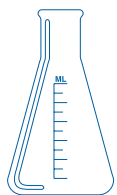


Biopharmaceutical Section



American Statistical Association

# Biopharmaceutical Report

Volume 9, No. 1

Summer 2001

Chair: *Jeff Meeker*

Editors: *Kannan Natarajan, Neal Thomas, and Demissie Alemayehu*

## A 20,000 Foot Overview of Population Pharmacokinetics and Its Applications in Drug Development

**Z. Gary Ge,  
Robert A. Smith,  
and Ralph H. Raymond**

*Bristol-Myers Squibb Pharmaceutical Research Institute,  
Princeton, NJ 08543-4000*

### Abstract

The concept of population pharmacokinetics is introduced. Several aspects of the population pharmacokinetic approach are addressed, including values of this approach in the drug development process, integration of population pharmacokinetics into the clinical development and life cycle management, issues in design and conduct of population pharmacokinetic studies, commonly used statistical methodologies and population pharmacokinetic model building procedures.

### 1 Introduction: What is population pharmacokinetics?

Population pharmacokinetics (population PK), according to the definition of the US Food and Drug Administration (FDA), is "the study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest" (FDA, 1999). This definition summarizes the basic characteristics of population PK. It is concerned with patients the drug intends to treat rather than healthy volunteers. It studies the variability in drug exposure for clinically safe and effective doses and in a relevant time frame. It focuses on identification of patient characteristics, which significantly affect or are highly correlated to this variability.

Population PK originated as a therapeutic drug monitoring mechanism, and with the advent of new technologies and statistical methodologies for the

## Contents

*FEATURED ARTICLE*

A 20,000 Foot Overview of Population Pharmacokinetics and Its Application in Drug Development.

.....GE, SMITH & RAYMOND 1

Discussion

.....NEDELMAN, HSU, MA,  
.....& SALLAS 8

Rejoinder

.....GE, SMITH & RAYMOND 10

### *BIOPHARMACEUTICAL SECTION NEWS*

Letter from the Chair

.....MEEKER 12

Highlights of Executive Committee Meeting, March 2001

.....MEEKER 13

FDA-Industry Workshop

.....LACHENBRUCH & ENAS 13

Continuing Education for the 2002 JSM

.....OPPENHEIMER 13

2001 Annual FDA/Industry Statistics Workshop

..... 14

analyses of PK data collected in routine clinical practices, its roles have been expanded not only in the study of clinical pharmacology, but also throughout almost the entire drug development process. Both the pharmaceutical industry and major regulatory bodies have become much more aware of its scientific values, its clinical implications and its importance as a development research tool to assist the design and analysis of clinical studies. To encourage and provide general guidelines on the design, conduct, analysis and reporting of population PK studies, FDA issued in February 1999 the 'Guidance for Industry: Population Pharmacokinetics.' Wider applications of population PK, in turn, have sparked greater interests in the development of new population PK methodologies among academia, regulatory and industry scientists. The participation of the pharmaceutical research statisticians is needed, as there are many opportunities in the development of population PK methodologies and applications.

While the primary goal is to give an overview of population PK and its applications, most of the methodologies discussed below are transferable to other population assessments such as population pharmacodynamics (PD) and determination of population pharmacokinetic / pharmacodynamic (PK/PD) relationships.

## 2. Why do population pharmacokinetics?

Population PK can overcome many limitations of traditional pharmacokinetic studies and provide a better understanding of the dose-exposure relationship among the target patient population. Objectives of traditional pharmacokinetic studies are to assess the systemic exposure of administered drugs and factors likely to affect this exposure. These studies are carried out mostly during Phase I of the drug development process. They are usually small, and conducted in a well-controlled clinical environment. Study subjects are typically normal healthy volunteers except for specific disease state studies such as renal and hepatic impairment studies. Frequent blood samples are collected on each of the study subjects, and concentration-time data are generally analyzed using non-compartmental pharmacokinetic methods to derive exposure endpoints such as the observed maximum concentration,  $C_{max}$ , and the area under the concentration-time curve, AUC. (Compartmental models are parametric models derived from a conceptualized division of body parts into compartments and a kinetic system that links these compartments. Non-compartmental methods are usually based on nonparametric summary measures like  $C_{max}$  and AUC. For a detailed account on compartmental and non-compartmental methods, readers may refer to Gibaldi and Perrier, 1982, or Rowland and Tozer, 1995.) Mean concentration profiles are compared, and traditional statistical analyses are performed on derived exposure endpoints. These studies are not always sufficiently powered to show desired effects or lack of effects. Due to differences in design, dosing regimen, dosage and formulation, pharmacokinetic data may be difficult to pool across studies to perform more powerful analyses or to better explore the interactions between factors with the traditional statistical analysis methods. Tra-

ditional assessment of PK variabilities normally investigates one factor at a time. As such, a comprehensive Phase I program may consist of many separate studies consuming significant amount of time, money and resources. Even with a comprehensive Phase I program, potentially important demographic, pathophysiological and other factors which alter the drug exposure, may still be left undetected, since it is very difficult to anticipate all possible prognostic factors and their interactions.

In contrast to traditional pharmacokinetic evaluation, population PK collects relevant pharmacokinetic information in patients the drug intends to treat. The more representative the study patient population is, the better this information reflects the characteristics of the target population. It is generally recognized that pharmacokinetics in healthy subjects may be irrelevant for certain drugs and certain diseases (Sheiner and Benet, 1985). When the drug is administered in clinically relevant doses and under routine therapy conditions, the observed PK variability in the sample patient population may mimic the real PK variability in the target population at large.

Multiple factors, such as age, race, gender, weight, renal impairment, liver function, clinical lab indicators, health conditions, disease state and concomitant therapies may be studied in one well designed population PK study. Diversity of patient characteristics in population PK studies and large sample sizes allow for the exploration of possible problems and factors that may affect drug exposure and for testing of interactions among factors. The better the PK variability can be explained with these factors, the better drug exposure can be predicted for patient subpopulations or even individuals, and the more appropriately a priori dose adjustment can be made. Well-conducted population PK studies can better address simultaneously many issues that normally are the objectives of separate traditional PK studies and hence reduce or eliminate the need for some of these studies with the approval of regulatory agencies. Significant savings in time and resources can be gained for sponsors of human drugs and biological products not only in terms of the sizes and timelines of their phase I programs, but also in terms of rational and efficient large scale efficacy and safety clinical studies that the timely population PK information helps to design.

Population PK studies do not require frequent blood sampling from individual patients, and concentration-time data can be directly modeled. Flexible population PK methodologies allow analyses to be performed on data pooled across studies of different designs, dosing regimens, dosages and formulations, even those data not suitable for traditional analysis methods. Limited and flexible sampling can be optimized based on statistical and practical considerations to minimize the impact on the conduct of individual clinical studies to achieve their primary objectives, yet statistical information in these combined pharmacokinetic data can still allow for powerful and convincing findings.

Monitoring drug levels during the conduct of a clinical trial or post marketing surveillance remains an important functionality of population PK. Under-exposed patients may have limited or no therapeutic responses, potentially

resulting in failure to demonstrate satisfactory effectiveness. Likewise, over-exposed patients may be prone to drug toxicity. PK monitoring allows for rational dose adjustments and individualized dosing regimens in flexible dose trials and in routine clinical use to maximize the benefit to risk ratio of the drug and minimize the chance of losing a good drug.

For large efficacy/safety clinical trials with fixed doses, the desired drug-effect manifestation or comparison may be compromised by the large dose-exposure variability, so that the desired statistical significance level may not be achieved. Concurrent blood sample collection for drug concentration assessment and/or a good prior understanding of population PK profile of the drug may help to re-evaluate the outcomes of these studies by stratifying the study population into pharmacokinetically homogeneous subpopulations and comparing the treatment effects within strata. Such stratification may separate the treatment variability from the inter-stratum variability, and reveal the desired treatment effects with desired statistical significance level for some or all of the subpopulations. Differences in systemic drug exposure can provide scientific bases for identifying patient subpopulations which respond to the same dose of the drug differently, and hypotheses on these subpopulations can be tested in further studies.

From a regulatory standpoint, a well designed and conducted population PK study can enhance a submission by better depicting the overall drug-concentration relationship. In fact, more and more reviewers are recommending the inclusion of a population PK analysis in the dossier. Findings from well-conducted population PK studies can be used to support critical labeling claims. In addition, the FDA 'Guidance for Industry: Providing Clinical Evidence for Human Drug and Biological Products' issued in May 1998, provides sponsors of human drugs and biologics an opportunity to utilize population PK results as critical evidence in support of a single adequate and well-controlled clinical investigation in seeking regulatory approval of a new use of a drug. The logic behind this provision is that well-studied pharmacokinetic properties, together with well-defined PK/PD relationships, can be used to translate results from a single controlled trial of one dose, regimen, or formulation to a new dose, regimen, or formulation. Population PK facilitates this translation.

### **3 Integration of population pharmacokinetics into the clinical drug development and life cycle management**

Population PK can be implemented in all phases of clinical development, as well as post-approval investigations. In the early phase I studies, the primary objectives are usually the safety and tolerability of the drug under investigation. Additionally blood and/or urine samples are usually collected to conduct PK evaluation. Typically frequently sampled PK data from a relatively small number of healthy subjects are available. In addition to the non-compartmental PK analysis, these data can be used to develop structural compartmental PK models, which serve as the basis for

modern population PK analysis, as well as intra-subject error models. The assumptions here are that the drug follows linear kinetics, and that the same linear kinetic structure applies to both healthy volunteers and the patient population. Of course, in phase I trials of some drugs, such as cancer drugs, HIV drugs and certain diabetes, hypertension and inflammation drugs, patients instead of healthy volunteers are enrolled, and the second assumption is not necessary.

Sparse PK sampling strategies can be used in phase II clinical trials in patients. With the structural compartmental model identified, a preliminary population PK analysis can be done with sufficient amount of data either collected in one study or pooled from multiple studies. The results of the analysis can provide dose-concentration or dose-exposure information for rational design of phase IIb/III trials. Additionally, exposure-response relationships can be explored with estimates of individual drug exposure from the preliminary population PK analysis. For the purpose of population PK characterization in patients, preliminary estimates of population parameters can be obtained, and the information is very helpful in developing optimal sampling strategy for large-scale population PK studies in phase IIb/III stage of the drug development. Some of these objectives can be achieved with phase I data, if these data are collected on patients.

If sufficiently large dose-exposure variability and drug effect variability are found in the early phases of clinical trials, then a large-scale population PK study may be desirable. A sufficient amount of PK samples can be collected from phase IIb/III trials and/or from stand-alone clinical studies designated exclusively to collect population PK information. Pooling data across different studies may provide enough diversity in patient characteristics, since usually study populations tend to be relatively homogeneous within study. The merit of stand-alone population PK studies is that important special patient subpopulation, if any, that normally would be excluded from the phase IIb/III clinical studies can be included. Stand-alone studies may also be convenient if simultaneous PK sampling would interfere with achieving the objectives of phase IIb/III studies. Early population PK results can be used to suggest subpopulations for more efficient treatment comparisons and/or a priori dose adjustment in later large scale efficacy/safety trials, and population PK data from these trials, in turn, can be used to define sub-populations with more confidence and/or to make new findings.

Population PK studies may be desirable even after drug approval for safety surveillance or marketing purposes. The scale and extent of the population study will depend on existing knowledge of PK characteristics among the patient population and the new needs for exploring the exposure-response relationships. For instance, if a significant safety problem occurs, then population PK results may help to determine whether the problem is related to elevated drug exposure due to certain patient characteristics and in turn identify new sub-populations that require a priori dose adjustment. New findings in population exposure-response relationships that differentiate the drug from

competitors may be used to support certain marketing claims.

The population PK strategy discussed above is a typical pathway of integrating population PK studies into different stages of drug development. In practice, population PK analysis can be used flexibly depending on properties of the drug and the stage of development. More thorough discussions on this topic can be found in Steimer et al. (1994), Vozech et al. (1996) and Williams and Ette (2000).

## 4 Issues in design and conduct of population pharmacokinetic studies

There are some prerequisites for a successful population PK analysis. The first requirement is a valid assay for the relevant analyte. The assay should be sensitive enough to detect concentrations well below those expected to be seen prior to dosing at steady-state. The assay should also be specific for the active moiety. In some cases the parent drug may not be the only active moiety or it might not even be the primary active moiety. Separate assays may be needed for more than one active metabolite.

The second requirement is a structural pharmacokinetic model usually developed from early phase I studies in which eight to twelve or more blood samples were collected to form concentration-time profiles from each of several subjects. While the model should be sufficiently complex to reasonably predict drug concentrations, it should still be simple enough even after the addition of several covariates to permit parameter estimation from the more sparsely collected samples typical of a population PK analysis. For this reason, in some cases, a simpler model might be used in the population PK analysis than was developed to fit the fuller concentration-time profiles, as Steimer, et al. (1994) recommended.

Most population PK analyses are done on data pooled from several clinical trials. The usual practice is to add population PK sampling as a secondary objective onto one or more phase II or later clinical studies in patients. Occasionally population PK data needed for analysis are collected from clinical studies conducted solely for that purpose. The study protocol(s) might call for pharmacokinetic samples to be collected from every subject, or a protocol might provide for a pharmacokinetic substudy in which samples are only collected from consenting subjects at certain study sites with the ability or interest in participating. In any case, sample collection for pharmacokinetic analysis cannot affect the subjects' prognoses, the power of the trial to meet its primary objectives, or otherwise seriously compromise the integrity of the clinical study.

### **Sampling Designs:**

Typically in a population PK study, a large number of patients are required to provide enough variability in patient characteristics, which include the demographic, pathophysiological and environmental factors. However, resource restrictions and/or clinical considerations often limit the amount of sampling that can be drawn per patient, so that only sparse blood sampling of these patients is permissible.

Several sampling designs have been proposed for population PK studies. The most commonly used designs are discussed in Sheiner and Benet (1985) as well as in the FDA population PK guidance. Some have called for a single pre-dose (or "trough") concentration to be drawn from each subject that has been dosed to a presumed steady-state. Although this single-trough screen design has the obvious advantage of simplicity for the subjects and investigators, it has the equally obvious fault of not providing adequate data for estimating intra-subject variability. For a little additional effort, a multiple-trough sampling design calling for several pre-dose concentrations from each subject would allow estimation of intra-subject variability. Trough designs are generally concerned with estimating one pharmacokinetic parameter (albeit usually the most important one), and in general they do not facilitate non-linear mixed effects modeling.

Another type of design is the full pharmacokinetic screen design, also called experimental population PK design. In full pharmacokinetic screening, sampling time points are not restricted to trough, and the number of samples for individual patients could range from single to a few. These sampling time points usually cover a meaningful span of the dosing interval. Full screening can take all kinds of flexible forms such as fixed sampling, random sampling and window sampling. In a fixed sampling design, the sampling times are taken from a given set of fixed time points. In a random sampling design, the sampling times are not controlled. They are completely up to clinical convenience. In a window sampling design, sampling times are random within a pre-specified range or ranges in the dosing interval. Although a fixed sampling scheme may be desirable for maximizing the statistical efficiency, it may be clinically inconvenient and result in poor compliance or unfeasibility. Random sampling, on the other hand, could be less efficient and could lead to poor data carrying insufficient information about some PK parameters of interest. It seems that window sampling is preferred in most practical situations.

Usually only limited resources are allocated for population PK studies. This requires efficient use of these resources to acquire maximum amount of useful information. In terms of study design, timing and number of samples affect directly how well the PK parameters can be estimated. For fixed sampling schemes, model based optimality criteria can be used to determine location of these time points. Literature in this area includes those of D'Argenio (1981), Landaw (1985) and D'Argenio (1990). For window sampling, locations and widths of windows can be chosen through, for example, statistical simulation. In any case, it should be pointed out that the best designs are not based solely on statistical optimality but also on practical considerations.

### **Clinical Monitoring and Data Management:**

Accurate clinical data are as important for a successful population PK analysis as an accurate assay for measuring drug concentrations. First, the times, routes, and sizes of the doses preceding sample collection, and the times at

which the samples are drawn must be accurately recorded. For many drugs, the timing and even the content of meals preceding the dosing and sample collection may also be relevant. Moreover, the number and timing of the sample collections should follow the protocol specifications, and procedures to handle the pharmacokinetic samples must be strictly followed. Biostatisticians, pharmacokineticists, and pharmacologists must convince the study monitors to prevent any clinical investigators from neglecting the data and procedures needed for the population analyses.

Once the data have been collected, it will be entered into one or more databases. Frequently, the drug concentrations are in a database separate from the clinical database containing the demographic and patient data. Therefore, the biostatisticians, pharmacokineticists, and pharmacologists planning the analysis need to involve their data management and clinical programming colleagues to plan and test procedures for the easy and accurate merger of the databases.

#### Coordination:

Inter-disciplinary cooperation is critical in the conduct of population PK studies. Particularly communication and education play significant roles in such complex process involving several parties with different backgrounds. All parties must have a clear understanding of the objectives of the population PK studies, especially the investigators of the phase II/III clinical trials and their staffers. Biostatisticians, pharmacokineticists, and pharmacologists responsible for the population PK study need to educate their clinical colleagues, especially those who are not familiar with the clinical pharmacology settings, about the importance of population PK objectives, and the PK sample handling and data collection procedures. During the clinical studies, the population PK activities should be closely monitored, so that any deviations or mistakes due to inexperience or negligence can be discovered and corrected in a timely fashion. The population PK scientists need to be updated about the progress or any problems occurring along the way. In addition, it is advantageous for the population PK scientists to convince the senior management about the benefits of the population analysis and obtain their support.

## 5 Statistical Issues

### 5.1 Population PK model specifications

Population PK models have two basic hierarchies: the intra-subject level model specification and the inter-subject level model specification. The intra-subject component consists of the structural model and the intra-subject error model, and is represented as follows:

$$y(t) = C(t; \beta) + \varepsilon(t),$$

where  $y(t)$  represents the observed concentration profile as a function of the time  $t$ ;  $C(t; \beta)$  represents the model-based underlying concentration profile, which usually is the solution of a compartmental linear kinetic system characterized by the PK parameter vector  $\beta$ ; and  $\varepsilon(t)$  represents

the intra-subject error process. The variability structure of the error process could be constant, proportional to the concentration level, or a combination of both.

Because population PK analysis normally relies on sparse individual data collected from a relatively large number of patients, the structural PK compartmental model usually is determined either outside the population analysis with frequently sampled PK data from individual healthy volunteers, or by the performance of the model to describe available data within the population PK analysis. Either way it should be noted that this structural model usually cannot be well-specified and validated within population PK analysis except in some special situations.

The inter-subject component is the statistical model to explain variabilities in PK parameters among the patient population. For subject  $i$ , the subject-specific PK parameters  $\beta_i = (\beta_{i1}, \beta_{i2}, \dots, \beta_{ip})$  can be conventionally modeled as follows:

$$\begin{aligned} \beta_{i1} &= \bar{\beta}_{i1} e^{\eta_{i1}}, \\ \beta_{i2} &= \bar{\beta}_{i2} e^{\eta_{i2}}, \\ &\dots \\ \beta_{ip} &= \bar{\beta}_{ip} e^{\eta_{ip}}, \end{aligned}$$

where  $(\bar{\beta}_{i1}, \bar{\beta}_{i2}, \dots, \bar{\beta}_{ip})$  are typical values of parameters given the  $i$ -th subject's covariates. The random effect vector  $\zeta_i = (\eta_{i1}, \eta_{i2}, \dots, \eta_{ip})$  has mean  $\mathbf{0}$  and a variance-covariance matrix  $D$ . The residual term  $\eta_i$  represents the unexplained variability in the PK parameters.

Quantification of both the intra-subject variability and the inter-subject unexplained variability helps to assess the clinical values of the population PK models in predicting individual drug exposure and to decide the level of drug exposure monitoring needed in normal clinical settings.

### 5.2 Estimation approaches

Different estimation approaches are available to fit population PK models. The major ones are the two-stage approach, the parametric non-linear mixed effects (NLME) approach, the non-parametric maximum likelihood approach (NPML) and the Bayesian approach. Comprehensive discussions of these general statistical methodologies of non-linear repeated measurement analysis and their applications in the population analysis can be found in two outstanding books, one by Davidian and Giltinan (1995) and the other by Vonesh and Chinchilli (1997).

The two-stage approach includes primarily the standard two-stage (STS) method, the global two-stage (GTS) method and the iterated two-stage method (ITS). They are discussed in Steimer et al. (1984). In a two-stage method, subject-specific PK parameters are estimated separately with individual data, and then statistical regression is done on these estimates of subject-specific parameters. Two-stage methods are intuitive and easy to implement, but there are some general criticisms to them. Firstly, the first stage estimates of subject-specific parameters are unavailable for those subjects who do not have enough samples to allow for such estimation. Data from those subjects have to be excluded from the analysis. Secondly, the estimates of individual PK parameters and their covariance matrices

from the first stage are treated as fixed data in the second stage. These values are subject to estimation error. Particularly the estimates of covariance matrices are usually based on asymptotics and hence may be unreliable. Thirdly, two-stage methods tend to be less statistically efficient compared to single stage approaches such as the NLME approach.

The NLME approach is considered the current gold standard. Unlike the two-stage methods, the NLME approach handles repeated measurement data from all subjects in a single stage, and all data can be utilized to estimate the population parameters. Furthermore, for subjects who do not have enough data to perform individualized estimation, strength can be borrowed from other subjects to obtain estimates of individual PK parameters. The most popular algorithms of the NLME approach are the first-order algorithms (available in NONMEM<sup>®</sup>) and conditional first-order algorithms (available in both NONMEM<sup>®</sup> and SPLUS<sup>®</sup>). Both of them are linearization algorithms in which the original statistical model is approximated by one that is linear in terms of the random effects. Variations of linearization algorithms are discussed in a number of publications such as Beal (1984), Beal and Sheiner (1985, 1992-1998), Lindstrom and Bates (1990) and Vonesh and Carter (1992). Although linearization algorithms have many successful applications in population analysis, it should be noted that they may provide unreliable results if the unexplained (by the model) variability in PK parameters is large.

The Bayesian approach adds a third hierarchy on top of the usual population PK models. It imposes Bayesian priors to all model parameters including regression coefficients and variance-covariance parameters. The posterior mode, moments, probabilities, and credible intervals are obtained for Bayesian inferences. The numerical procedure makes use of Markov chain Monte-Carlo (MCMC) algorithms such as the Gibbs sampler. A popular computer program for general Bayesian application with the Gibbs sampler is the BUGS software developed by the Medical Research Council Biostatistics Unit in Cambridge, UK. A good example of the application of Bayesian methods in population PK analysis is given by Wakefield (1996). Bayesian approach allows incorporation of prior knowledge about model parameters. However the sensitivity of Bayesian estimates with respect to choices of prior distributions may not be easy to assess.

The NPML approach (Mallet, 1986) makes no assumption about the random effect distribution. Instead it takes the family of all simplex distributions which put probability mass at no more than  $n$  points in the random effect space, where  $n$  is the number of subjects in the data. The joint statistical likelihood is then maximized over the model parameters and the  $n$  points. The NPML approach requires less modeling assumptions. However it can be much more computer intensive than the NLME algorithms, since the numerical parameter space grows in an order of  $n$ . The stability of numerical optimization algorithms in such a situation is not completely understood. A variation of the NPML approach is the maximum likelihood procedure

with a smooth random effects density proposed by Davidian and Gallant (1993).

### 5.3 Model building procedures

The most popular model building procedures are based on the NLME approach. The FDA guidance to the industry on population PK studies provides a good discussion of recommended general procedures and many reference articles.

Typically an exploratory analysis is first carried out with the empirical Bayesian estimates of subject-specific PK parameters obtained from a population PK model fitted without covariates. The purpose of this analysis is to check modeling assumptions, explore the correlation among covariates, and perform an initial screening of these covariates. In addition, by regressing those estimates of subject-specific PK parameters on candidate covariates using flexible non-parametric methods such as the generalized additive models (GAM), appropriate parametric function forms of relationships between these parameters and potential prognostic factors can be selected.

To explain the variability in subject-specific PK parameters, a non-linear mixed effects model selection procedure is carried out with covariates selected from the list of the candidate potential prognostic factors. To reduce the chance of spurious findings, usually a small inclusion significance level such as 0.005 or 0.001 is used in the model selection procedure. The reliability of the final model can be checked with diagnostic procedures such as standard diagnostic plots, sensitivity analysis for robustness and case deletion diagnostics.

According to the FDA guidance to the industry on population PK, if the results of such analyses are intended to support labeling claims, then the population PK model needs to be validated. There are two types of validation procedures: external validation and internal validation. In an external validation, the predictive performance of the model is checked against data from a new study. In an internal validation, the existing population PK database can be split or resampling techniques such as bootstrap and cross-validation can be applied to create learning data sets and test data sets. The whole model building procedure (not just the final model fitting) is repeated with the learning data sets, and prediction is made into and compared against the test data sets. With either validation procedure, validation can be done through the prediction of concentrations or through the prediction of model parameters.

## 6 Summary and Discussion

Population PK represents a tremendous opportunity to systematically obtain valuable information about sources and correlates of PK variability in the patient population, and to refine the current clinical development practice. Its scientific foundation is well established, and its values are becoming more widely recognized. It may be particularly useful where the target population is a special population (e.g. pediatrics) for which sampling is highly limited, where the target population is heterogeneous enough in terms of drug exposure, where the drug has narrow thera-

peutic window, and where there is little knowledge about the compound class (e.g. first in class). It can significantly enhance knowledge of the population clinical pharmacology profile of a drug by a much more thorough understanding of how patient characteristics affect drug bioavailability. This will help to identify patient subpopulations for a priori dosage adjustment that can be included in the drug label, and even to achieve individualized dosing regimens to maximize the benefit. In addition, population PK information can help evaluate/re-evaluate outcomes (both efficacy and safety) of phase II/III clinical studies to identify subpopulations for which drug responses are different. Integration of population PK into clinical development may help reduce the sizes of phase I programs and provide very useful information for the rational design of targeted and efficient large scale clinical studies and post-approval surveillance/marketing studies, and hence results in significant savings in terms of both time and resources for sponsors of drugs and biologics.

Despite its increasing popularity, it should be pointed out that population PK should not and will never completely replace the traditional PK studies. For one thing, the basic PK properties that the population analysis depends upon, such as the drug's basic kinetics, have to be derived from early human studies where frequent concentration-time profile data are collected. For another, if a drug is known to have hepatic and/or renal metabolic pathways, the critical renal and/or hepatic impairment studies may have to be done separately for confirmatory evidence. Population PK is not appropriate for all drugs. The presumptions for successful application of population PK are that there are well-characterized concentration-time profile and reasonably well-defined exposure-effect correlations, and that there is sufficient drug effect variability among the target population. The effect could be either efficacy or toxicity or both. For drugs which do not meet these presumptions, there is either no reliable basis for population analyses or no PK variability to study with, or the PK variability plays little or no role in clinical responses. Lastly it is important to keep in mind that population PK is exploratory in nature. The study results and interpretations are subject to shortfalls associated with all exploratory analyses. It is likely that some important factors are left undiscovered, whereas spurious findings might still occur regardless of how carefully the analysis is carried out. Nonetheless, all these problems will not reduce the values of population PK in the drug development.

Population PK, especially if used in conjunction with the exploration of exposure-response relationships, will play more and more significant roles in the drug development process.

## References

- Beal, S.L. (1984). "Population pharmacokinetic data and parameter estimation based on their first two statistical moments." *Drug Metabolism Reviews*, 15, 173-193.
- Beal, S.L. and L. B. Sheiner (1985). "Methodology of population pharmacokinetics." *Drug Fate and Metabolism: Methods and Techniques*, Vol. 5, Garrett, E.R. and Hirtz, J. (Eds.), Chapter 4, 135-183. New York: Marcel Dekker.
- Beal, S.L. and L. B. Sheiner (eds) (1992-1998). *NONMEM User's Guides*. NONMEM Project Group, University of California, San Francisco.
- D'Argenio, D. Z. (1981). "Optimal sampling times for pharmacokinetic experiments." *Journal of pharmacokinetics and biopharmaceutics*, 9(6), 739-756.
- D'Argenio, D. Z. (1990). "Incorporating prior parameter uncertainty in the design of sampling schedules for pharmacokinetic parameter estimation experiments." *Mathematical Biosciences*, 99, 105-118.
- Davidian, M. and A. R. Gallant (1993). "The nonlinear mixed effects model with a smooth random effects density." *Biometrika*, 80, 475-488.
- Davidian, M. and D. M. Giltinan (1995). *Nonlinear Models for Repeated Measurement Data*. Chapman and Hall.
- Gibaldi, M. and D. Perrier (1982). *Pharmacokinetics (second edition)*. Marcel Dekker.
- Landaw, E.M. (1985). "Optimal design for individual parameter estimation in pharmacokinetics," in Rowland, M. et al. (eds), *Variability in Drug Therapy: Description, Estimation, and Control*, Raven Press, New York, 187-200.
- Lindstrom, M.J. and D. M. Bates (1990). "Nonlinear mixed effects models for repeated measures data." *Biometrics*, 46, 673- 687.
- Mallet, A. (1986). "A maximum likelihood estimation method for random coefficient regression models." *Biometrika*, 73, 645-656.
- Rowland, M. and T. N. Tozer (1995). *Clinical pharmacokinetics concepts and applications (third edition)*. Lea and Febiger.
- Sheiner, L.B. and L. Z. Benet (1985). "Premarketing observational studies of population pharmacokinetics of new drugs." *Clinical pharmacology and therapeutics*, 38(5), 481-487.
- Steimer, J.L., A. Mallet, J. L. Golmard and J. F. Boisvieux (1984). "Alternative approaches to estimation of population pharmacokinetic parameters: comparison with the nonlinear mixed-effect model." *Drug Metabolism Reviews*, 15, 265-292.
- Steimer, J.L., S. Vozeh, A. Racine-Poon, N. Holford and R. O'Neill (1994). "The population approach: Rationale, methods, and applications in clinical pharmacology and drug development" (Chapter 15), in Welling, P.G. and L. P. Balant (eds.), *Pharmacokinetics of Drugs* (Handbook of Experimental Pharmacology), Springer-Verlag. 110, 404-451.
- US Food and Drug Administration (1999). *Guidance for Industry: Population Pharmacokinetics*.

Wakefield J. (1996). "The Bayesian analysis of population pharmacokinetic models." *Journal of the American Statistical Association*, 91(433), 62-75.

Williams, P.J. and E. I. Ette (2000). "The role of population pharmacokinetics in drug development in light of the Food and Drug Administration's 'Guidance for Industry: Population Pharmacokinetics.'" *Clinical Pharmacokinetics*, 39(6), 385-395.

## Discussion of "A 20,000 Foot Overview of Population Pharmacokinetics and Its Applications in Drug Development"

**Jerry R. Nedelman,  
Chyi-Hung Hsu,  
Peiming Ma,  
and William M. Sallas**

*Novartis Pharmaceuticals, East Hanover, NJ 07936*

### Congratulations

We congratulate the authors (henceforth referred to as GSR) on a well organized and well written introduction to population pharmacokinetics. Their paper provides thoughtful coverage of the what, why, when, and clinical and statistical how of the topic. From 20,000 feet, one cannot resolve many differences in the principles and practice of population PK between Princeton and East Hanover. Nonetheless, for the sake of scholarly discourse we will address a few features of the scientific landscape visible from that high altitude.

### Definitions

The definition of population PK provided by GSR might be supplemented by other definitions that capture related or more restrictive senses of the term. GSR define population PK as "the study of the sources and correlates of variability in drug concentrations among individuals who are the target population receiving clinically relevant doses of the drug of interest" (GSR, Section 1). But then how can one think of applying population PK to preclinical evaluations (van Bree et al, 1994; Ette et al, 1995)?

The answer is that population PK has also come to mean the application of nonlinear mixed-effects modeling to any pharmacokinetic data sampled sparsely such that AUC and C<sub>max</sub> cannot be computed for each individual (even non-human) using that individual's data alone. Indeed, population PK has in some minds become synonymous with the

software NONMEM. The name of that software sometimes even gets used as a verb, as in "would you please NONMEM this data".

The FDA Guidance offers another definition of population PK that explicitly contains the association with hierarchical modeling: "These models, their parameter values, and the use of study designs and data analysis methods designed to elucidate population pharmacokinetic models and their parameter values, are what is meant by population pharmacokinetics" (FDA, 1999, p. 3).

### Reasons

GSR list the reasons for doing population PK in Section 2 of their paper. Most of those reasons presume the objective of characterizing the "dose-exposure relationship". Bluntly, who cares? Is characterization of "the sources and correlates of variability in drug concentrations" an important end in itself?

Interestingly, the very first sentence of the FDA Guidance suggests that population PK is only a means to an end: "This guidance makes recommendations on the use of population pharmacokinetics in the drug development process to help identify differences in drug safety and efficacy among population subgroups" (FDA, 1999, p.1).

The implications of this debate are more than philosophical. Pharmaceutical companies must decide whether to allocate resources for population PK. Although as a fraction of the overall cost to bring a drug to market the cost of population PK may be small, for the involved departments, notably bioanalytics, pharmacokinetics, and statistics, the impact on resources may be substantial.

Some purists have a simple answer to the question of why and when to do population PK. Do it always, because clinical trials to support registration provide the last, best opportunity to intensively study the PK of the compound in conditions that closely approximate clinical practice. It is a scientific, moral imperative.

Some not-so purists reach the same plan of action for a different reason. Do it always, because the FDA expects it.

The more hard-nosed might demand a cold calculation in terms of return on investment. GSR concede in their final section that "Population PK is not appropriate for all drugs". Not only do they recognize the need for a well-characterized structural PK model and sufficient interpatient variability to make characterizing variability worthwhile, but they also cite the need for "reasonably well-defined exposure-effect correlations", where by "effect" is meant either efficacy or toxicity. The FDA Guidance puts it thusly: "Population modeling is most likely to add value when a reasonable a priori expectation exists that intersubject kinetic variation may warrant altered dosing for some subgroups in the target population. Likely circumstances would include (1) when the population for which the drug is intended is quite heterogeneous and (2) when the target concentration window is believed to be relatively narrow" (FDA, 1999, p. 5). Thus, population PK is appropriate when it might have an impact on dosing to optimize efficacy and safety.

The trouble with these kinds of statements is their fuzziness. What is sufficient? reasonably? quite? relatively?

In their Section 3, GSR provide a relatively sufficient strategy that is quite reasonable. Full steam ahead through Phase II. Identify the structural and intrasubject-variability models in Phase I. From the patients studied in Phase II, examine the major factors that might affect the dose-exposure relationship, e.g., body size, age, sex, and important comedications, to the extent that the patient pool allows. From these results decisions can then be made about the potential value of continuing population PK efforts in Phase III. Partly siding with the purists, we propose that the burden of proof be on those who argue against continuing. Surprises may still be lurking in the more heterogeneous, larger Phase III patient pool. But at least decision makers should be aware that the option to cease further population PK activity is legitimate.

## Traditions

GSR describe traditional PK as a Phase-I activity. Nomenclature may vary, but traditional PK studies can occur at the same time as Phases II and III are being conducted. Certainly, traditional PK studies in children would generally occur after Phase I, and sometimes much later if IRBs request demonstration of efficacy in adults before exposing children. Other traditional PK studies could also be conducted after Phase I if their results would have little impact on the conduct of Phase II or III, or if their deferral made strategic sense.

Traditional PK does have its advantages. Such studies generally can be run quickly, allowing rapid assessment of needs for dosing differences, e.g., in elderly vs young, or fed vs fasted states. The composition of the patient sample can be controlled, as can the collection of the PK data; the data are fully experimental, rather than mostly observational, as in population PK. One needs to think about what traditional PK studies and what population PK studies to run in each phase, in order to provide needed input at the right time. Also one needs to consider what traditional PK studies to pool into a population pharmacokinetic analysis.

## Covariates

In their Section 5.1, GSR might have made the dependence on covariates more explicit. It is a terse statement hiding useful structure to say merely that  $\bar{\beta}_{ij}$  is the typical value of the  $j$ 'th parameter for the  $i$ 'th subject given the  $i$ 'th subject's covariates. Although Section 5.3 does refer to model-building procedures for finding how  $\bar{\beta}_{ij}$  might depend on covariates, we would like to present an approach that we commonly use for incorporating and screening covariates, as might be summarized in the methods section of a report:

Let  $x_{hi}$  be the  $h$ 'th covariate for the  $i$ 'th subject. The covariates  $x_{hi}$  are incorporated into NONMEM models generally as follows. First, suppose  $x_{hi}$  is a continuous covariate. A standard or reference value of  $x_{hi}$ , denoted by  $x_{h0}$ , is selected. Next suppose  $x_{hi}$  represents a dichotomous covariate – e.g., gender. Then  $x_{hi}$  is assigned the numerical

value 1 for females, 0 for males. In general, categorical covariates with  $k$  categories are assigned  $k-1$  dichotomous variables:  $x_{hi,1}, \dots, x_{hi,k-1}$ . Then  $x_{hi}$  is modeled as affecting  $\bar{\beta}_{i1}$ , the typical value for clearance, via:

$$\bar{\beta}_{i1} = \theta_1 \times \dots \times z_{hi} \times \dots$$

where

$$z_{hi} = (x_{hi}/x_{h0})^{\theta_{h1}}$$

if  $x_{hi}$  is continuous, and

$$z_{hi} = \theta_{h1}^{x_{hi}}$$

if  $x_{hi}$  is dichotomous, and

$$z_{hi} = \theta_{h1,1}^{x_{hi,1}} \times \dots \times \theta_{h1,k-1}^{x_{hi,k-1}}$$

if  $x_{hi}$  is categorical with  $k$  categories. The  $z_{hi}$  are screened for inclusion in models using graphical methods and stepwise selection procedures (Sallas and Nedelman, 1997).

## Validations

GSR claim that the FDA Guidance demands validation of the population PK model "if the results of such analyses are intended to support labeling claims" (GSR, Section 10). In fact, the FDA Guidance may be interpreted as being somewhat more liberal by distinguishing stability from validation.

Recognizing that validation must be application specific and that as yet no consensus exists on what validation methods are appropriate, the FDA Guidance restricts the discussion of validation to its "predictive performance aspect" (FDA, p. 16). This is the aspect of validation also described by GSR.

Stability assesses the variability of the inferred parameters of the model over repeated bootstrap resampling of subjects in the analysis data set (Ette, 1997). It may be considered a test of model robustness to outlying data.

According to the FDA Guidance (FDA, p.16), if the labeling claims involve dosage recommendations based on the model, then the model should be validated for predictive performance. But if the labeling claims involve only descriptive information about PK variability, then the model may be tested for stability only.

## Additional references

Ette, E.I. (1997). "Stability and performance of a population pharmacokinetic model." *Journal of Clinical Pharmacology* 37, 486-495.

Ette, E.I., C.A. Howie, A.W. Kelman, and B. Whiting (1995). "Experimental design and efficient parameter estimation in preclinical pharmacokinetic studies." *Pharmaceutical Research* 12, 729-737.

Sallas, W.M. and J.R. Nedelman (1997), "Selection of covariates in population pharmacokinetic models", *Computing Science and Statistics* 29, 487-496.

Van Bree, J., J. Nedelman, J.-L. Steimer, F. Tse, W. Robinson, and W. Niederberger (1994). "Application of sparse sampling approaches in rodent toxicokinetics: a prospective view." *Drug Information Journal* 28, 263-279.

## Rejoinder to "Discussion of 'A 20,000 Foot Overview of Population Pharmacokinetics and Its Applications in Drug Development'"

**Z. Gary Ge, Robert A. Smith,  
and Ralph H. Raymond**

*Bristol-Myers Squibb Pharmaceutical Research Institute,  
Princeton, NJ 08543-4000*

We thank our colleagues in Novartis (henceforth referred to as NHMS) for their compliments and valuable points. We would like to take this opportunity to clarify some of our positions and throw in some additional arguments.

We present a narrow definition of population PK because most population PK applications and the FDA guidelines on population PK are concerned with the use of this approach in human studies. However, we are receptive to a broader definition to cover pre-clinical animal PK studies as well. It should be pointed out that the word "population" has different connotations in human and animal studies, and in drug development the population of interest is the target patient population. Nonetheless, the statistical methodologies are the same, hence from the statistical point of view, it makes sense to generalize the concept of population PK to the application of nonlinear mixed-effects modeling to any pharmacokinetic data sampled sparsely.

We do not question that the ultimate goal of collecting population PK information is to help identify differences in drug safety and efficacy among patient subpopulations. To achieve this end, it is desirable to characterize both the dose-exposure relationship and the exposure-effect relationship. Population PK approach may help us to identify the factors which alter the dose-exposure relationship, whereas PK/effect type of analyses may help us to explore the exposure-effect relationship. Population PK alone cannot do both. The direct objective of the population PK approach is therefore the characterization of the sources and correlates of variability in drug exposure. This characterization is in itself an important end. Not only can it provide the basis for dosage adjustment recommendations when the PK/effect findings justify such needs, but it can also help re-evaluate clinical trial outcomes and help ratio-

nally design further targeted and more efficient clinical studies. The former feature is more appealing from the scientific and regulatory perspectives, and the latter more appealing to the drug sponsors.

Regardless of the original mindsets of purists, not-so-purists and the hard-nosed, population PK should not be viewed only as a means to fulfill regulatory requirements or as a scientific, moral imperative. It can also be proactively used as a powerful tool to help expedite and enhance the overall clinical research and development including both clinical pharmacology and clinical safety/efficacy investigations. It is true that the population approach may be a substantial logistic undertaking for the parties involved. However, if we put this into the big picture of the overall clinical development, the overall benefits brought by successful applications of population PK for suitable drug candidates may far more than offset the additional costs. It is the duty of population PK scientists (including population PK statisticians) to educate our colleagues and senior management about the high potentials of the population PK approach. With their support, enough resources will be allocated.

To clarify our nomenclature, what we meant by clinical Phase I program includes early clinical safety, human drug metabolism / pharmacokinetics and human clinical pharmacology studies such as single-dose ascending, multiple-dose ascending, ADME, bioequivalence / bioavailability, food effect, renal / hepatic impairment, age-gender, drug interaction and dose-proportionality studies. Although it is conventional to divide clinical development of a drug into Phases I-III, this classification by no means establishes the order of study execution.

Traditional PK studies have all the advantages that NHMS noted. We did not highlight the benefits of traditional studies in our article, since we intended to emphasize that the population PK approach has its exceptional values in addressing some important issues that the traditional approach cannot adequately address, such as PK in the relevant population (patients versus normal healthy volunteers) and multi-factor interactions. We fully agree with NHMS that the appropriate use of traditional approach and/or the population approach at different development stages can provide desired information at the right time to support decision making. As we pointed out in our article, the population approach is not likely to completely replace the traditional approach.

NHMS provides an example on how the typical values of the population parameters may depend on relevant clinical covariates. This example fills in between the ground level and the 20,000 foot altitude and gives the readers something more tangible. It should be mentioned that the specific form of covariate equations in Sallas and Nedelman (1997) is one of the conventional forms in the population PK practice, and usually there are no compelling reasons why these equations must take such conventional forms. Practitioners in this field tend not to pay as much attention to the forms of the covariate equations as to the covariate selection, as long as the specific forms in use do not seem unreasonable or farfetched. Sallas and Nedelman (1997)

discussed a good practical strategy for covariate selection when the computing resource requirements for classic model selection procedures cannot be met.

We agree with NHMS on when population PK models should be validated. "Labeling claims" in our article actually meant dosage adjustment recommendations. The stability of population PK models, however, refers to "replication stability for inclusion of covariates in a model" (Ette, 1997 and Gifi, 1990). Stability assessment may help identify potential spurious associations that some covariates bring, and check the "robustness" of covariate selection to a few "influential" data.

## Acknowledgments

The authors would like to thank the editors for their valuable comments.

## Additional references

Ette, E.I. (1997). "Stability and performance of a population pharmacokinetic model." *Journal of Clinical Pharmacology* 37, 486-495.

Gifi, J. (1990). *Nonlinear multivariate analysis*. Chichester: Wiley.

Sallas, W.M. and J.R. Nedelman (1997), "Selection of covariates in population pharmacokinetic models", *Computing Science and Statistics* 29, 487-496.

## Section News

### Letter from the Chair

**Jeff Meeker**

*Chair*

The leadership of the Biopharmaceutical Section has often been called an old-boys club, and in many ways, that image is justified. The "boy" part is becoming less so - there are currently 5 women of the 15 on the Executive Committee. The question now is "old". Unquestionably, part of it is whom you know. However, another part, which also increases who you know, is participation in Biopharmaceutical Section activities, i.e., volunteer.

Unfortunately, we don't deal with volunteers well. The obvious place to get volunteers is JSM and last year, when I was making appointments, many people gave me their name and/or card. I did appoint some. Other names I passed on, particularly those who were interested in helping in the FDA/Biopharmaceutical Section Joint Workshop.

Perhaps the biggest job of the Chair-elect is to make appointments. Each year, the Chair-elect appoints two at-large members of the Executive Committee, a Workshop Chair, an associate editor of the Biopharmaceutical Report, and a member of the Fellows Committee. One objective of Bob Small, our current Chair-elect, is to make sufficient appointments to the Student Paper Committee and the Membership Committee to put those two committees on a three year rotation. Future Chair-elects will then appoint one new member to each. The Webmaster and Mail List Coordinator, while appointed each year, are often reappointments due to the technical requirements of these two positions. A Round Table Coordinator and Contributed Paper Chair are usually appointed from the current Executive Committee members. At the Spring Executive Committee meeting, we decided to select the Workshop Chair a year ahead to ease planning, i.e., a Workshop Chair-elect.

The Committees may be filled out by the Committee chairs. For instance, Greg Enas, this year's symposium co-chair, appointed his own Committee. Anne Cross, chair of the Contributed Paper Committee, Tom Bradstreet, chair of the Student Paper Committee, and David Carlin, chair of the Membership Committee have also made appointments to their committees. Anyone interested in those committees could contact the chair directly.

We often need other help. For example, at JSM we need people to help pass out and collect the forms for the Contributed Paper awards. Anyone interested can contact Anne Cross. We also need people to chair contributed paper sessions at JSM. The Program Chair makes these selections. Unfortunately, they are made early in the year, and JSM is too late. The same is true of Round Tables leaders at JSM, selected by the Round Table Coordinator.

Unfortunately, Section Officers (i.e., me this year) have generally not done a good job responding to volunteers.

When Bob Davis was Chair, he developed a list which he then distributed at the beginning of each Executive Committee meeting. He encouraged us to contact those on the list when we needed help. I intend to restart that list so we have a record of those who are interested and don't lose much needed help. I will have a pad of paper at the front table during the Biopharmaceutical Section reception and business meeting. If you are willing to help, please look for that pad and add your name, how we can contact you (e-mail or phone), and what you are interested in doing. For those not going to JSM, you can e-mail that information to either Bob Small (bob@twocrows.com) or me (jeff.meeker@bms.com).

For those of you going to JSM, I encourage you to attend the Biopharmaceutical Section mixer and meeting on Tuesday evening, 5:30-7:00. The business part will be kept brief to allow as much interaction among Section members as possible.

---

### Executive Committee Meeting Monday, March 26, 2001 Charlotte, NC

**Jeff Meeker**

*Chair*

- 2001 ENAR - The Section provided two invited sessions and one theme session
- 2001 JSM - The Section has five invited sessions (a record for us), six topic contributed sessions, nine regular contributed sessions, and 10 luncheon round tables.
- 2000 FDA/Industry Workshop. Six publications based on presentations at the workshop have been submitted to the DIA Journal. Papers in future years can be published in our Proceedings
- 2001 FDA/Industry Workshop. Program details for the workshop have been finalized. There is a modest increase in registration fees. The Executive Committee decided that workshop chairs will be appointed a year in advance so the chairs develop experience and can start the process well in advance.
- 2002 ENAR - The deadline for proposals for sessions is May 31, 2001.
- 2002 JSM - The theme will be "Statistics in an Era of Technological Change". Proposals for sessions are needed by July.
- Proceedings - 33 Papers are included in the 2000 Biopharmaceutical Section Proceedings.
- The Section business meeting will be 5:30-7:00 on Tuesday, August 7, at JSM.

## FDA/INDUSTRY WORKSHOP

**Peter Lachenbruch and Gregory Enas**

The 4th annual FDA/Industry Workshop for 2001 will be held on September 24 – 25 at the Hyatt Regency in Bethesda, Maryland. The previous workshops have been very successful and are cosponsored by the Biopharmaceutical Section of the American Statistical Association and the FDA Statistical Association. This two-day meeting offers a chance to exchange views with a broad range of people from the Food and Drug Administration, the pharmaceutical industry, academia, and others interested in drug development and related topics.

The theme for this year's workshop is "The Information Revolution - Who's Mining the Store?"

The first day includes plenary sessions on "Strategic Planning for Substantial Evidence", "E-Predictions, e-Design, e-Analysis", "Causal Inference: Anything but Casual", and "Experimental Studies: Ethical Norms and Fraud".

The second day will be composed of parallel sessions designed as workshops. Speakers will set the stage for the discussion and then small groups based on disciplines and/or interests will be formed. Attendance in each session will be limited so that all sessions have enough participants to engage in good discussions.

The morning choices are "Safety Evaluation", "Choice of Control Group for Non-Inferiority Trials", "Issues in Design and Analysis of Diagnostic Clinical Trials", and "Current State of the Art in HRQoL Measurement and Future Directions".

The afternoon choices will include "Genomic Statistics in the Regulated Medical Products Industry", "Informatively Censored Longitudinal Studies", "Flexible Designs", and "Bridging Strategies".

In the late afternoon there will also be an additional special interest parallel session. The two topics of choice are "Statistical Issues with Medical Devices" and "Analysis of Mixed Models".

Registration will begin in July. For more information, please contact Linda Minor of the Meetings Department at [meetings@amstat.org](mailto:meetings@amstat.org) or 703-684-1221 x148.

## Continuing Education for the 2002 JSM in New York City

**Len Oppenheimer**

The Biopharmaceutical Section would like to sponsor several Continuing Education courses at the Joint Statistical Meetings in New York City on August 11 - 15, 2002. If you would like to teach a course or have suggestions with respect to course topics that you a/o other Biopharmaceutical Section members would be interested in attending, please send them to Len Oppenheimer. I can be reached as follows: [Leonard\\_Oppenheimer@merck.com](mailto:Leonard_Oppenheimer@merck.com); 732-594-5490; Merck & Co., P.O. Box 2000, Rahway, NJ 07065.

# Annual FDA/Industry Statistics Workshop

September 24-25, 2001 • Bethesda Hyatt • Bethesda, MD

"The Information Revolution - Who's Mining the Store?"

Although the Workshop is sponsored by the Biopharmaceutical Section of the American Statistical Association and the Food & Drug Administration, we encourage attendance by our non-statistician colleagues in the medical, regulatory and data management areas.

**Location:** The Workshop will be held at the Hyatt Regency Bethesda, conveniently located on Metro Rail (Red Line) just six miles from the U.S. Capitol.

**Hotel Reservations:** Hotel rooms at the Hyatt Regency Bethesda are available at the single or double rate of \$170 plus tax. To make reservations, please call +1 301-657-1234 or 1-800-233-1234 and ask for the group rate for the "FDA Workshop 2001". These rates are available from the Hyatt Regency until August 23, 2001. Hotel rooms are also available at the Holiday Inn Bethesda at a rate of \$119 plus tax. Call +1 301-652-2000 and ask for the "American Statistical Association" group rate. These rates are available from the Holiday Inn until August 24, 2001. There are a limited number of hotel rooms available at the group rate. Make your reservations early.

**For information** contact ASA Meetings Department, 1429 Duke Street, Alexandria, VA 22314, phone +1 703-684-1221 ext. 148, fax +1 703-684-8069, email: [meetings@amstat.org](mailto:meetings@amstat.org).

## Monday, September 24, 2001

8:00am **Continental Breakfast**

8:30am **Welcome** — Greg Enas (Eli Lilly), Anna Nevius (FDA)

8:45am **Plenary Session I**

"Strategic Planning for Substantial Evidence"

**Chairs:** Ronald W. Helms (Rho), Aloka Chakravarty (FDA)

1. "Design Strategies for Phase II through III: The Traditional Approach Compared to New Strategies Using Fewer, Larger Studies With Multiple Intermediate Analyses" - Ronald W. Helms (Rho), Katherine L. Monti (Rho), Dennis D. Wallace (Rho), Karen L. Kesler (Rho)
2. "Meta-Analysis in Global Regulatory Submissions" - Phil Poole (Pfizer)
3. "Strategic Planning Issues: A FDA Reviewer's Perspective" – Stan Lin, (FDA)

10:15am Break

10:45am **Plenary Session II**

"e-Predictions, e-Design, e-Analysis"

**Chairs:** David Stock (BMS), Stella Machado (FDA), Steve Wilson (FDA)

1. "Predicting Human Safety Data: Screening and Computational Approaches" - Grushenka H.I. Wolfgang (ddplatform), Dale E. Johnson (ddplatform)
2. "Application of Computer Assisted Trial Design (CATD) to Better Design and Interpret Clinical Trials" Dan Weiner (Pharsight)

12:15pm **Lunch on your own**

1:30pm **Plenary Session III**

"Causal Inference: Anything but Casual"

**Chairs:** Cathy Melfi (Eli Lilly), Gene Pennello (FDA)

1. "Missing Data Sensitivity Analysis: A Case Study" - Kinley Lantz (University of Minnesota)
2. "Inference From Multiple Studies" - Chuck Anello (FDA)
3. "Getting More Information From Complex Randomized Experiments" - Donald Rubin (Harvard)

3:00pm Break

3:30pm **Plenary Session IV**

"Experimental Studies: Ethical Norms and Fraud"

**Chairs:** Ram Suresh (Schering-Plough), Peter A. Lachenbruch (FDA),

**Panel Discussion:** Susan Ellenberg (FDA), Samuel Heft (Schering-Plough), Peter A.Lachenbruch (FDA), Victor DeGruttola (Harvard)

5:00pm **Reception at Fellini's**

6:00pm **Dinner on your own**

## Tuesday, September 25, 2001

8:00am **Continental Breakfast**

8:30am **Parallel Sessions I**

*Pick one of the following sessions. These sessions allow for small group discussion following the speakers presentations. A break is included around 2:00pm  
These sessions include a break for 20 minutes around 9:45AM*

### A. Safety Evaluation

**Chairs:** Greg Wei (Pfizer), Yi Tsong (FDA)

1. "The Role of Statistics in Nonclinical Safety Evaluation" – Wherly Hoffman (Eli Lilly)
2. "Statistical Methods and Interpretation of Data in Special Populations" – Timothy H Montague (GlaxoSmithKline)
3. "Model-Based Correction to QT Interval for Heart Rate for Assessing Mean QT Interval Change Due to Drug Effect" – Greg Wei (Pfizer)
4. "Statistical Issues in Safety Evaluation" – George Rochester (FDA)
5. "The Role of FDA Postmarketing Drug Safety Surveillance on Liver Events" – Min Chen (FDA)

(continued)

## B. Choice of Control Group For Non-Inferiority Trials

**Chairs:** Devan Mehrotra (Merck), Chuck Anello (FDA),

1. "Choosing the Non-Inferiority Margin – Delta: How Creative Can It Be" - Irving Hwang (Harvard)
2. "Noninferiority is Not Enough" - Janet Wittes (Statistics Collaborative)
3. "Clinical Trial Control Groups: The Great Debate on Ethics" - Susan Ellenberg (FDA)

**Discussant:** Steve Snapinn (Merck)

## C. Issues in the Design and Analysis of Diagnostic Clinical Trials

**Chairs:** John Castellana (Berlex) , Mike Welch (FDA)

### Session I

1. "Designing Clinical Trials with Diagnostic Endpoints"- Mike Welch (FDA)
2. "Challenges When Assessing Efficacy Using Multiple Blinded Readers" – Rocco Ballerini (Nycomed Amersham)
3. "ROC Thinking in the Clinical Development of Diagnostic Agents" – Jim Goin (DataMedix)

### Session II

1. "Statistical Issues in Diagnostic Imaging - A CBER Perspective"– Satish Misra (FDA), Peter A. Lachenbruch (FDA)
2. "Evaluation of Diagnostic Accuracies of Medical Tests with Partial Verification" Xiao-Hua (Andrew) Zhou (Indiana University)
3. "Nonparametric Methods for Analyzing Diagnostic Test Performance" – Joerg Kaufmann (Schering AG)

## D. Current State of the Art in HRQoL Measurement and Future Directions

**Chairs:** Chris Barker (Roche), Lisa Kammerman (FDA), Clare Gnecco (FDA)

1. "Prospects and Problems in the Use of IRT in Health Outcomes Assessment", Colleen McHorey (Indiana University)
2. "Evidence Supporting Psychometric Characteristics of Health-Related QoL Instruments for Labeling and Promotional Claims", Dennis Revicki (MEDTAP), Nancy Klein Leidy (MEDTAP)
3. "Interpretation of QoL Outcomes: Issues that Affect Magnitude and Meaning", Ralph Turner

**Discussants:** Robert Meyer (FDA), Nancy Santanello (Merck), Dennis Revicki (MEDTAP), Nancy Klein Leidy (MEDTAP), Zafar Hakim (Roche), Marcia Testa (Phase V)

11:15am Lunch on your own

12:30pm **Parallel Sessions II**

*Pick one of the following sessions. These sessions allow for small group discussion following the speakers presentations. A break is included around 2:00pm*

### A. Genomic Statistics in the Regulated Medical Products Industry

**Chairs:** Randy Davis (GlaxoSmithKline), Greg Campbell (FDA), Sue-Jane Wang (FDA)

1. "Statistics, Genomics and Genetic Tests: An FDA Perspective" - Greg Campbell (FDA)
2. "Current Status of Therapeutic Drug Discovery Using Genetic Information" - Sue-Jane Wang (FDA)
3. "Interactive Analysis of Genetic Data of Clinical Trials" – Stan Young (GlaxoSmithKline)
4. "National Center for Toxicological Research: Statistical Issues in Normalizing cDNA Array Data" Robert Delongchamp (NCTR), Cruz Velasco (NCTR)
5. "Statistical Issues in Analyzing Protein Chip Data" - Lu-Ping Zhao (Fred Hutchinson Cancer Research Center)

### B. Informatively Censored Longitudinal Studies

**Chairs:** Gary Littman (Wyeth), Janice Derr (FDA)

1. "An Overview of Current Methods of Dealing with Clinical Data with Informative Censoring" – Richard Entsuah (Wyeth-Ayerst)
2. "Analysis of Longitudinal Data with Random Effects and Informative Censoring" - Margaret Wu (NHLBI)

### C. Flexible Designs

**Chairs:** Corsee Sanders (Genentech), Kooros Mahjoob (FDA)

1. "Strategies of Adaptive Clinical Trial with the Option to Drop One of the Two Active Treatments at Interim Look" – Yi Tsong (FDA)
2. "Examples of Mid-Study Design Adjustments" - Mark Ashby, Ph.D. (Genentech)
3. "Problems and Issues in Implementing Trial Designs" - Gordon Lan (Pfizer)
4. "Phase 2/3 Combination Clinical Trials to Accelerate Drug Development" – Qing Liu (Cephalon)

### D. Global Bridging Strategies

**Chairs:** Kim Perry (Pharmacia), James Hung (FDA)

1. "Experiences with Bridging Data From a Single Japanese Study to a Large Western Analysis" - Scott Haughie (Pfizer)
2. "On Sample Size Determination in Evaluation of Bridging Evidence for Pharmaceutical Products" Dr. Jen-Pei Liu (National Health Research Institutes)
3. "Bridging Strategies for Global Integration of Clinical Studies and Registration" - Tamie K. Bergstrom, Ph.D. (Pharmacia)
4. "Geotherapeutics: A Science Based Approach to Global Bridging Programs" - Ted Grasela, PharmD, Ph.D. (Cognigen)

**Discussant:** H.M. James Hung (FDA)

3:15pm **Special Interest Parallel Sessions**

1. "Statistical Issues with Medical Devices" - Greg Campbell (FDA)
2. "Analysis of Mixed Models" - Ron Helms (Rho)

5:00pm **Adjourn**

## Let's Hear from You!

If you have any comments or contributions, contact Editor Kannan Natarajan, Director, Biostatistics, Bristol-Myers Squibb PRI, P.O. Box 5400, Princeton, NJ 08543; Phone 609-818-4299; email: [kannan.natarajan@bms.com](mailto:kannan.natarajan@bms.com); Associate Editor Neal Thomas, Principal Statistician, Biostatistics, Bristol-Myers Squibb PRI, 5, Research Parkway, Wallingford, CT 06492; Phone 203-677-7270; email: [neal.thomas@bms.com](mailto:neal.thomas@bms.com); or Past Editor Demissie Alemayehu, Biometrics Director, 235 East 42nd Street, Bldg 205/4, Pfizer Inc, New York, NY 10017; Phone 212-573 2084; e-mail: [alemad@pfizer.com](mailto:alemad@pfizer.com);

The *Biopharmaceutical Report* is a publication of the Biopharmaceutical Section of the American Statistical Association.

© 2001 The American Statistical Association  
Printed in the United States of America

NON-PROFIT ORG  
U.S. POSTAGE  
**PAID**  
ALEXANDRIA, VA  
PERMIT NO. 361

**Biopharmaceutical Report**  
c/o American Statistical Association  
1429 Duke Street  
Alexandria, VA 22314-3415  
USA

