- Traditional pharmacokinetic studies involve taking multiple blood samples periodically over time in a few individual patients, and characterizing basic pharmacokinetic parameters such as K, V_D and Cl.

- Traditional pharmacokinetic parameters estimation is very accurate, provided that enough samples can be taken for the individual patient. The disadvantage is that only a few relatively homogenous healthy subjects are included in pharmacokinetic studies, from which dosing in different patients must be projected.

- In the clinical setting; patients are usually not very homogeneous; patients vary in sex, age, body weight; they may have concomitant disease and may be receiving multiple drug treatments.

- Even the diet, life style, ethnicity, and geographic location can differ from a selected group of

"normal" subjects.

- Further, it is often not possible to take multiple samples from the same subject, and, therefore, no data are available to reflect intrasubject difference, so that iterative procedures for finding the maximum likelihood estimate can be complex and unpredictable due to incomplete or missing data.
- However, the vital information needed about the pharmacokinetics of drugs in patients at different stages of their disease with various therapies can only be obtained from the same population, or from a collection of pooled blood samples
- The advantages of population pharmacokinetic analysis using pooled data and included a summary of population pharmacokinetics for dozens of drugs.
- Pharmacokinetic analysis of pooled data of

plasma drug concentration from a large group of subjects may reveal much information about the disposition of a drug in a population, and inter- and intrasubject variations must be considered.

- Both pharmacokinetic and nonpharmacokinetic factors, such as age, weight, sex and creatinine concentration, should be examined in the model to determine the relevance to the estimation of pharmacokinetic parameters.

- The nonlinear mixed effect model (or NONMEM) is so called because the model uses both fixed and random factors to describe data. Fixed factors such as patient weight, age, gender, and creatinine concentration are assumed to have no error, whereas random factors include inter- and intraindividual differences

- NONMEM is a statistical program that allows

Bayesian pharmacokinetic parameters to be estimated using an efficient algorithm called the first-order (FO) method.

.The parameters may now be estimated also with a first-order conditional estimate (FOCE) algorithm.

.In addition, to pharmacokinetic parameters, many examples of population plasma data have been analyzed to determine population factors. Multiplicative coefficients or parameters for patient factors may also be estimated.

NONMEM fits plasma drug concentration data for all subjects in the groups simultaneously and estimates the population parameter and its variance. The parameter may be clearance and/or V_D. The model may also test for other fixed effects on the drug due to factors such as age, weight

and creatinine concentration.

•The model describes the observed plasma drug concentration (C_i) in terms of a model with:

1. P_K = fixed effect parameters, which include pharmacokinetic parameters or patient factor parameters.

.For example, P_1 is cl, P_2 is the multiplicative coefficient include creatinine factor, and P_3 is the multiplicative coefficient for weight.

2 Random effect parameters, including (a) the variance of the structural (kinetic) parameter P_K or intersubject variability within the population ω_K^2, and

(b) the residual intrasubject variance or variance due to measurement errors, fluctuations in individual parameter values, and all other

errors not accounted for by the other parameters.

•There are generally two reliable and practical approaches to population pharmacokinetic data analysis.

1. Standard two-Stage (STS) method:

Estimates parameters from the plasma drug concentration data for an individual subject during the first stage. The estimates from all subjects are then combined to obtain an estimate of the parameters for the population.

•The method is useful because unknown factors that affect the response in one patient will not carry over and bias parameter estimates of the others. The method works well when sufficient drug concentration-time data are available.

2. First-order (FO) method:

-is also used but is perhaps less well understood. The estimation procedure is based on minimization of an extended least-squares criterion, which was defined through a first-order Taylor series expansion of the response vector about the fixed effects and which utilized a Newton-Raphson-like algorithm (Beal and Sheiner, 1980).

-This method attempts to fit the data and partition the unpredictable differences between theoretical and observed values into random error terms. When this model includes concomitant effect, it is called a mixed-effect statistical model (Beal and Sheiner, 1985).

-The advantage of the first-order model is that it is applicable even when the amount of

time-concentration data obtained from each individual is small, provided that the total number of individuals is sufficiently large.

- Typically, a computer method is used in the data analysis based on a statistical model using either the weighted least-squares (WLS) or the extended least-squares (ELS) method in estimating the parameters.

NONMEM has been regularly updated and improved. Many drugs have been analyzed with population pharmacokinetics to yield information not obtainable using the traditional two-stage method (Sheiner and Ludden, 1992). An added feature is the development of a population model involving both pharmacokinetics and pharmacodynamics, the so-called population PK/PD models.

One example involving analysis of population plasma concentration data involved the drug procainamide. The drug clearance of an individual in a group may be assumed to be affected by several factors (Whiting et al, 1986). These factors include body weight, creatinine clearance, and a clearance factor P_1 described in the following equation:

$$Cl_{drug\ j} = P_1 + P_2 (C_{creatinine}) + P_3 (weight_j) + \eta_{Cl_j}$$

where η_{Cl_j} is the intersubject error of clearance and its variance is $\omega^2_{Cl_j}$.

- Model selection Criteria:

- Data analysis in pharmacokinetics frequently selects either a monoexponential or polyexp-

onential that will better describe the concentration-time relationship.

- The selection criterion for the better model is determined by the goodness-of-fit, taking into account the number of parameters involved.
- Three common model selection criteria are:

1) the AKaike information Criterion (AIC)

2) the Schwarz Criterion (SC)

3) the F test (alpha = 0.05).

- The performance characteristics of these criteria were examined by Ludden et al (1994) using Monte Carlo (random or stochastic) simulations
- The precision and bias of the estimated parameters were considered.
- The Akaike information criterion and the Schwarz criterion lead to selection of the

correct model more often than does the Ftest, which tends to choose the simpler model even when the more complex model is correct.

- The Ftest is also more sensitive to deficient sampling designs.
- Clearance was quite robust among the different methods and generally well estimated. Other pharmacokinetic parameters are more sensitive to model choice, particularly the apparent elimination rate constant.

Prediction of concentration is generally more precise when the correct model is chosen.