigmoid E_{max} [E (S)] models:

| % CV in PK | % CV in Cp resulted from | % CV in E (L) resulted from | % CV in E (S) resulted from |
|------------|--------------------------|----------------------------|-----------------------------|
|            | Change in CL | Change in RA | Change in CL | Change in CL | Change in R_{abs} | Change in CL | Change in RA |
| 5          | 4.74         | 1.05         | 1.09         | 0.29         | 4.59             | 0.9          |
| 10         | 9.35         | 1.45         | 2.23         | 0.39         | 9.23             | 1.22         |
| 15         | 13.92        | 2.09         | 3.21         | 0.53         | 14.19            | 1.74         |
| 30         | 28.12        | 5.66         | 6.49         | 1.48         | 28.62            | 4.16         |
| 45         | 45.99        | 35.56        | 10.65        | 3.67         | 40.19            | 16.04        |

The response was measured every 12 hours over a 10-day period. Hundred replications were performed giving a total of 2000 responses.
Table II.3. Variability (% CV) in PD parameters of the linear model and its influence on drug response:

| % CV in PD parameter | % CV in E (L) resulted from change in $E_0$ | % CV in E (L) resulted from change in $m$ |
|----------------------|-------------------------------------------|-------------------------------------------|
| 5                    | 3.96                                      | 1.15                                      |
| 10                   | 7.58                                      | 2.32                                      |
| 15                   | 11.67                                     | 3.45                                      |
| 30                   | 22.90                                     | 6.89                                      |
| 45                   | 34.27                                     | 10.24                                     |

The response was measured every 12 hours over a 10-day period. Hundred replications were performed giving a total of 2000 responses.
Table II.4. Variability (% CV) in the PD parameters of the sigmoid $E_{\text{max}}$ model and its influence on the drug response:

| % CV in PD parameter | % CV in E (S) resulted from change in $EC_{50}$ | % CV in E (S) resulted from change in $E_0$ | % CV in E (S) resulted from change in MAE | % CV in E (S) resulted from change in $\gamma$ |
|----------------------|-----------------------------------------------|--------------------------------------------|------------------------------------------|------------------------------------------|
| 5                    | 4.93                                          | 2.00                                       | 6.99                                     | 0.38                                     |
| 10                   | 9.79                                          | 3.87                                       | 13.8                                     | 0.77                                     |
| 15                   | 14.55                                         | 5.87                                       | 21.01                                    | 1.19                                     |
| 30                   | 27.42                                         | 11.68                                      | 41.57                                    | 2.31                                     |
| 45                   | 36.63                                         | 16.85                                      | 63.03                                    | 3.47                                     |

The response was measured every 12 hours over a 10-day period. Hundred replications were performed giving a total of 2000 responses.
Table II.5. Variability (% CV) in PK and PD parameters and their influences on plasma concentration (Cp) and drug response using linear [E (L)] and sigmoid E_{max} [E (S)] models:

| % CV        | % CV in Cp | % CV in E(L) | % CV in E(S) |
|-------------|------------|--------------|--------------|
| 10% in PK   | 9.37       | 2.39         | 8.13         |
| 10% in PD   | N/A        | 8.04         | 17.54        |
| 10% in PK & PD | 9.37      | 8.21         | 18.75        |
| 30% in PK   | 30.28      | 7.74         | 27.21        |
| 30% in PD   | N/A        | 23.76        | 53.73        |
| 30% in PK & PD | 30.84    | 24.67        | 56.79        |
| 45% in PD   | N/A        | 34.57        | 77.76        |
| 45% in PK (CL) & PD | 45.99 | 35.93        | 82.19        |

N/A: not applicable.

45% CV in PK/PD was studied using 45% CV in CL only (with no variability in rate of drug absorption) together with 45% CV in all PD parameters.
The response was measured every 12 hours over a 10-day period. Hundred replications were performed giving a total of 2000 responses.
Table II.6. Variability (% CV) in dose, PK and PD parameters and their influences on plasma concentration (Cp) and drug response using linear \([E (L)]\) and sigmoid \(E_{\text{max}} [E (S)]\) models:

| % CV in dose, % CV in PK & PD | % CV in Cp | % CV in E (L) | % CV in E (S) |
|-----------------------------|-----------|---------------|---------------|
| 3%                          | 9.98      | 8.26          | 19.06         |
| 6%                          | 31.63     | 25.4          | 57.77         |
| 10%                         | 47.00     | 37.32         | 85.39         |

45% CV in PK/PD was studied using 45% CV in CL only (with no variability in rate of drug absorption) together with 45% CV in all PD parameters. The response was measured every 12 hours over a 10-day period. Hundred replications were performed giving a total of 2000 responses.
Figure II.1. Effect of variability in PK parameters on plasma concentration (Cp).

Sources of Variability (%CV)

%CV in Cp

Rate of absorption

PK (combined)

CL
Figure II.2. Effect of variability in PK and PD parameters on drug response using linear model (separate).
Figure II.3. Effect of variability in PK and PD parameters on drug response using sigmoid Emax model (separate).
Figure II.4. Effect of variability in PK and PD parameters on drug response using linear model (combined).
Figure II.5. Effect of variability in PK and PD parameters on drug response using sigmoid Emax model (combined).
III.1. ABSTRACT

Simulation studies are useful for providing convincing objective evidence of the merits of a proposed study design and analysis. In this study, data were simulated and used to investigate the optimum sampling design for a pharmacodynamic (PD) modeling study. The various designs were evaluated by consideration of the bias and precision of the PD parameters and their associated variability parameters.

Response data were simulated from concentration input data for an inhibitory sigmoid $E_{\text{max}}$ model using NONMEM (Non-linear Mixed Effect Modeling) from a population of 100 individuals. Subsequently, these data were used to estimate the PD and variability parameters using the first order conditional method (FOCE) in NONMEM. The estimation step was based on the population of 100 individuals each providing three concentration-effect data sets from specific concentration-sampling windows. Four sets of concentration sampling windows were initially investigated. The accuracy of parameter estimates, obtained after 100 replications was assessed using mean and standard deviation of percent prediction error as measures of bias and precision, respectively. The effects of population size and level of inter-individual variability were further studied using the most optimum design. The optimum design for the
determination of the equilibrium rate constant associated with an effect compartment was also studied. Response data were also simulated from time input data for an inhibitory sigmoid $E_{\text{max}}$ model. The equilibrium rate constant and its variability parameter were then estimated using the first order method (FO) in NONMEM. Two designs were investigated.

The most optimum design for determination of PD parameters in the absence of an effect compartment was found to be the one with low concentration input in which samples were taken from the following concentration windows: 0.1-0.5, 0.5-1 and 1-2 EC$_{50}$ units. However, in the presence of high inter-individual variability (60%) estimates of variability parameters, using the most optimum design, were biased and imprecise. More precise estimates of the parameters were obtained with a larger population. All designs failed to give accurate estimates of the variability in the sigmoidicity parameter. The most optimum design for the equilibrium rate constant was found to be the one in which two samples were taken from the following sampling windows: 0.25-1.5 and 1.5-3 equilibrium half-life units (using 50 individuals) but it gave poor estimates of the variability parameter. In conclusion, accurate estimates of all PD parameters were obtained when samples were taken from 0.1-0.5, 0.5-1 and 1-2 EC$_{50}$ units. Increasing the level of inter-individual variability to 60% in the most optimum design gave precise estimates of all PD parameters but variability parameters were poorly estimated. Accurate estimates of the equilibrium rate constant were obtained but not of its variability parameter.
III.2. INTRODUCTION

In drug development, the application of population pharmacodynamic (PD) modeling can help increase understanding of the quantitative relationships among drug-input patterns, patient characteristics, and drug response. This approach is useful when wishing to identify factors that affect drug behavior, or explain variability in a target population. The population approach can be used to estimate population parameters in many phases of clinical drug development, where information is gathered on how drug will be used in subsequent stages of drug development (1). The population approach is designed to take advantage of observational, randomly obtained data. It can be used to analyze sparsely sampled data (2-4). It, also, encompasses the identification and measurement of variability during drug development and evaluation.

The design of a PD study is critical in determining the accuracy of parameter estimates, especially when data are sparse (5,6). When designing a population study, practical design limitations such as sampling times, number of samples per individual, and number of individuals should be considered. Also, it is important to consider factors such as the clinician-time, the time spent by the patient in the clinic, especially if the study is conducted on an outpatient basis, and the sampling assay cost. Consequently, a study design that involves taking as few samples as possible from each individual is preferable.

Simulation is a useful tool to provide convincing objective evidence of the merits of a proposed study design and analysis (7). Simulation enables the pharmacometrician to
better predict the results of a population study and to choose the study design that will best meet the study objectives\textsuperscript{(6-13)}.

Several PD models have been used to describe the drug pharmacological response. These models describe the relation between the drug response (dependent variable) and its concentration (independent variable). The sigmoid $E_{\text{max}}$ model has been proposed as a useful model to describe the in vivo relationship between dose/concentration and continuous pharmacological effect for many drugs\textsuperscript{14}. This model has three PD parameters, namely efficacy ($E_{\text{max}}$), potency ($E_{C50}$) and sigmoidicity constant ($\gamma$) that control the drug response. Using this model, the concentration-effect relationship is sigmoidal in shape. The sigmoid $E_{\text{max}}$ model has the advantage over other PD models in that it incorporates the sigmoidicity constant, which is the number of drug molecules bound to each receptor. Although this model is based on receptor theory it cannot be assumed, even if the concentration-effect data fits the model, that the drug response is truly described by the model. It must be kept in mind that data drive the model. For example, sigmoidicity has been found to be a non-integer in some cases even though the receptor theory would predict it to be always an integer\textsuperscript{(15-18)}. In some cases a baseline response ($E_0$) can be incorporated in the model. If the drug has an inhibitory effect on a physiologic response, such as reduction of the heart rate or reduction of the number of eosinophils, the model equation is subtracted from the baseline effect.

The inhibitory sigmoid $E_{\text{max}}$ model has been widely used to describe the PD of many drugs such as suppression of ventricular ectopic depolarizations by tocainide\textsuperscript{(15)}.
theophylline's induced eosinopenia and hypokalemia\textsuperscript{(16)}, percent reduction in heart rate by diltiazem from the baseline\textsuperscript{(19)} and reduction of the pain score by the analgesic effect of acetaminophen\textsuperscript{(18)}.

In early PD studies, investigators often made the assumption that drug concentrations measured in plasma were in equilibrium with those at the effect site. This assumption may be valid, if the drug effect is direct, receptor site rapidly equilibrates with plasma and the receptor interaction and response occurs rapidly. However, sometimes a delay between the pharmacological effect and the plasma concentration occurs\textsuperscript{(20)}.

Sheiner et al 1979\textsuperscript{(20)} developed a hypothetical effect compartment to model the time lag between the pharmacokinetic (PK) and PD responses by estimating the half-time for effect equilibration when plasma concentrations are not constant. These investigators proposed a model to describe the time course of muscle paralysis with d-tubocurarine where they linked the central compartment of the PK model with a hypothetical effect compartment. The rate constant ($k_{1e}$) for the effect compartment was very small relative to other rate constants in the PK model and its specific value was unimportant in determining the drug response. On the other hand, the rate constant for drug loss from the effect sites, $k_{e0}$, characterized the equilibration time between plasma concentrations and pharmacological effect.

The effect compartment method has been widely used to link PK and PD models of many drugs that exhibit a distributional delay. Examples of the use of the effect compartment
model in the literature are, the study of the effect of ergotamine on peripheral arteries where $k_{e_0}$ is 0.07 hr$^{-1}$, with an equilibration time of 9.9 hours$^{(21)}$, the effect of terbutaline on bronchodilation where the equilibration time is 11.5 minutes$^{(22)}$, the influence of age and gender on the PD of remifentanil, where the $k_{e_0}$ is found to be 0.516 min$^{-1}$$^{(17)}$ and the study of the PD of acetaminophen in children where the equilibration time equals to 1.6 hr$^{(18)}$.

In population studies, the variability in parameters and the search for factors controlling variability is also an important focus. A lot of information in the literature is available on the study designs for PK$^{(1-7, 9-12, 23-31)}$. However, there is very little information about the study designs for PD. Only too often major emphasis is placed on the PK, rather than on PD, however plasma concentration (the PK output) is no more than a surrogate for the pharmacological and/or clinical effects, which require information about the PD of the drug$^{(32)}$. The incorporation of PD in drug development leads to a more informative drug development program especially in identification of drug dosage regimens for optimal therapeutic outcome through strategies for individualization of dosage$^{(33)}$. Recognition of PD importance on drug response recently increases. Failure to appreciate the magnitude of variability in PD of a drug can compromise fixed dose clinical trial outcomes making the drug appear less effective or more toxic$^{(34)}$.

The objectives of this study were: (1) To determine the optimum sampling design of a PD study. (2) To study the effect of total sample size on the accuracy of parameter estimates. (3) To study the effect of high level of inter-individual variability on the accuracy of
parameter estimates. (4) To determine the optimum sampling design of the equilibrium rate constant using the effect compartment method.

In this study, response data were simulated from concentration input data to determine the accuracy of PD and variability parameters with different sampling designs. The effect compartment model was used to link a one compartment PK model with the inhibitory sigmoid $E_{\text{max}}$ model to study the optimum sampling design for the equilibrium rate constant where the response data were simulated from time input data.

III.3. METHODS

III.3.1. Simulation of response data from concentration input data:

An integrated PD model of theophylline was constructed in NONMEM (version 5) (Nonlinear Mixed Effect Modeling)\(^{(35)}\).

III.3.1.1. Pharmacodynamic Model:

An inhibitory sigmoid $E_{\text{max}}$ model, as shown in Equation III.1, was used to simulate response data from concentration input data.

$$E = E_0 - \left[ \frac{(E_0 - E_{\text{max}})C^r}{EC_{50}^r + C^r} \right]$$  \hspace{1cm} \text{III.1}
Where $E$ is the drug response, $E_0$ is the baseline, $E_{\text{max}}$ is the drug efficacy, which is the maximum drug effect, $C$ is the drug concentration and $EC_{50}$: is the drug concentration at 50% of the $E_{\text{max}}$ (potency). Gamma ($\gamma$): is the sigmoidicity constant.

Data were simulated based upon the population PD parameters of theophylline-induced eosinopenia \(^\text{(16)}\) as follows: $E_0 = 183/\mu L$, $E_{\text{max}} = 37/\mu L$, $EC_{50} = 5.06$ mg/L and $\gamma = 6.22$

III.3.1.2. Statistical Model:

An exponential model was used to describe the inter-individual variability in all PD parameters as follows:

$$\theta_i = \theta_m \times (\text{EXP}(\eta_{0i}))$$ III.2

Where, $\theta_i$ is the estimate for a PD parameter in the $i$th individual, $\theta_m$ represents the population mean value of this parameter and $\eta_{0i}$ is a normally distributed random variable with an average value of 0 and variance of $\omega^2$.

Intra-individual variability (Residual error) was also described by exponential error model as follows:

$$E_{ij} = E_{mij} \times (\text{EXP}(e_{ij}))$$ III.3
Where, $E_{ij}$ is the observed effect for the $i$th individual at time $j$, $E_{mij}$ is the model-predicted effect for the $i$th individual at time $j$ and $\epsilon_{ij}$ is the residual error that represents the difference between the observed response and the model predicted response. $\epsilon_{ij}$ is a normally distributed random variable with an average value of 0 and variance of $\sigma^2$.

For the residual error, the formula for the exponential model was written in NONMEM control file as follows:

\[ \text{Response} = \log(E) + \epsilon \]  \hspace{1cm} \text{III.4}

As a result, the simulated response values were in the log form. Consequently, the data had to be protected from zero to avoid error resulting from log zero, by using IF-ELSE statement.

When the exponential model is used to describe inter-individual and intra-individual variability, $\omega$ and $\sigma$ may be regarded as approximate coefficients of variation. The coefficient of variation of the inter-individual variability was chosen to be 30% for all PD parameters. The coefficient of variation of the residual error was chosen to be at the moderate variability level of 25% $^{(27)}$.

\textbf{III.3.1.3. Data:}
For each design studied, a data set was created based on 100 "individuals" each of whom contributed three samples. Thus, one data set consisted of 300 observations of response data.

III.3.1.4. Sampling Schedules:

Initially, four basic designs were investigated using windows of increasing concentrations. To mimic a real life situation, in which it is unrealistic to take samples at exactly the same concentration for each individual, sampling windows were used (9). The sampling windows for each of the four basic designs are shown in Table III.1. In Design 1 and 2, samples were taken at low to moderate concentration levels. While in Design 3 and 4, samples were taken at moderate to high concentration levels and high concentration levels, respectively. In order to generalize the results to any drug, not specifically theophylline, the designs were created based on EC\textsubscript{50} units.

III.3.1.5. Data Simulation:

For each design of the basic designs, 3 random concentration points from within the appropriate sampling window were generated for each individual in Excel. The corresponding response data were then simulated using NONMEM. For each scenario, 100 data sets were replicated. The PRED type model (15) was used to simulate the effect data directly from concentration input data.
11.3.1.6. Effect of Changing Total Sample Size:

As outlined above, initially each data set consisted of 100 individuals and 100 replications. Once the most optimum design was identified, the effect of total sample size was further studied using population of 50, 200 and 1000 "individuals". The total number of observation data was 150, 600 and 3000 with 50, 200 and 1000 individuals, respectively.

11.3.1.7. Effect of Increasing Inter-individual Variability:

Initially inter-individual variability in PD parameters was set at 30% for the basic four designs. Additionally, the performance of the most optimum design was further assessed at a level of inter-individual variability of 60%.

11.3.1.8. Parameter Estimation:

For each simulated data set, estimation of PD parameters (EC$_{50}$, $E_{\text{max}}$, $E_0$ and $\gamma$) and variability parameters (variability parameter in EC$_{50}$ ($\omega_{\text{EC}_{50}}$), variability parameter in $E_{\text{max}}$ ($\omega_{\text{E}_{\text{max}}}$), variability parameter in $E_0$ ($\omega_{E_0}$) and variability parameter in $\gamma$ ($\omega_{\gamma}$) was carried out in NONMEM using the first order conditional estimation method (FOCE). Although this method is time consuming compared to the first order (FO) method, it is the only way to get accurate estimates for the variability parameters using exponential error model (35).
III.3.1.9. Bias and Precision of Parameter Estimates

The accuracy of the estimates from each data set were evaluated using the percent prediction error (%PE) as described by the following equation:

\[
\%PE = \frac{\theta_{\text{sim}} - \theta_{\text{true}}}{\theta_{\text{true}}} \times 100
\]

Where \( \theta_{\text{sim}} \) is the estimated population value of the parameter from one simulated data set and \( \theta_{\text{true}} \) is the true population value for the parameter. The %PE was calculated for the 100 simulated data sets in each scenario. The mean and standard deviation of %PE were used to measure bias and precision of parameter estimates respectively. A mean of %PE for a parameter estimate \( \leq 15\% \) was accepted as being unbiased \(^{11}\). A standard deviation of %PE for a parameter estimate \( \leq 35\% \) was accepted as being precise \(^{11}\).

III.3.2. Simulation of response data from time input data:

An integrated PK/PD model of theophylline was constructed using NONMEM. A one-compartment PK model was linked to the inhibitory sigmoid \( E_{\text{max}} \) PD model through an effect compartment.
III.3.2.1. Pharmacokinetic Model:

A one-compartment PK model with intravenous bolus input was used. Response data were simulated following a single dose of 300 mg based upon the population PK/PD parameters of theophylline induced eosinopenia. The values used for PK parameters were 2.75 L/hr for clearance (CL) and 28.4 L for volume of distribution (VD)\(^{(16)}\).

III.3.2.2. Effect Compartment Model:

The inhibitory sigmoid \(E_{\text{max}}\) model, as previously described in Section III.3.1.1 was linked to the PK model through an effect compartment with equilibrium rate constant, \(k_{\text{eo}}\), of 2.04 hr\(^{-1}\)\(^{(16)}\) to account for the lag between plasma concentration and pharmacological response.

III.3.2.4. Statistical Model:

A proportional model was used to describe the inter-individual variability in all PK and PD parameters as follows:

\[
\theta_i = \theta_m \ast (1+\eta_{\theta_i})
\]
Where, $\theta_i$ is the estimate for a PD parameter in the $i$th individual, $\theta_m$ represents the population mean value of this parameter and $\eta_{0i}$ is a normally distributed random variable with an average value of 0 and variance of $\omega^2$.

Intra-individual variability (Residual error) was described by exponential error model as in Equation III.3.

The coefficients of variation of inter-individual variability and residual error were chosen to be at 30% and 25%, respectively.

III.3.2.5. Data:

Two designs were studied as shown in Table III.2. Designs A consisted of 100 individuals, each of whom contributed one sample. Thus, one data set consisted of 200 observations of response data. Design B consisted of 50 individuals, each of whom contributed two samples. Thus, one data set consisted of 150 observations of response data.

III.3.2.6. Sampling Schedules:

The sampling times in the two designs were chosen from the range of three equilibrium half lives ($3 \, k_{e0}$) since distribution would be 90 % complete by three half lives. Again, sampling windows were used to mimic a real life situation, in which it is very difficult to
take samples at exactly the same time for each individual. The sampling windows for Design A and B are shown in Table III.2. In Design 1, one sample was taken per individual while two samples per individual were taken in Design B. In order to generalize the results to any drug, not specifically theophylline, the designs were created based on equilibration half-life units.

III.3.2.7. Data Simulation:

For design A and B, 1 and 2 random time points from within the appropriate sampling windows, respectively, were generated in Excel. The corresponding response data were then simulated using the ADVAN 3 subroutine \(^{(15)}\) in NONMEM. For each scenario, 100 data sets were replicated.

III.3.2.8. Parameter Estimation:

At the beginning of this study, the FOCE method was used for the estimation step but it took a very long time (more than 3 hours) for each run due to the structural complication of this method with the complex model, ADVAN 3, used. Also, an enormous amount of overflow error was encountered which delayed the runs remarkably. Thus the estimation of the equilibrium rate constant \((k_{eq})\) and its variability parameter was carried out in NONMEM using the FO method with each simulated data set.
The accuracy of the estimates from each data set was evaluated using %PE as described by Equation III.5, Section III.3.1.9.

III.4. RESULTS

III.4.1. PD Parameters:

Bias and precision of parameter estimates were used to judge the performance of the designs studied where a mean and standard deviation of %PE for a parameter estimate ≤ 15% and 35% was accepted as being unbiased and precise, respectively (11).

Design 1 gave unbiased estimates of all PD parameters; however γ was only just achieved unbiased status (Tables III.3 & III.5 and Figures III.1 & III.3). Design 2 and 3 gave unbiased estimates of EC<sub>50</sub>, E<sub>max</sub>, E<sub>0</sub>, but slightly biased estimates of γ (Tables III.3 & III.5 and Figure III.1) Design 4 gave unbiased estimates of EC<sub>50</sub>, E<sub>max</sub>, and marginally biased estimate of γ but the estimate of E<sub>0</sub> was highly biased (Tables III.3 & III.5 and Figure III.1).

All basic designs gave precise estimates of all PD parameters except Design 4, which gave a highly imprecise estimate of E<sub>0</sub>, but other parameters were precise. The precision of parameter estimates of the four basic designs is shown in Tables III.4 & III.5 and Figure III.2.
III.4.2. Variability Parameters:

All basic designs gave unbiased estimates of the variability parameter in EC₅₀ (ω_EC₅₀). Design 1 gave biased estimates of the variability parameter in E_max (ω_E_max), Design 2 gave marginally unbiased estimates of ω_E_max and Design 4 gave biased estimates of the variability parameters in E₀ (ω_E₀).

Regarding the precision of the parameter estimates, Designs 1 and 2 gave imprecise estimates of ω_E_max. Designs 3 and 4 gave imprecise estimates of ω_EC₅₀. All but Design 4 gave precise estimates of ω_E₀. All designs failed to give accurate (unbiased and precise) estimates of the variability parameter in γ (ω_γ). Estimate of the residual error (σ) was unbiased and precise with all the basic designs studied.

From the initially studied four designs, Design 1 was found to be the most optimal design. It was the only design to give accurate (unbiased and precise) estimates of all PD parameters. However, it did give inaccurate estimates of ω_E_max and ω_γ. Consequently, it was further studied for the effect of total sample size and the effect of increasing inter-individual variability on the accuracy of the parameter estimates.

III.4.3. Effect of Total Sample Size:

The effect of sample size was studied by using the most optimum design with 50, 100, 200 and 1000 individuals. The bias of PD and variability parameters appeared to be the
same for all population sizes, with the exception of the estimation of $\gamma$ which became more biased as the population size increased. By looking at the confidence intervals for the bias of $\gamma$ estimates with different sample sizes, it was found that as the sample size increased, the confidence intervals got smaller. The confidence intervals for bias of $\gamma$ were 4.31, 2.62, 1.88 and 0.64 with sample sizes of 50, 100, 200 and 1000 individuals, respectively.

All estimates of PD parameters were precise with all population sizes studied. Increasing population size resulted in more precise estimates of the variability parameters. For example, reducing sample size to 50 individuals resulted in marginally imprecise (35.5%) estimates of the variability parameter in $EC_{50}$ ($\omega_{EC_{50}}$) and increasing population size to 1000 individuals resulted in precise estimates of the variability parameter in $E_{max}$ ($\omega_{E_{max}}$). However, increasing total sample size failed to give precise estimates of the variability parameter in $\gamma$ ($\omega_{\gamma}$). Estimates of the residual error were precise with all sample sizes studied. Effect of total sample size on bias and precision of parameter estimates is shown in Table III.6 & Figure III.4 and Table III.7 & Figure III.5, respectively.

**III.4.4. Effect of Increasing Inter-individual Variability:**

When inter-individual variability was increased from 30 to 60%, the most optimum design still resulted in unbiased and precise estimates of $EC_{50}$, $E_{max}$ and $E_0$. Although estimate of $\gamma$ at the higher level of inter-individual variability was still precise, its estimate was biased. Increasing inter-individual variability to 60% resulted in very biased
and imprecise estimates of all variability parameters. Estimates of the residual error were biased but precise with this high level of inter-individual variability. This was the only design, from the eight designs studied, to give biased estimate of the residual error. The effect of increasing inter-individual variability to 60% on bias and precision of parameter estimates is shown in Table III.8 & Figure III.6 and Table III.9 & Figure III.7, respectively.

III.4.5. Effect Compartment Parameter Estimates:

Both Designs A and B gave unbiased and precise estimates of the equilibrium rate constant, $k_{eq}$, but its variability parameter ($\omega$) was very poorly estimated. Design B gave more precise and unbiased estimates of $k_{eq}$ than that of Design A. Estimates of the residual error ($\sigma$) were biased and imprecise with Design A and slightly biased and precise with Design B. The bias and precision of parameter estimates of Designs A and B are shown in Tables III.10 & III.11, respectively and Figures III. 8, III.9 & III.10.

III.5. DISCUSSION

The magnitude and duration of drug response is controlled by the PK and PD phases. The determination of clinically useful guidelines thus must account for the parameters of each phase and also any link models necessary to account for delays in the distribution of drug from the plasma to the site of action $^{16}$. The expanded application of PK/PD models has been found to be highly beneficial for establishing doses used during drug development.
In recognition of the value of PD’s importance, the FDA recently called for PD modeling of clinical data as a component of new drug application (34). Additionally, the increased availability of more sophisticated PD alternatives to the therapeutic range is anticipated to improve the effectiveness of applied therapeutics (37).

In the past, it was assumed that PK variability is primarily responsible for quantitative differences in drug response (38). The probable reason for this assumption is that PD studies in human were rare until the last couple of decades (34). Several studies have demonstrated that PD variability in humans is large, reproducible and usually more pronounced than PK variability (34,39-42). Failure to appreciate the magnitude of PD inter-individual variability of a drug can compromise fixed dose clinical outcomes, making the drug appear less effective or more toxic (34). Thus, it is important to quantify PD variability and try to identify patient covariates in population studies.

The application of the population approaches to drug development is recommended in several FDA guidance documents (43,44). Prospective implementation of large-scale population PD evaluation is feasible in early drug development and this approach generates clinically relevant findings (45). The population approach can be applied in situations where extensive sampling is not done on all or any of the participants (44). It can use sparse data collected during the course of other studies (26). One major task in clinical pharmacology is to determine the PK/PD parameters of a drug in a patient population. The software NONMEM is commonly used to model response data to build population PK-PD models that characterize the relationship between a patient’s PK-PD parameters
and other patient specific covariates such as the patient's pathological, physiological conditions and concomitant drug therapy \(^{(46)}\).

When planning a population PD study, several aspects must be given careful attention. These include the primary objectives of the study, the PD characteristics of the drug under study, number of subjects required, number of samples per subject, and timing of these samples and the cost of collecting and analyzing samples \(^{(28,43,44)}\).

Simulation studies are ideal tools to investigate different design issues prior to execution of the study and are useful for selecting the study design that will best meet study objectives. In this study, the ability of various PD designs to provide accurate parameters estimates was investigated by simulating drug response data from concentration and time input data using inhibitory sigmoid \(E_{\text{max}}\) model. It is important to simulate the response data directly from concentration input not time input since the PD model describes the concentration-effect relationship and the effect is independent of time. With the effect compartment model, the response data has to be simulated from time because in this model time is an important variable to describe the lag between plasma concentration and pharmacological response. The designs used to investigate the accuracy of the parameter estimates differed in their sampling windows. The use of sampling windows ensures that samples are taken at random. This has been shown in the past to be a robust design \(^{(8,25,36)}\). The use of random sampling can protect against misspecification of the underlying structural model and situations where a single model is not adequate for all individuals. Parameter estimates obtained from the different designs were evaluated in
terms of bias and precision. It has been shown that estimates of bias and precision give better descriptions of predictive performance than correlation coefficients and/or the regression of predictions on true values \(^{(47)}\). Bias is the degree to which the typical prediction is either too high or too low and precision is a measurement of the typical magnitude of error about a true value \(^{(43)}\).

The FOCE method was used in the estimation step. This method requires more computer time to perform an analysis especially with large data sets or/and complex structural models. It was very difficult to use this method with sigmoid \(E_{\text{max}}\) model. It has been shown that the sigmoidicity constant causes a lot of problems in the estimation step and results in many overflow errors \(^{(35)}\), such as a division by zero or floating point overflow. In the present study, in some cases more than 600 runs were necessary to get 100 correct runs without an overflow error. Also, the use of the FOCE method causes an unsuccessful termination of the simulation step for many runs \(^{(10)}\). However, this method provides more accurate estimates of the variability parameters \(^{(10,35)}\).

Initially, three basic designs were investigated. These designs differed in their concentration inputs as follows: Design 1 had concentration samples up to 2 \(EC_{50}\) units, Design 3 had concentration samples up to 5 \(EC_{50}\) units and Design 4 had concentration samples up to 16 \(EC_{50}\) units. Design 1 gave unbiased and precise estimates of all PD parameters but it gave imprecise and biased estimates of \(\omega_{E}\max\). Thus, it would seem that good estimates of \(\omega_{E}\max\) might require high concentration samples. The samples from the design that gave imprecise estimate of \(\omega_{E}\max\) were only 2 \(EC_{50}\) units. Consequently,
Design 2 was studied in which 2 samples windows were the same as Design 1 but the third window was slightly higher than that of Design 1 (1-2 EC_{50} and 1-3 EC_{50} in Design 3 and 4, respectively). All parameter estimates of Design 2 were like that of Design 1 regarding the terms bias and precision, except estimates of \( \gamma \) and \( \omega_{E_{\text{max}}} \), where Design 2 gave biased estimate of \( \gamma \) and marginally unbiased and better but still imprecise estimates of \( \omega_{E_{\text{max}}} \) than that of Design 1. Thus, by looking at the accuracy of parameter estimates, Design 1 was found to be the most optimal design for a PD study because it gave precise and unbiased estimates to all PD parameters and the variability parameters in \( \text{EC}_{50}, E_0 \) and residual error. Design 1 has the advantage of using samples of low concentration level, which made it optimum for narrow therapeutic range drugs. However, this design had few disadvantages such as: it gave imprecise and biased estimates of \( \omega_{E_{\text{max}}} \), possibly due to the low concentration input, and \( \omega_{\gamma} \), which may be due to the inaccurate estimates of \( \omega_{E_{\text{max}}} \). The variability parameter in \( \gamma \) might be more sensitive than any other parameter to the inter-individual variability as none of the designs investigated in this study was able to get accurate estimates of \( \omega_{\gamma} \).

In general, PK/PD parameters are estimated more accurately than the variability parameters. Al-Banna et al. (7) and Ette et al. (28) found that the population PK fixed-effect parameters were efficiently estimated but the inter-individual variability parameters were inaccurate and imprecise for most of the sampling schedules.

The most optimum design identified in this study, was used to study the effect of total sample size on the accuracy of the parameter estimates. Increasing sample size to 1000
individuals gave more precise estimates of all PD and variability parameters. Increasing total sample size resulted in biased estimates of $\gamma$. By conducting hypothesis testing on the population means for the bias of $\gamma$ estimates with different sample sizes (level of significance of 0.05), it was found that as the total sample size increased the power to reject the null hypothesis that $\gamma$ estimate is unbiased increased. Also, the confidence intervals for bias of $\gamma$ were wide for population sizes of 50 and 100 individuals (4.31 and 2.62, respectively) compared with that for population sizes of 200 and 1000 individuals (1.88 and 0.64, respectively). Therefore small sample size had a little power to detect a departure from the null hypothesis that the estimate is unbiased. Thus as the total sample size increased, the confidence intervals got smaller and the power to detect the bias increased.

Inter-individual variability in PD may result from variability in receptor density and affinity, formation and elimination kinetics of endogenous ligands, postreceptor transduction processes, Homeostatic responses, the kinetic characteristics of transporters involved in drug transfer between fluids of distribution and the biophase and variability in the baseline ($E_0$) among population. It is important to identify and quantify the variability in PD parameters for the clinical safety and effectiveness of drug use.

When the inter-individual variability was increased from 30% to 60%, the precision and bias of PD parameters was the same, except that of $\gamma$ where the estimate was biased. However at this higher level of inter-individual variability, all variability parameters were very poorly estimated. Sun et al 1996 found that there was an increase in bias and
imprecision in parameter estimation as inter-subject variability was increased. Increasing inter-individual variability in the most optimum design resulted in biased estimate of the residual error. This may be due to the difficulty in partitioning error between inter and intra individual variability at this high level of inter-individual variability. Ette et al (6) found that positively biased estimates of residual variability were obtained irrespective of the sample size used (30 to 1000 subjects) at coefficient of variation of 60% or more.

It is accepted that for a fixed sample size, PK/PD parameters are estimated more accurately than the associated variability parameters (6,23,28). This was confirmed here in this study at both levels of inter-individual variability (30% & 60%). When inter-individual variability was low, Design 1 gave accurate estimates of all PD parameters but two of the variability parameters were poorly estimated. When the inter-individual variability was high (60%), the most optimum design gave accurate estimates of almost all PD parameters but it failed to give accurate estimates to any of the variability parameters.

The equilibrium rate constant determines the onset of drug action and the duration of the pharmacological effect. Contin et al (49) studied the PD of levodopa in patients with Parkinson's disease over 4 years of disease progression. They found that the onset of drug effect occurred earlier and the duration of effect became shorter over this four-year period. They found that $k_{eo}$ gradually increased with disease progression and hysteresis became less pronounced. The equilibrium half-life decreased from 173 minutes to about 43 minutes (50). In a study of the influence of age on PD of remifentanil (17), it was found
that age was a significant covariate of $k_{e0}$, which decreased by approximately 50% for the age range of 20-85 years.

The magnitude of $k_{e0}$ depends on many factors such as perfusion of the effect site ($^{31}$), rate of drug diffusion from capillaries to the effect site, blood tissue partition coefficient of the drug, rate of drug-receptor association and dissociation, time course of subsequent pharmacological response and by age ($^{17}$).

In present study, both designs A & B gave precise and unbiased estimates of $k_{e0}$. However, Design B in which 2 samples were taken from each individual of 50 subjects gave more precise and unbiased estimates of $k_{e0}$ than that of Design A in which one sample was taken from each individual of 100 subjects. Estimates of the variability parameter in $k_{e0}$ were very poor for both designs. Estimates of the residual error ($\sigma$) were precise with Design B and imprecise with Design A. This is in accordance with the work of Ette et al ($^{29}$). They used half (50 subjects) the total number of subjects required for accurate parameter estimation with the one sample per subject design and doubling the total number of observations per subject. They found that with one observation per subject, the design yielded biased and imprecise estimates of inter-individual variability, and residual variability could not be estimated. Obtaining a second sample from each subject gave better estimates of the residual error, because it facilitated the partitioning of inter-subject variability and residual intra-subject variability, by introducing information about the latter. Two samples from 50 individuals appeared to be enough to get accurate estimate of one parameter. Breant et al ($^{30}$) found that two samples from each individual
of 15-20 patients were enough to perform a reasonable population analysis to get accurate estimates of two parameters (CL and VD). They also found that the values of the PK parameters were very similar to those obtained with 3 to 5 blood levels and with more patients.

Large inter-individual variability in $k_{e0}$ has been found for many drugs, for example the percent coefficient of variation in $k_{e0}$ of acetaminophen in children undergoing outpatient tonsillectomy is 131% $^{(18)}$ and that of theophylline induced eosinopenia is 191% $^{(16)}$. The variability parameter in $k_{e0}$ was very poorly estimated in this study, possibly because the percent coefficient of variation in $k_{e0}$ used was very small (30%) compared to the real one (191%) $^{(16)}$ or may be due to misspecification of the error model used.

III.6. CONCLUSION

Simulating a planned study offers a potentially useful tool for evaluating and understanding the consequences of different study designs. Simulation can reveal the effect of input variables and assumptions on the results of a planned population PD study.

From this work, the following general conclusions on a PD study design can be drawn:

1. Optimal sampling and pre-experiment simulation is a useful tool for designing informative population study $^{(24)}$. 

134
2. Design 1, in which concentration samples were taken from the following sampling windows: 0.1-0.5, 0.5-1 and 1-2 EC50 performed best overall and it was considered to be the most optimum design for a PD study specially its input concentration was low which is suitable for a narrow therapeutic range and potent drugs.

3. Increasing the total sample size improved the accuracy of the parameter estimates.

4. When inter-individual variability was increased to 60%, with the exception of the sigmoidicity constant's estimate which was biased, accurate estimates of all PD parameters were found. The variability parameters were very poorly estimated.

5. All the designs failed to give accurate estimates of the variability parameter in the sigmoidicity constant.

6. Accurate equilibrium rate constant estimates were obtained with the two designs studied, however Design B in which 2 samples were taken per individual with total sample size of 50 individuals performed better.

7. Both Designs A and B gave very poor estimates of the variability parameter in the equilibrium rate constant.

In summary, Design 1 was considered to be the most optimum design for studying the PD parameters, namely efficacy, potency, baseline response and sigmoidicity constant.
Design B was considered to be the most optimum design for studying the equilibrium rate constant but it gave poor estimates of the variability parameter.
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Table III.1. Sampling windows for the four basic designs:

| Design | Sampling Windows (EC<sub>50</sub> units) |
|--------|----------------------------------------|
|        | (1)     | (2)    | (3)  |
| 1      | 0.1 - 0.5 | 0.5 - 1 | 1 - 2 |
| 2      | 0.1 - 0.5 | 0.5 - 1 | 1 - 3 |
| 3      | 0.1 - 0.5 | 1 - 2.5 | 3 - 5 |
| 4      | 1 - 4    | 6 - 9   | 13 - 16 |
Table III.2. Sampling windows for Designs A & B:

| Design | Sampling Windows (Equilibrium half life units) |
|--------|-----------------------------------------------|
|        | (1)                                           |
|        | (2)                                           |
| A      | 1.5 - 3                                       |
| B      | 0.25 - 1.5                                    |

Design A: only one sample was taken per individual.
Design B: two samples were taken per individual.
Table III.3. Percent bias of parameter estimates using the four basic designs:

| Design | EC\(_{50}\) | E\(_{\text{max}}\) | E\(_0\) | \(\gamma\) | \(\omega_{\text{EC}_{50}}\) | \(\omega_{E_{\text{max}}}\) | \(\omega_{E_{0}}\) | \(\omega_{\gamma}\) | \(\sigma\) |
|--------|--------------|-----------------|--------|---------|-----------------|-----------------|-------------|-------------|-------|
| 1      | -0.51        | 0.54            | -0.73  | -14.98  | -5.15           | -25.77          | -1.27       | 35.39      | 6.87  |
| 2      | -3.24        | 0.81            | 0.11   | -19.26  | -5.12           | -14.41          | -0.75       | 74.63      | 4.52  |
| 3      | -0.72        | 1.1             | -0.13  | -17.86  | -10.4           | -0.42           | -1.64       | 33.76      | 3.94  |
| 4      | -1.3         | 0.82            | 432.7  | -15.51  | -10.16          | -0.05           | 56.52       | 33.13      | 0.49  |

Based on 100 replications.

Design 1: Samples were taken at 0.1-0.5, 0.5-1 and 1-2 EC\(_{50}\) units.
Design 2: Samples were taken at 0.1-0.5, 0.5-1 and 1-3 EC\(_{50}\) units.
Design 3: Samples were taken at 0.1-0.5, 1-2.5 and 3-5 EC\(_{50}\) units.
Design 4: Samples were taken at 1-4, 6-9 and 13-16 EC\(_{50}\) units.
Table III.4. Percent precision of parameter estimates using the four basic designs:

| Design | $EC_{50}$ | $E_{\text{max}}$ | $E_0$ | $\gamma$ | $\omega_{EC_{50}}$ | $\omega_{E_{\text{max}}}$ | $\omega_{E_0}$ | $\omega_{\gamma}$ | $\sigma$ |
|--------|----------|-----------------|------|----------|---------------------|--------------------------|---------------|----------------|--------|
| 1      | 4.73     | 12.6            | 4.1  | 13.35    | 22.91               | 62.11                    | 22.22         | 161.3         | 18.66  |
| 2      | 5.06     | 7.35            | 4.35 | 11.74    | 25.5                | 41.45                    | 23.76         | 185           | 22.3   |
| 3      | 8.39     | 4.22            | 4.25 | 15.99    | 37.55               | 26.82                    | 27.57         | 178.7         | 20.92  |
| 4      | 33.4     | 3.45            | 2104 | 31.55    | 68.01               | 18.7                     | 283.2         | 263.6         | 12.27  |

Based on 100 replications.
Design 1: Samples were taken at 0.1-0.5, 0.5-1 and 1-2 $EC_{50}$ units.
Design 2: Samples were taken at 0.1-0.5, 0.5-1 and 1-3 $EC_{50}$ units.
Design 3: Samples were taken at 0.1-0.5, 1-2.5 and 3-5 $EC_{50}$ units.
Design 4: Samples were taken at 1-4, 6-9 and 13-16 $EC_{50}$ units.
Table III.5. Bias and precision of parameter estimates using the four basic designs:

| Parameters | Bias | | | | Precision |
|------------|------|---|---|---|---|---|---|
|            | 1    | 2  | 3  | 4  | 1  | 2  | 3  | 4  |
| $EC_{50}$  | -    | -  | -  | -  | -  | -  | -  | -  |
| $P_{max}$  | -    | -  | -  | -  | -  | -  | -  | -  |
| $E_0$      | -    | -  | -  | +  | -  | -  | -  | +  |
| $\gamma$   | -    | +  | +  | +  | -  | -  | -  | -  |
| $\omega_{EC_{50}}$ | -    | -  | -  | -  | -  | -  | +  | +  |
| $\omega_{E_{max}}$ | +    | -  | -  | -  | +  | +  | -  | -  |
| $\omega_{E_0}$ | -    | -  | -  | +  | -  | -  | -  | +  |
| $\omega_{\gamma}$ | +    | +  | +  | +  | +  | +  | +  | +  |
| $\sigma$   | -    | -  | -  | -  | -  | -  | -  | -  |

Based on 100 replications.

(-) means unbiased or precise, (+) means biased or imprecise.

Design 1: Samples were taken at 0.1-0.5, 0.5-1 and 1-2 $EC_{50}$ units.
Design 2: Samples were taken at 0.1-0.5, 0.5-1 and 1-3 $EC_{50}$ units.
Design 3: Samples were taken at 0.1-0.5, 1-2.5 and 3-5 $EC_{50}$ units.
Design 4: Samples were taken at 1-4, 6-9 and 13-16 $EC_{50}$ units.
Table III.6. Effect of total sample size on percent bias of parameter estimates:

| Sample Size | EC50  | Emax  | E0    | γ     | ωEC50 | ωEmax | ωE0  | ωγ    | σ     |
|-------------|-------|-------|-------|-------|-------|-------|------|-------|-------|
| 50          | -1.43 | -0.02 | 1.16  | -13.21| -4.82 | -34.58| -10.6| 36.11 | 7.4   |
| 100         | -0.51 | 0.54  | -0.73 | -14.98| -5.15 | -25.77| -1.27| 35.39 | 6.87  |
| 200         | -0.81 | -1.86 | -0.1  | -19.49| -1.46 | -27.59| -1.81| 36.52 | 6.36  |
| 1000        | -1.17 | -1.76 | -0.2  | -20.34| -0.78 | -34.44| -2.85| 58.27 | 6     |

Using Design 1 in which samples were taken at 0.1-0.5, 0.5-1 and 1-2 EC50 units.
Table III.6. Effect of total sample size on percent precision of parameter estimates:

| Sample Size | EC$_{50}$ | E$_{max}$ | E$_0$ | $\gamma$ | $\omega_{EC50}$ | $\omega_{E_{max}}$ | $\omega_{E0}$ | $\omega_{\gamma}$ | $\sigma$ |
|-------------|-----------|-----------|-------|----------|-----------------|-------------------|----------|-------------------|--------|
| 50          | 5.96      | 19.44     | 5.58  | 22       | 35.5            | 75.26            | 28.39    | 261               | 25.5   |
| 100         | 4.73      | 12.57     | 4.1   | 13.35    | 22.9            | 62.11            | 22.22    | 161.3             | 18.7   |
| 200         | 3.67      | 9.87      | 3.14  | 9.58     | 25.4            | 65.7             | 41.1     | 111               | 13.5   |
| 1000        | 1.59      | 3.87      | 1.25  | 3.26     | 7.18            | 21.93            | 7.64     | 58.46             | 6.55   |

Using Design 1 in which samples were taken at 0.1-0.5, 0.5-1 and 1-2 EC$_{50}$ units.
Table III.8. Effect of increasing inter-individual variability (IIV) on percent bias of parameter estimates:

| IIV  | EC₅₀ | Eₘₐₓ | E₀  | γ   | ω_EC₅₀ | ω_Eₘₐₓ | ω_E₀ | ω_r | σ   |
|------|------|------|-----|-----|-------|--------|------|-----|-----|
| 60%  | 4.14 | -4.69| -1.02| -32.05| 225.7 | 203.85 | 311.17| 101.35| 22.85|
| 30%  | -0.51| 0.54 | -0.73| -14.98| -5.15 | -25.77 | -1.27 | 35.39 | 6.87 |

Using Design 1 in which samples were taken at 0.1-0.5, 0.5-1 and 1-2 EC₅₀ units.
Table III.9. Effect of increasing inter-individual variability (IIV) on percent precision of parameter estimates:

| IIV | EC$_{50}$ | E$_{max}$ | E$_0$ | $\gamma$ | $\omega_{EC_{50}}$ | $\omega_{E_{max}}$ | $\omega_{E_0}$ | $\omega_{\gamma}$ | $\sigma$ |
|-----|-----------|-----------|-------|----------|-----------------|-----------------|----------------|----------------|---------|
| 60% | 12.8      | 24.96     | 7.06  | 15.14    | 103.9           | 191.58          | 73.2           | 200.75         | 23.53   |
| 30% | 4.73      | 12.57     | 4.1   | 13.35    | 22.91           | 62.12           | 22.22          | 161.32         | 18.66   |

Using Design 1 in which samples were taken at 0.1-0.5, 0.5-1 and 1-2 EC$_{50}$ units.
Table III.10. Percent bias of $k_{e0}$ and variability parameter estimates using Design A & B:

| Design | $k_{e0}$ | $\omega$     | $\sigma$    |
|-------|---------|-------------|-------------|
| A     | -9.33   | 1.56E+08    | 19.34       |
| B     | -8.71   | 1.55E+10    | -17.25      |

Design A: one sample was taken between 1.5-3 equilibrium half-life units. Design B: two samples were taken, the first one between 0.25-1.5 equilibrium half-life units and the second one between 1.5-3 equilibrium half-life units.
Table III.11. Percent precision of $k_{e0}$ and variability parameter estimates using Design A & B:

| Design | $k_{e0}$  | $\omega$   | $\sigma$  |
|--------|-----------|------------|-----------|
| A      | 29.71     | 1.48E+09   | 99.72     |
| B      | 26.21     | 1.4E+11    | 28.80     |

Design A: one sample was taken between 1.5-3 equilibrium half-life units. Design B: two samples were taken, the first one between 0.25-1.5 equilibrium half-life units and the second one between 1.5-3 equilibrium half-life units.
Figure III.1. Percent bias of parameter estimates using the four basic designs.
Figure III.2. Percent precision of parameter estimates using the four basic designs.
Figure III.3. Percent bias and precision of parameter estimates using Design 1.
Figure III.4. Effect of total sample size on percent bias of parameter estimates.
Figure III.5. Effect of total sample size on percent precision of parameter estimates.
Figure III.6. Effect of increasing inter-individual variability on percent bias of parameter estimates.

- EC50
- Emax
- E0
- \(\gamma\)
- \(\omega_{E0}\)
- \(\omega_{E50}\)
- \(\omega_{E\gamma}\)
- \(\sigma\)

For 60% variability:
- EC50: 225.7
- Emax: 203.9
- E0: 311.2

For 30% variability:
- EC50
- Emax
- E0
- \(\omega_{E0}\)
- \(\omega_{E50}\)
- \(\omega_{E\gamma}\)
- \(\sigma\)
Figure III.7. Effect of increasing inter-individual variability on percent precision of parameter estimates.

- EC50
- Emax
- E0
- γ
- 0EC50
- 0Emax
- 0E0
- 0γ
- σ

Values:
- 191.6
- 200.8
- 161.3
Figure III.8. Percent bias of ke0 and variability parameter estimates using Designs A and B.

- ke0
- ω
- σ

- □ A
- ■ B

Values:
- 1.56E+08
- 1.55E+10
Figure III.9. Percent precision of $ke_0$ & variability parameter estimates using Designs A and B.
Figure III.10. Percent bias and precision of parameter estimates using Designs A and B.
APPENDIX A
Figure A.1. The effect of $n$ on drug response using single IV dose* in presence of an effect compartment of $k_{eo}=0.2$. (Manuscript I)

*: this dose gave MOE of 90% at $n$ and EC50 of 1 in absence of the effect compartment.
Figure A.2. The effect of n on drug response using single IV dose* in presence of an effect compartment of keo=1. (Manuscript I)

*: this dose gave MOE of 90% at n and EC50 of 1 in absence of the effect compartment.
Figure A.4. The effect of EC50 on drug response using single IV dose* in presence of an effect compartment of $k_{ae}=1$. (Manuscript I)

*: this dose gave MOE of 90% at nand EC50 of 1 in absence of the effect compartment
Figure A.3. The effect of EC50 on drug response using single IV dose in presence of an effect compartment of \( k_{eo}=0.2 \). (Manuscript I)

*: this dose gave MOE of 90% at EC50 of 1 in absence of the effect compartment.
Figure A.5 Drug response vs time with different multiple IV doses at n and EC50 of 1.

(Manuscript I)
Figure A.6. Drug concentration vs time with different multiple IV doses at \( n \) and EC50 of 1.

(Manuscript I)
Figure A.7. Concentration-effect relationship using the linear model. (Manuscript II)

\[ y = 0.0403x + 1.58 \]
\[ R^2 = 1 \]
Figure A.8. Steady state plasma concentrations at different theophylline doses. (Manuscript II)
Figure A.9. NONMEM control file of the pharmacodynamic model (PRED model): (Manuscript III)

$PROBLEM SIMULATION OF POPULATION DATA
$INPUT ID CON EF=DV
$DATA PD.DAT

$PRED
C50=THETA(1)*EXP(ETA(1))
EMAX=THETA(2)*EXP(ETA(2))
E0=THETA(3)*EXP(ETA(3))
GAMMA=THETA(4)*EXP(ETA(4))

IF (EMAX.GT.E0) EXIT 11
TY = E0-(E0-EMAX) * CON**GAMMA / (CON**GAMMA + C50**GAMMA)

IF (TY.LE.0) THEN
LTY=-10000
ELSE
LTY=LOG(TY)
ENDIF
Y=LTY+EPS(1)

$THETA (0,5.06) (0,37) (0,183) (0,6.22)
$OMEGA 0.09 0.09 0.09 0.09
$SIGMA 0.0625
$SIMULATION(3575821) SUBPROBLEM=100;SEED 1-7 DIGITS
$ESTIMATION METHOD=1 MAX=5000,PRINT=5 NOABORT
$COVARIANCE
$STABLE ID CON DV FILE=P1.out
Figure A.10. NONMEM control file of the effect compartment model (ADVAN3): (Manuscript III)

$PROBLEM SIMULATION OF POPULATION DATA
$DATA Ke0.DAT
$INPUT ID TIME DOSE=AMT DV
$SUBROUTINES ADVAN3

$PK
CL=THETA(1)*(1+ETA(1))
V1=THETA(2)*(1+ETA(2))
S1=V1
K=CL/V1
K12=0.001*K
K21=THETA(3)*(1+ETA(3))
EMAX=THETA(4)*(1+ETA(4))
C50=THETA(5)*(1+ETA(5))
E0=THETA(6)*(1+ETA(6))
S2=S1*K12/K21
GAMMA=THETA(7)*(1+ETA(7))

$THETA (0,2.75) (0,28.4) (0,2.04) (0,37) (0,5.06) (0,183) (0,6.22)
$OMEGA 0.09 0.09 0.09 0.09 0.09 0.09 0.09
$ERROR
TY=E0-(E0-EMAX)*F**GAMMA/(F**GAMMA+C50**GAMMA)

IF (TY.LE.0) THEN
LTY=-10000
ELSE
LTY=LOG(TY)
ENDIF

Y=LTY+EPS(1)

$SIGMA 0.0625
$SIMULATION(2190998) SUBPROBLEM=100;SEED 1-7 DIGITS
$ESTIMATION MAX=5000,PRINT=5 NOABORT
$COVARIANCE
$TABLE ID TIME AMT DV FILE=KI.out
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