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The Application of Population Pharmacokinetics to the Drug Development Process

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ABSTRACT

Population pharmacokinetics is playing an increasing role in clinical drug development. An overview of the population approach, including software and the advantages and limitations of the approach compared to the traditional approach to pharmacokinetic studies, is given. This paper also documents how the area has evolved over the past 15 years and addresses some of the issues that have arisen over the design and conduct of population studies. Finally, some alternative applications of the population approach are given for areas other than clinical drug development.

INTRODUCTION

Pharmacokinetics is the study of the relationship between the dose of a drug and the manner in which its plasma concentrations change over time. A pharmacokinetic model provides a mathematical representation of this relationship and relates the independent variables of time and dose to the dependent variable, plasma concentration, using pharmacokinetic parameters such as clearance (CL) and volume of distribution (Vd). Pharmacodynamics is the study of the relationship between concentrations of the drug at the site of action and its physiological effect.

The traditional approach to pharmacokinetic studies involves taking intensive samples, up to 10 or 20 per individual, from a small group of subjects or patients. The data from each subject are individually fitted to a pharmacokinetic model (e.g., a one- or two-compartment model) to obtain that individual's pharmacokinetic parameters. Then, summary statistics such as the mean and the variance of the group are calculated based on each individual's pharmacokinetic parameters. Initially, these studies are often performed on healthy volunteers, especially in phase I clinical studies.

The population approach to the analysis of pharmacokinetic data also provides estimates of the average value of pharmacokinetic parameters in a study population and gives a measure of the variability of these parameters within that population (1). In contrast to the traditional approach, the population approach is based on only a few samples from each subject in a larger number of subjects. In addition, the population approach provides parameter

estimates from the population of individuals in a single step. A population model generally consists of two components: a pharmacokinetic or structural model and a pharmacostatistical model. As a result, the term mixed effects modeling is often used to describe the modeling process since two types of parameters are estimated: the fixed effect parameters associated with the pharmacokinetic model and the random effect parameters that describe the pharmacostatistical model (2).

Fixed effect parameters describe the relationship between the plasma concentration and the fixed effects. Fixed effects include the dose, physiological factors such as age, weight, and creatinine clearance, and other factors such as concomitant medications. Fixed effect parameters include typical pharmacokinetic parameters such as volume of distribution (Vd) and clearance (CL) and proportionality constants that quantify the relationship between a pharmacokinetic parameter such as clearance and a fixed effect such as creatinine clearance (1–3).

Random-effect parameters are used to quantify variability in pharmacokinetic parameter estimates that arise due to interindividual (between subjects) and intraindividual (within subject) variations (1). Interindividual variability is the random between subject variability that cannot be explained in terms of fixed effects. It is important to obtain an estimate of unexplainable variability for a new drug because the safety and efficacy of a drug tends to decrease as unexplainable variability increases (4). Intraindividual variability is the variability that occurs within an individual. It includes errors that arise from the measurement of drug concentrations, model misspecification due to oversimplification of the model, and random variation in a patient's pharmacokinetic parameters that can occur over time (1,2,4,5).

There are numerous articles in the literature that can be consulted to provide a more comprehensive review of the theory and methodology underlying the population approach to pharmacokinetic analysis (1–3,5–8).

COMPUTER SOFTWARE

Software development for population analyses is an active area of investigation, and a number of programs are currently available. A meeting of experts was held in 1994 to discuss software issues associated with the analysis of population pharmacokinetic and pharmacodynamic data. The participants concluded that programs need to be user friendly with good graphical interfaces, have the ability to specify complex pharmacokinetic and pharmacodynamic models, and be able to handle sparse data (9). NONMEM (Nonlinear Mixed Effects Modeling) (10) is the software most often used and tested for these analyses (9,11). Other currently available software includes NPML (Non-Parametric Maximum Likelihood) (12), NPEM (Non-Parametric Expectation Maximization) (13), and the programs that implement the Bayesian approach using Gibbs sampling (14).

Each method of applying the population approach has its own assumptions and limitations. Some researchers have advocated using several methods to analyze one data set as a means of confirming results and of highlighting problems in methodology (9,15). A comparative study carried out in 1992 under the initiative of the American Statistical Association compared four population modeling methods. NONMEM, Gibbs sampling, SPML (semiparametric maximum likelihood), and NPML. They showed that the different methods gave similar results, with only minor discrepancies observed (9). In 1997, the Population Pharmacokinetic Modeling Workgroup formed by the Biopharmaceutical Section of the American Statistical Association compared population methods using two simulated data sets (11). Their report included analyses performed using seven different modeling programs: NONMEM, a conditional first-order method implemented in S-Plus (16), two alternative first-order methods implemented in SAS (17–19), the Bayesian approach using Gibbs sampling (14), a semi-nonparametric approach (20), and NPML (12). The statistical theory and methodology underlying these software programs can be found in the literature (5,7,12–14,16–20). The group observed differences in some parameter estimates when the different approaches were compared. Thus, there appears to be conflicting evidence regarding the comparability of some methods of implementing the population approach and this subject requires further investigation.

ADVANTAGES AND LIMITATIONS OF THE POPULATION APPROACH

In contrast to traditional studies, the population approach to pharmacokinetic studies requires fewer samples per patient. Thus, these designs are more suited to the study of subpopulations such as pediatrics, geriatrics, and the very ill (e.g., AIDS and cancer patients or patients with renal and hepatic impairment), for whom there are ethical constraints to taking many blood samples per patient (3,5,7).

Traditional pharmacokinetic studies often involve volunteers or patients with mild forms of the disease of interest, and inclusion and exclusion criteria are often very strict. Thus, these patients/subjects are not very representative of the population to be treated, and the pharmacoki-

netics of the study drug for these patients may differ significantly from the pharmacokinetics of patients who receive the drug in clinical practice (21). As fewer samples are required per patient in a population study, it is feasible to study a greater number of patients. For example, if a population pharmacokinetic study is incorporated into a phase III clinical trial, patients under study are more representative of the population for which the drug will eventually be used; thus the results of the analysis are of more relevance to the population of interest. Also, as the patient population is generally more heterogeneous, it becomes possible to examine the effect of various patient characteristics (e.g., age, weight, renal function, concomitant medications) on the pharmacokinetics of the drug. Thus, if a population analysis is incorporated into a phase II or III trial, then drug disposition can be evaluated early in the development process, and the results can be used to guide dosage recommendations in different subpopulations (4).

Traditional studies are expensive to conduct due to their strict scientific design, so only a small number of individuals can be studied, which can result in poor estimates of interindividual variability. In contrast, a population study can be done using observational data, that is, data collected under less-restrictive conditions, such as in routine clinical practice, than in a traditional study. The requirement for fewer samples per individual and the use of routine data enables a population study to be conducted less expensively. Plasma samples are often obtained periodically from subjects enrolled in phase III trials to monitor compliance. Therefore, if these samples were used in a population pharmacokinetic study, there would be minimal additional cost to the sponsor.

A limitation to the use of population pharmacokinetic methods is the complex data analysis techniques involved. In contrast, the analysis of traditional pharmacokinetic data is relatively straightforward and is performed using common, simple statistical methods (3). The observational design of a population study does not provide as convincing evidence for causation as the rigid scientific control of a traditional pharmacokinetic study. However, traditional studies are done in patients often not representative of the population of interest, which makes the relevance of the results questionable.

INTEGRATION OF POPULATION PHARMACOKINETICS IN THE DRUG DEVELOPMENT PROCESS

In 1983, a discussion paper on the testing of drugs in the elderly was issued by the Food and Drug Administration (FDA). It advocated the inclusion of population pharmacokinetic studies as part of phase III clinical trials (22). Initially, there was a negative reaction from the pharmaceutical industry to this suggestion for a number of reasons (4). First, the method of data analysis was unfamiliar to most scientists, and the complex nature of the analytical technique demanded specialized expertise. There was the belief that identification of a factor influencing the pharmacokinetics of the drug during drug development could result in the FDA requiring a prospective study to investigate this possible influence. Some believed that incorporating a population pharmacokinetic study into a trial protocol could result in additional cost and reduced compliance with the study protocol. Finally, there were questions regarding the quality of the data used in such an analysis (3,4,23,24).

By the late 1980s to early 1990s, a number of applications of the population approach had appeared in the literature; they were summarized by Sheiner and Ludden in 1992 (7). However, the majority were carried out in a clinical setting after marketing of the drug and were not performed in the preapproval process (25).

At this time, Grasela and colleagues published a series of articles in which they evaluated the use of population pharmacokinetics in clinical drug development (21,26–28). They applied the population approach in four different scenarios: a phase III clinical trial of patients who contributed only a few plasma samples each, a phase III clinical trial designed to detect a drug-drug interaction, a prospectively designed clinical trial that included forms designed to collect and record information relating to plasma sampling and dosing specifically for determining population pharmacokinetics, and finally, a postmarketing surveillance study that had limited control of design issues. They found that parameter estimates obtained using the population approach in all situations were comparable to estimates obtained in traditional pharmacokinetic studies and thus confirmed the potential use of this methodology in phase III and IV studies.

An interdisciplinary conference was held in April 1991 to discuss the integration of pharmacokinetics in rational drug development (29). The report from the conference advocated the use of population approaches in phase III trials to identify those patient characteristics that influence the pharmacokinetics of a drug in different subpopulations and to use this information in drug labeling. It was accepted that a population pharmacokinetic analysis was not the primary objective of phase II, III, and IV trials; thus, the methods for a population pharmacokinetic study, which must be incorporated into the efficacy protocol, should be as simple as possible and not have an impact on the major goals of the study (30,31).

In March 1995, a meeting of experts was held to discuss design issues associated with conducting population pharmacokinetic and pharmacodynamic studies (30). The experiences of the committee were that the population approach had frequently been implemented successfully in phase II and phase III studies. The consensus was that population pharmacokinetics should be included in clinical trials, and the discussion focused on design issues associated with the inclusion of a population pharmacokinetic study in a phase II or phase III efficacy trial.

A report published in 1996 on the implementation of the population approach in clinical drug development proposed many instances in which the population approach could successfully be employed in the drug development process from the preclinical stage to postmarketing studies (15). Phase I studies provide initial information on the pharmacokinetics and pharmacodynamics of a drug in human subjects, usually healthy volunteers (29). Intensive sampling, as employed in traditional pharmacokinetic studies, is advocated at this stage to establish an initial pharmacokinetic profile for the drug (15). However, if data from sufficient patients can be pooled, then the population approach can be applied at this stage. An advantage in doing this is that the data from all patients can be fit to the same pharmacokinetic model (i.e., a one-or two-compartment model), whereas in traditional studies, different models may sometimes be fit to data from different patients (15).

Phase II studies are used to determine initial efficacy data in relatively small groups of patients with the disease to be treated and to investigate the dose-response relationship (29). A more rational design of subsequent clinical studies can be undertaken if the population approach is applied at this stage to investigate variability in response and relationships with covariates (15).

Phase III clinical trials are designed to confirm the efficacy of a drug and to establish a toxicity profile (29). It is often the nature of these studies to exclude patients with diverse characteristics (e.g., patients with renal or hepatic disease) to increase the statistical power of the study. It is these patients whose pharmacokinetic profile is most likely to differ and whose dosage regimen may need to be individualized. As a solution to this problem, Vozeh et al. proposed that these patients be included in the study as a satellite group whose data would be excluded from the efficacy assessment, but included in the population pharmacokinetic analysis (15).

In September 1997, the FDA issued proposed guidelines to govern the conduct and analysis of population pharmacokinetic studies in the drug development process (32). Design issues associated with these studies were discussed in the guidelines. Obviously, the issues depend to some extent on the stage in the drug development process (preclinical, phases I–III, or postmarketing) in which the analysis is being conducted as this drives the kind of data collected. The new regulations proposed by the FDA, which are to require companies to conduct extensive clinical studies in the pediatric population during drug development, provide an opportunity for the wide application of the population approach (33).

ISSUES ASSOCIATED WITH THE DESIGN AND CONDUCT OF A POPULATION PHARMACOKINETIC STUDY

There are a number of fundamental requirements to fulfill in order to conduct a good population pharmacokinetic study. A sensitive and specific assay is needed to measure plasma concentrations of parent drug and clinically relevant metabolites; confirmation from preliminary studies is required to demonstrate a correlation between drug or metabolite concentrations and clinically relevant effects; and last, preliminary pharmacokinetic studies should have established the basic pharmacokinetic model to describe the drug's disposition, although population analyses of sparse data may use less-complex structural models than are required in data-rich situations (2,4,9).

The draft documentation issued by the FDA governing the conduct of population pharmacokinetic studies discussed some of the issues involved in designing a population pharmacokinetic study. These include the number of subjects required for a population analysis, the number of samples required per subject, and the optimum time of sampling (32). Simulation studies and real data sets are being used to investigate these issues.

In the early 1980s, Sheiner and Beal conducted three simulation studies with designs that were based on three experiments, each consisting of 10 subjects who were extensively sampled. They found that estimates of interindividual variability were imprecise as a result of the small number of individuals, even though each individual provided many samples (34). In another study, they used a one-compartment intravenous model to simulate data. They found that when the total number of samples was fixed at approximately 100, the bias and precision of pharmacokinetic and variability parameters were comparable when the data consisted of three samples from 33 patients or two samples from 50 patients. However, estimates were less precise and more biased when the data consisted of four samples from 25 patients (35).

One study investigated the number of samples per patient and the total number of samples necessary to provide accurate pharmacokinetic parameter estimates of cyclosporine in liver transplant patients (36). The data consisted of 203 samples from 42 individuals and was analyzed using a one-compartment model implemented in NPEM. Estimates of clearance and volume of distribution converged and showed very little variation once there were two levels per patient and the total number of patients in the analysis reached 15–20. Others found that analyses using either two or three samples per patient provided estimates that were not significantly biased or imprecise when compared with the intense sampling strategy (37).

A simulation study using a two-compartment model with intravenous input found that pharmacokinetic parameter estimates were accurate using from four to six samples per subject for 100 subjects, but interindividual variabilities were biased using the four-sample design (38). Also in this study, the effect of the number of subjects was assessed using a six-sample design. They evaluated seven levels from 20 to 100 subjects and found that all pharmacokinetic parameters were comparable irrespective of the sample size, but estimates of interindividual variability became less biased as the number of subjects increased.

Another group used simulated data to mimic sparsely sampled data for 100 patients from a phase III clinical trial in which either one or two blood samples were taken per patient on two occasions (39). They compared various sampling strategies for bias and precision of population parameter estimates and found that parameter estimates were often more precise and less biased when patients provided two samples per visit as compared to only one.

Thus, it appears that two samples per individual for 30 to 50 individuals can provide accurate estimates of population average parameters. However, more individuals and more samples per patient may be required to obtain unbiased estimates of interindividual variability (40). Obviously, the specific pharmacokinetic model used to fit the data and the number of parameters to be estimated has an impact on the number of samples required per individual.

Some researchers have advocated the use of random sampling of plasma concentrations within the population (21,30). However, it is likely that the quality of information obtained will increase if informative sampling times are selected. Samples obtained at the time of peak serum concentrations usually contain the most information about the volume of distribution, whereas samples obtained in the middle of a dosing interval are informative about clearance (2). Others have employed optimal sampling theory (OST) to reduce the number of samples required per subject (41,42). This method ensures that data are collected at informative times for estimation of pharmacokinetic parameters (37,43–47). These studies investigated various sampling schedules and pharmacokinetic models; in all cases, the optimally sampled, reduced data sets provided accurate estimates of clearance, often the parameter of most interest. In some, but not all, cases, other pharmacokinetic parameters were also accurately estimated.

The quality of the data used in a population analysis is of paramount importance. Ette, Sun, and Ludden investigated the use of balanced (i.e., equal number of samples per patient) versus unbalanced data and found that the precision of parameter estimates, but not accuracy, was affected by missing data (48). Sun et al. conducted a simulation study to investigate the effect of misrecorded sample times on parameter estimation in NONMEM (49). Obviously a well designed study may not provide good results if sample times are not recorded accurately. Sun, Ette, and Ludden found that estimates of clearance tended to be unbiased when errors were random or systematically positive whereas the estimate of clearance was biased when there was a negative systematic error.

One study compared prospectively and retrospectively collected data (27). Specific forms were designed to collect and record information related to plasma sampling and dosing in the prospective study. Patient records were used to obtain information in the retrospective study. The prospective study was found to produce pharmacokinetic estimates comparable to previously reported estimates from traditional studies, whereas the retrospective study yielded biased estimates. The results from these studies demonstrate the need for good quality data in order to conduct a meaningful population pharmacokinetic analysis.

Validation of population pharmacokinetic models (i.e., if the parameter estimates and covariates included in a model based on one set of data be reproduced with another set of data) is an area of current interest (32). The various approaches that have been used to date, such as data splitting and the bootstrap resampling technique, have recently been discussed (50).

In summary, there are many ongoing issues in the design and conduct of population pharmacokinetic analyses. It appears that two samples per patient for 100 patients would be a reasonable minimum number of patients and samples required to develop a population pharmacokinetic model. It should be noted that the number of samples obtained from each subject depends on

the number of pharmacokinetic parameters to be estimated (21). Thus, care should be taken when extrapolating results from specific situations that use particular pharmacokinetic models to other situations. A well-planned study protocol that describes the objectives and methodology for conducting a population pharmacokinetic analysis is required. It should include a specific form that is simple in design to record sample times and dosing history. Education of clinical investigators is also essential to ensure that good quality data is obtained.

OTHER APPLICATIONS OF POPULATION PHARMACOKINETICS

Although the majority of the discussion has involved the implementation of the population approach in clinical drug development, there is interest in using these methods in preclinical development, although application of the population approach in preclinical studies is still relatively sparse (15,51–54). Two examples can be found in the literature that investigate the use of the population approach in one animal species only (53,54).

Both studies used a a one sample per animal design, which is often the case in preclinical studies. The first study showed that variability in volume of distribution could be partially explained due to gender differences, and the second study produced unbiased and precise estimates of the pharmacokinetic parameters. However, both studies were unable to separate interindividual from intraindividual variability and thus did not provide good estimates of variability.

The use of the population approach to investigate the pharmacokinetics and influence of covariates in a single species requires further study to show that it is a meaningful and cost-effective analysis to undertake. A potential application of the population approach in preclinical studies is to analyze data from a number of animal species in order to investigate allometric relationships using weight as a covariate (15).

Therapeutic drug monitoring (TDM) is applied in clinical practice to monitor the plasma concentrations of drugs that have a narrow therapeutic range. TDM is used to individualize the dose in order to avoid subtherapeutic levels of the drug or unwanted toxic effects (55). Relevant prior pharmacokinetic parameter estimates are required in order to implement TDM (56). Population pharmacokinetic studies can be used to provide these a priori estimates, and there are many examples in the literature of pharmacokinetic parameters that have been derived from population analyses to be used in this manner (see the summary by Thomson and Whiting, Ref. 56).

CONCLUSION

The population approach to pharmacokinetic studies is a new field that is rapidly growing and gaining acceptance in the pharmaceutical arena. The population approach can be used to analyze data that consist of only a few samples per individual. Thus, it is ideally suited to analyze observational data collected during clinical studies to monitor compliance, data pooled from early phase traditional pharmacokinetic studies, and data collected through routine clinical practice in postmarketing studies.

The population approach provides estimates of the mean population pharmacokinetic parameters within a population and variability of these estimates within that population. This method partitions the variability into between variability and within variability, and it can be used to explain the variability in pharmacokinetic parameter estimates in terms of physiological fixed effects. In doing so, this method can provide information on possible patient subgroups at risk of excessive drug accumulation or subtherapeutic levels, and it can be used to develop guidelines for drug dosage individualization (2,4).

The advent of proposed guidelines from the FDA that govern the design and conduct of population pharmacokinetic studies supports the use of these studies in the drug development process.

REFERENCES

1. B. Whiting B, A. W. Kelman, and J. Grevel, Population pharmacokinetics: Theory and clinical application, Clin. Pharmacokinet., 11, 387–401 (1986).
2. T. M. Ludden, Population pharmacokinetics, J. Clin. Pharmacol., 28, 1059–1063 (1988).
3. L. B. Sheiner and T. H. Grasela, An introduction to mixed effect modeling: Concepts, definitions and justification, J. Pharmacokinet. Biopharm., 19(3), 11S–24S (1991).
4. L. B. Sheiner and L. Z. Benet, Premarketing observational studies of population pharmacokinetics of new drugs, Clin. Pharmacol. Ther., 38(5), 481–487 (1985).
5. S. E. Rosenbaum, A. A. Carter, and M. N. Dudley, Population pharmacokinetics: Fundamentals, methods and applications, Drug Dev. Ind. Pharm., 21(9), 1115–1141 (1995).
6. L. Aarons. Sparse data analysis, Eur. J. Drug Met. Pharmacokinet, 18(1), 97–100 (1993).
7. L. B. Sheiner and T. M. Ludden, Population pharma-

cokinetics/pharmacodynamics, Annu. Rev. Pharmacol. Toxicol., 32, 185–209 (1992).
8. S. L. Beal and L. B. Sheiner, Estimating population kinetics, CRC Crit. Rev. Biomed. Eng., 8(3), 195–222 (1982).
9. L. Aarons, L. P. Balant, F. Mentre, et al., Population approaches in drug development: Report on an expert meeting to discuss population pharmacokinetics/pharmacodynamic software, Eur. J. Clin. Pharmacol., 46, 389–391 (1994).
10. S. L. Beal and L. B. Sheiner (eds.), *NONMEM Users Guides*, NONMEM Project Group, University of California at San Francisco, San Francisco, CA, 1992.
11. D. J. Roe, Comparison of population pharmacokinetic modeling methods using simulated data: Results from the Population Modeling Workgroup, Stat. Med., 16, 1241–1262 (1997).
12. A. Mallet, A maximum likelihood estimation method for random coefficient regression models, Biometrika, 73, 645–656 (1986).
13. A. Schumitzky, Nonparametric EM algorithms for estimating prior distributions. Applied Mathematics and Computation, 45, 141–157 (1991).
14. J. Wakefield, A. F. M. Smith, A. Racine-Poon, and A. Gelfand, Bayesian analysis of linear and nonlinear population models using the Gibbs sampler, Appl. Stat., 43, 201–221 (1994).
15. S. Vozeh, J. L. Steimer, M. Rowland, et al., The use of population pharmacokinetics in drug development, Clin. Pharmacokinet., 30(2), 81–93 (1996).
16. M. J. Lindstrom and D. M. Bates, Nonlinear mixed effects models for repeated measures data, Biometrics, 46, 673–687 (1990).
17. E. F. Vonesh and R. L. Carter, Mixed-effects nonlinear regression for unbalanced repeated measures, Biometrics, 48, 1–17 (1992).
18. E. F. Vonesh, Non-linear models for the analysis of longitudinal data, Stat. Med., 11, 1929–1954 (1992).
19. R. D. Wolfinger, Laplace's approximation for nonlinear mixed effects models, Biometrika, 80, 791–795 (1993).
20. M. Davidian and A. R. Gallant, The nonlinear mixed effects model with a smooth random effects density, Biometrika, 80, 475–488 (1993).
21. T. H. Grasela, E. J. Antal, R. J. Townsend, and R. B. Smith, An evaluation of population pharmacokinetics in therapeutic trials. Part 1. Comparison of methodologies, Clin. Pharmacol Ther., 39(6), 605–612 (1986).
22. R. Temple, Discussion paper on the testing of drugs in the elderly, memorandum of the Food and Drug Administration of DHHS, Washington, DC, 1983.
23. E. Samaŕa and R. Granneman, Role of population pharmacokinetics in drug development. A pharmaceutical industry perspective, Clin. Pharmacokinet., 32(4), 294–312 (1997).
24. W. A. Colburn, Controversy IV: Population Pharmacokinetics, NONMEM and the Pharmacokinetic Screen; Academic, Industrial and Regulatory Perspectives, J. Clin. Pharmacol., 29, 1–6 (1989).
25. L. Aarons, Population pharmacokinetics: Theory and practice, Br. J. Clin. Pharmacol., 32, 669–670 (1991).
26. T. H. Grasela, E. J. Antal, and R. B. Smith, An evaluation of population pharmacokinetics in therapeutic trials. Part II. Detection of a drug-drug interaction, Clin. Pharmacol. Ther., 42, 433–441 (1987).
27. E. J. Antal, T. H. Grasela, and R. B. Smith, An evaluation of population pharmacokinetics in therapeutic trials. Part III. Prospective data collection versus retrospective data assembly, Clin. Pharmacol. Ther., 46, 552–559 (1989).
28. C. L. DeVane, T. H. Grasela, E. J. Antal, and R. L. Miller. An evaluation of population pharmacokinetics in therapeutic trials. Part IV. Application to postmarketing surveillance, Clin. Pharmacol. Ther., 53, 521–528 (1993).
29. C. C. Peck, W. H. Barr, L. Z. Benet, et al., Conference report: Opportunities for integration of pharmacokinetics, pharmacodynamics and toxicokinetics in rational drug development, Clin. Pharmacol. Ther., 51, 465–473 (1992).
30. L Aarons, L. P. Balant, F Mentre, et al., Practical Experience and issues in designing and performing population pharmacokinetic/pharmacodynamic studies, Eur. J. Clin. Pharmacol., 49, 251–254 (1996).
31. E. J. Antal, T. H. Grasela, and R. B. Smith. The application of population pharmacokinetic analyses to large scale clinical efficacy trials, J. Pharmacokinet. Biopharm., 19(3), 37S–46S (1991).
32. *Guidance for Industry: Population Pharmacokinetics (Draft Guidance)*, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation (CDER) (September 1997).
33. *Proceedings from the Public Meeting on FDA's Proposed Regulation to Increase Pediatric Use Information for Drugs and Biologics*, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation (CDER) (October 27, 1997).
34. L. B. Sheiner and S. L. Beal, Evaluation of methods for estimating population pharmacokinetic parameters II. Biexponential model and experimental pharmacokinetic data, J. Pharmacokinet. Biopharm., 9(5), 635–651 (1981).
35. L. B. Sheiner and S. L. Beal, Evaluation of methods for estimating population pharmacokinetic parameters III. Monoexponential model: Routine clinical pharmacokinetic data, J. Pharmacokinet. Biopharm., 11(3), 303–319 (1983).
36. V Breant, B Charpiat, J. M. Sab, et al., How many patients and blood levels are necessary for population pharmacokinetic analysis? A study of a one compartment model applied to cyclosporine, Eur. J. Clin. Pharmacol., 51, 283–288 (1996).
37. G. L. Drusano, A. Forrest, G. Yuen, et al., Optimal Sampling Theory: Effect of error in a nominal parameter

value in bias and precision of parameter estimation, Clin. Pharmacol., 34, 967–974 (1994).
38. E. I. Ette, H. Sun, and T. M. Ludden, Design of population pharmacokinetic studies, Proc. Am. Stat. Assoc; 487–492 (1994).
39. E. N. Jonsson, J. R. Wade, and M. O. Karlsson, Comparison of some practical sampling strategies for population pharmacokinetic studies, J. Pharmacokinet. Biopharm., 24(2), 245–263 (1996).
40. M. K. Al-Banna, A. W. Kelman, and B Whiting, Experimental design and efficient parameter estimation in population pharmacokinetics, J. Pharmacokinet. Biopharm., 18(4), 347–360 (1990).
41. J. J. DiStephano III, Optimized blood sampling protocols and sequential design of kinetic experiments, Am. J. Physiol., 240, R259–R265 (1981).
42. D. Z. D' Argenio, Optimal sampling times for pharmacokinetic experiments, J. Pharmacokinet. Biopharm., 9(6), 739–756 (1981).
43. A. Forrest, C. H. Ballow, D. E. Nix, et al., Development of a population pharmacokinetic model and optimal sampling strategies for intravenous ciprofloxacin, Antimicrob. Agents and Chemother., 1065–1072 (1993).
44. G. L. Drusano, A. Forrest, K. I. Plaisance, and J. C. Wade, A prospective evaluation of optimal sampling theory in the determination of the steady-state pharmacokinetics of piperacillin in febrile neutropenic patients, Clin Pharmacol. Ther., 45, 635–641 (1989).
45. G. J. Yuen, G. L. Drusano, A. Forrest, et al., Prospective use of optimal sampling theory: Steady-state ciprofloxacin pharmacokinetics in critically ill trauma patients, Clin Pharmacol Ther., 46, 451–457 (1989).
46. G. L. Drusano, A. Forrest, M. J. Snyder, et al., An evaluation of optimal sampling strategy and adaptive study design, Clin. Pharmacol. Ther., 44, 232–238 (1988).
47. A. H. Burstein, P Gal, and A. Forrest, Evaluation of a sparse sampling strategy for determining vancomycin pharmacokinetics in preterm neonates: Application of optimal sampling theory, Ann. Pharmacother., 31, 980–983 (1997).
48. E. I. Ette, H. Sun, and T. M. Ludden, Ignorability and parameter estimation in longitudinal pharmacokinetic studies, J. Clin. Pharmacol., 38, 221–226 (1998).
49. H. Sun, E. I. Ette, and T. M. Ludden, On the recording of sample times and parameter estimation from repeated measures pharmacokinetic data, J. Pharmacokinet. Biopharm., 24(6), 637–650 (1996).
50. E. I. Ette, Stability and performance of a population pharmacokinetic model, J. Clin. Pharmacol., 37, 486–495 (1997).
51. L. Aarons, J. W. Mandema, and M. Danhof, A population analysis of the pharmacokinetics and pharmacodynamics of midazolam in the rat, J. Pharmacokinet. Biopharm., 19(5), 485–496 (1991).
52. I. F. Troconiz, L. G. Lopez-Bustamante, and D. Fos, Tenoxicam Pharmacokinetics in rats: A population model, J. Pharm. Sci., 84(12), 1482–1487 (1995).
53. E. I. Ette, A. W. Kelman, C. A. Howie, and B. Whiting, An application of the population approach to animal pharmacokinetics during drug development, Clin. Res. Regul. Affairs, 11(3 & 4), 243–255 (1994).
54. E. I. Ette, A. W. Kelman, C. A. Howie, and B. Whiting, Influence of inter-animal variability on the estimation of population pharmacokinetic parameters in pre-clinical studies, Clin. Res. Regul. Affairs, 11(2), 121–139 (1994).
55. R. W. Jelliffe, A. Schumitsky, D. Bayard, et al., Model-based, goal-oriented, individualized drug therapy, Clin. Pharmacokinet., 34(1), 57–77 (1998).
56. A. H. Thomson and B. Whiting, Bayesian parameter estimation and population pharmacokinetics, Clin. Pharmacokinet., 22(6), 447–467 (1992).