Biopharmaceutical Section

American Statistical Association

Biopharmaceutical Report

Volume 2, No. 2 Winter 1993

Chair: ***Bruce E. Rodda, Ph.D.*** **Editor:** ***Avital Cnaan, Ph.D.***

Individual Bioequivalence: A Problem of Switchability

Sharon Anderson
Bristol-Myers Squibb

Introduction

The area of bioequivalence testing is seeing rapid changes. It has been less than a decade since the use of the correct null hypothesis of nonequivalence was adopted and now, in the past two years, we have seen the adoption of the concepts of individual and population equivalence. The future should be exciting as the appropriate methodology is developed to address these types of equivalence.

This essay reviews the motivation for the new concepts of individual and population bioequivalence and provides a brief overview of where the research stands today. The Discussion Section will summarize where I believe we should be heading in the near future.

For reasons of brevity, this essay will be restricted to only bioequivalence trials for the approval of generic drugs. Also, while many methods have been proposed for testing bioequivalence, only those methods that directly address individual bioequivalence have been referenced. Finally, the concepts of individual and population equivalence extend to all equivalence studies.

Background

A bioequivalence study for the approval of a generic drug is an equivalence study of bioavailability. (Bioavailability is the rate and extent of absorption of the active drug or metabolite at the site of drug action). The outcome parameters are summary statistics based on the measured concentration of the active drug or metabolite in the plasma (or urine) over time. The most common parameters used to characterize the extent and rate of absorption are the area under the plasma concentration time curve (AUC), the maximum concentration (C_{max}) and the time of maximum concentration (T_{max}). Presently, standard two-period crossover designs are most common.

In contrast to most clinical equivalence problems, the test for bioequivalence is an interval hypothesis with the alternative hypothesis being that the ratio of the population means, say AUC, lie within (.80, 1.25). The choice of equivalence interval may differ by country, compound, drug class, and bioavailability parameter. The primary analyses are done on the log scale. Presently in the U.S., the recommended test to conclude bioequivalence requires that the narrowest 90% confidence interval falls within the equivalence interval or, equivalently, if two simultaneous one-sided t-tests are each significant at the 0.05 level. The important point to remember is that the present bioequivalence hypothesis test is a test only of the population means. The comparison of only population means is referred to as "average bioequivalence."

Contents

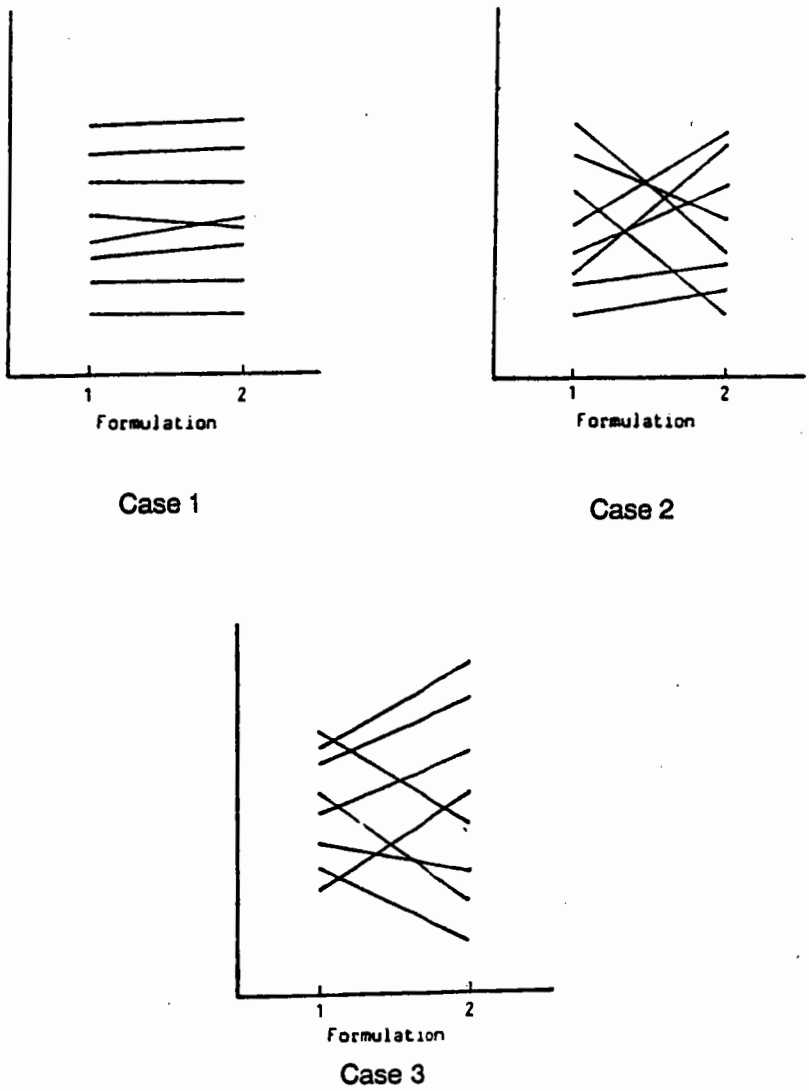


Figure 1: Different types of bioequivalence.

As an aside, in the specific type of bioequivalence study discussed in this essay, one is dealing with a surrogate measure problem. The demonstrated bioequivalence of a test and reference formulation allows the test formulation to claim the clinical results for the reference, i.e., assume the same efficacy and safety profiles. However, there is a catch. The relationships between plasma drug concentration level and therapeutic response or drug intolerance are not always known. Thus, one challenge is setting equivalence criteria for measures based on active drug concentration when the ultimate objective is equivalence of clinical efficacy and safety.

Motivation for Individual and Population Bioequivalence

The motivation for using individual and population bioequivalence came from a recognition that even with the correctly formulated testing procedures, the practical application of the results, namely the daily use of generic drugs, was not necessarily supported by the statistics (Anderson and Hauck, 1990). If you were to ask a physician what he or she thought it meant to be an approved generic drug, the answer would most likely be: "It doesn't matter which one I prescribe for my patient." If you were to ask the patient the same question, their response would be: "It doesn't matter which one I take." Also, in today's health care system, a patient's formulation may be changed without either the prescribing physician's or the patient's knowledge. This is the practical understanding of a statistical demonstration of bioequivalence and a test of only population means, without severe assumptions regarding the covariance structure, does not support this understanding and application.

There are, however, two different clinical situations that need to be distinguished. First, if the patient is drug naive, the physician has no information as to how the patient will respond to either formulation. This situation is referred to as "prescribability." For this situation, one needs to demonstrate the equivalence of the distributions or "population" bioequivalence. What about the patient who has been well controlled with minimum intolerance problems? In this situation, both the physician and the patient expect that the new formulation will provide the same efficacy and safety profile for that patient. This latter situation, where "switchability" is required, corresponds to the "individual" bioequivalence problem. The fact that both formulations were shown on average to have equivalent responses in a population (average bioequivalence) is not sufficient for either of these situations.

One way to understand the differences between these types of bioequivalence is to consider the plots of individual bioavailability responses on formulations labeled 1 and 2. See Figure 1 (from Ekbohm and Melander, 1991). Case 1 is the ideal case of individual bioequivalence. The average responses are the same on both formulations, the variances (total variation) are the same and an individual's response is the same across formulations. Case 1 data would satisfy individual, population and average bioequivalence. In Case 2, the individual responses are not similar. These data would satisfy population and average bioequivalence but not individual. Case 3, where only the average responses are similar, would only satisfy average bioequivalence.

Population and individual bioequivalence are not simply restatements of the problem of bioequivalence. They require that the distributions be equivalent and not just that the population means be shown to be equivalent as is presently done. Table 1 summarizes the three types of bioequivalence in terms of the underlying distributional parameters which are involved in the testing. The underlying model is shown at the top of the table. In the case of individual bioequivalence, the proposed methods differ in terms of whether they work with the individual means or the population means.

So far the argument for considering individual bioequivalence over average bioequivalence has been conceptual. Anderson and Hauck (1990) showed that one may conclude average bioequivalence (or even population) but the proportion of the population who will show individual bioequivalence need not be large. For example, in the case of a CV of 30%, a correlation of 0.7 and a 10% increase in the mean of the test formulation, only 57% of the population would have their individual ratios fall within the old equivalence interval of (0.8, 1.20). The parameter values used

Table 1: Underlying model and types of equivalence

Underlying Model
Let X_{ijk} denote the measure of bioavailability
where i = formulation (T,R)
j = 1,...,n subjects
k = 1 or 1,2 (replication)

$Y_{ijk} = \log (X_{ijk})$

Within subject: (Individual) $E[Y_{ijk}] = \mu_{ij}$ and $V[Y_{ijk}] = \sigma_{Wi}^2$

Between subject: (Population) $E[\mu_{ij}] = \mu_i$ and $V[\mu_{ij}] = \sigma_{Bi}^2$

Correlation $[\mu_{Tj}, \mu_{Rj}] = r$

Types of Equivalence

Average	—	population means (μ_i)
Population	—	population means (μ_i)
	—	total variation ($\sigma_{Bi}^2 + \sigma_{Wi}^2$) if two periods
	—	within subject (σ_{Wi}^2) if more than two periods
	—	between subject (σ_{Bi}^2) if more than two periods
Individual	—	population means (μ_i) if derived statistics
	—	individual means (μ_{ij}) if tolerance intervals
	—	within subject (σ_{Wi}^2)
	—	between subject (σ_{Bi}^2)
	—	correlation (r)

in these calculations are not extreme for bioavailability data.

Thus, the reassurance of switchability based on average bioequivalence may not exist for highly variable drugs.

A data set from Chow (1990) based on 24 subjects from a two-period crossover study also illustrates the distinction. The means for the reference and test formulations were 82.56 and 80.27 respectively. The ratio of the means is 0.972, sufficiently close to 1.0. The standard deviations were 20.80 and 21.12 respectively. The 90% confidence interval (untransformed from log scale) is (0.885, 1.067). Thus, according to the present guidelines these formulations are bioequivalent. Figure 2 plots the individual AUCs, with the newly adopted equivalence boundaries of 80 and 125% also drawn in. Applying the equivalence criteria to an individual, only 15 (63%) of the 24 subjects fall within the equivalence boundaries. (It is recognized that one might wish to loosen the criteria on individuals to allow for within-subject variation). Is it satisfactory for this percent of subjects to meet the criteria? This becomes a regulatory issue.

Before reviewing the methods, it is important that terminology be clear. There is a tendency for the proposed methods to be referred to by the types of bioequivalence, when in fact, a method for population bioequivalence may be appropriate for individual bioequivalence. The objective is to assure switchability and, in some regulatory situations, prescribability. The FDA Generics Advisory Committee in February, 1993, agreed with these concepts. However, how switchability is assessed may vary. For example, if the between subject variances for the test and reference formulations are equal and the correlation is close to 1.0, i.e., if the subject by formulation interaction is zero, then demonstrating what has been referred to as "average" bioequivalence, by the use of the two simultaneous one-sided tests, is sufficient. The challenge for the future is recognizing when a particular method can be applied to assure switchability.

Methods for Testing Individual Bioequivalence

To date, the methods for testing individual bioequivalence were developed from two approaches. One approach, referred to as "tolerance interval methods", works with the individual ratios (or differences) rather than functions of distributional parameters. Anderson and Hauck (1990) proposed TIER, test of individual equivalence ratios. (See Table 3). It tests whether the proportion of the population for whom the two formulations are equivalent is greater than the regulatory specified minimum proportion in the population for whom the two formulations must be equivalent. In a similar fashion, Esinhart and Chinchilli (1992) find the tolerance interval that contains 100 x% of the individual ratios with probability 1-α. They propose both parametric and nonparametric approaches but the latter is noted by the authors to be too conservative. While both methods are easy to understand, to implement and specify equivalence criteria for, both methods are inconsistent. Schall and Luus (1993) propose looking at the differences or the ratio of the probabilities that the difference between test/reference and reference/reference are bounded from above by some meaningful criterion. They proposed a one-sided test that the difference or ratio be sufficiently large to declare individual bioequivalence. Their proposed methods, however, are flawed. In the case of the difference in probabilities, the criteria are too easily satisfied and one is working with bounded probabilities. Similarly, the ratio of probabilities is flawed because it acts like a "relative risk" which would require prohibitively large sample sizes and the criterion is not independent of the probabilities.

The second approach to the problem of individual bioequivalence grew out of the simple concept that the difference between the test and reference formulations should be close to the difference between repeated tests of the reference. These methods are referred to as "derived statistics" since they are functions of the underlying distribution parameters and do not work directly with the individual ratios of the bioavailability measures. They have the advantage of directly addressing the FDA's interest in having methods which

Table 2: Percent of population satisfying individual bioequivalence

		$\mu_T/\mu_R = 1$	$\mu_T/\mu_R = 1.1$
CV%	Correlation	% of Population within (.8, 1.2)	
15	0.7	92	77
	0.5	82	70
30	0.7	63	57
	0.5	51	48

Taken from Anderson and Hauck (1990).
Note: μ denotes the population mean on the original scale and at the time this paper was written the accepted equivalence interval was (.8, 1.2).

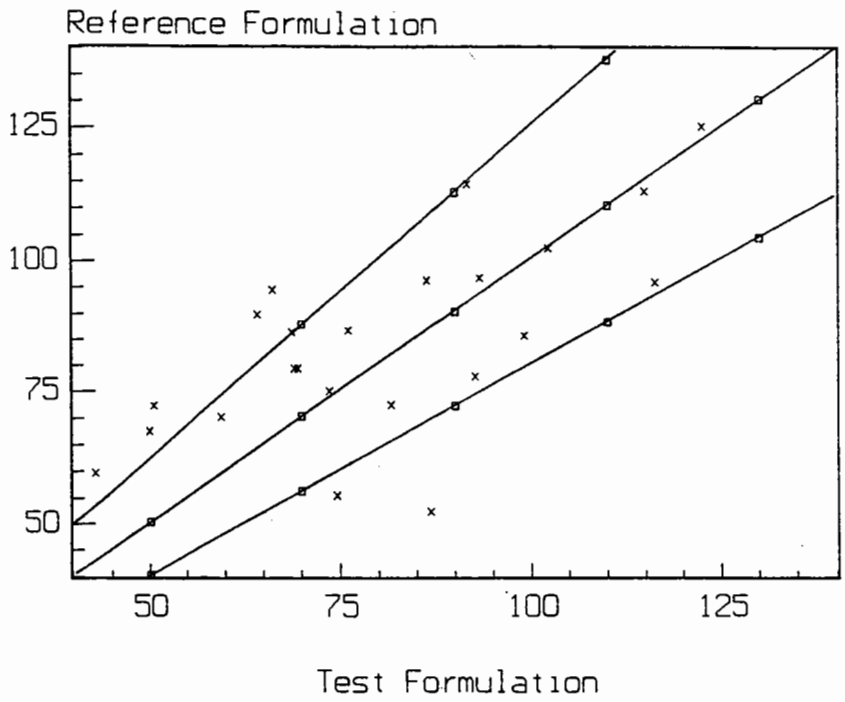


Figure 2: Example of average but not individual bioequivalence.
Note: AUC values from Chow (1990)

would explicity take into account the within subject variability of the reference formulation. With the present methods it is difficult to demonstrate bioequivalence to a highly variable reference formulation.

Schall and Luus (1993) proposed use of the difference in squared error loss between the test/reference and the reference/reference. (See Table 3). The actual test of this quantity being sufficiently small is based on the one-sided bootstrap 95% confidence interval. Sheiner (1992), while starting from a different premise than Schall and Luus, proposes a statistic which can be written as the ratio of test/reference squared error loss to that of the reference/reference. Sheiner's method, in my opinion, has the advantage of being a ratio which is the most common way people think about bioequivalence. In addition, a series of statistics were proposed by Ekbolm and Melander (1991) based on an approximate F distribution. Their most general case can be shown to be a simple scaling of Sheiner's statistic. Sheiner's method uses a one-sided likelihood confidence interval to demonstrate individual bioequivalence. However, it suffers from being biased and conservative. While the derived statistics do explicitly take into account the within subject variance of the reference formulation and may allow for adjustment of period effects, they are flawed. The major criticisms of the derived statistics are: they are not easily understandable statistics, meaningful equivalence criteria are difficult to specify, and the ability to specify sample sizes is not straightforward, particularly for the method proposed by Schall and Luus. Thus, each of the methods proposed to date suffers from some practical and/or statistical flaw. From a statistical perspective, we are not yet there in assessing individual (or population) equivalence.

Discussion

The real question, however, is where should we be? I believe that it is time for the statisticians to step back for awhile in terms of proposing new statistical methods and let our regulatory and pharmacology colleagues decide what they need. Having these proposed statistical methods on the table has helped to focus some of the issues, but we need more direction.

I believe that we need to develop criteria, both practical and statistical, by which we can assess proposed methods. For example, two criteria might be: the ability to set meaningful equivalence criteria and to do sample size (or power) calculations. I stress "practical" as well as statistical criteria, since the sponsors, as well as the reviewers of these studies, are not necessarily statistically sophisticated. It is important that, for any given study, what a statistical test is doing be clearly understood. A method that appears to be a "black box" would be less than fully desirable, in my opinion, for either the FDA or the generic drug sponsor. Ideally, we need methods that retain a "sense of the data."

At the same time, we need to see if some of the proposed methods can be improved. Presently, work is being done with respect to the tolerance interval methods as well as Sheiner's method. Any new methods that are proposed would need to be statistically validated.

Not only do the methods have to be statistically valid, but we need to understand how changes in the parameters of the underlying model shown in Table 2 (or functions of them), affect the methods. The objective is to get a better handle on how to set the equivalence criteria. For example, for Sheiner's method, should each of the three components of the numerator below

$$[(\mu_T - \mu_R)^2 + (\sigma_{BT}^2 + \sigma_{BR}^2 - 2r\sigma_{BT}\sigma_{BR}) + \sigma_{WT}^2]/\sigma_{WR}^2$$

receive equal weighting? Maybe unequal weighting is more desirable, in which case a new test would have to be developed. Work has begun to look at the influence of these parameters using simulations and real data.

Once we have a set of valid methods, we will need to identify the situations under which each method assures

Table 3: Overview of Methods for Individual Bioequivalence

	Core Statistic	Method
TOLERANCE INTERVALS		
Anderson & Hauck	$\ln(X_{Tj}/X_{Rj})$	Distribution free Binomial — P Confidence Intervals
Esinhart & Chinchilli	$\ln(X_{Tj}/X_{Rj})$	Parametric and distribution-free tolerance intervals
DERIVED STATISTICS		
Schall & Luus	$E[Y_{Tj}-Y_{Rj}]^2-E[Y_{Rj}-Y_{R'j}]^2$	Bootstrap confidence intervals
Sheiners	$E[Y_{Tj}-Y_{Rj}]^2/E[Y_{Rj}-Y_{R'j}]^2$	Likelihood confidence intervals
Ekbohm & Melander	$E[Y_{Tj}-Y_{Rj}]^2/E[Y_{Rj}-Y_{R'j}]^2$	Approximate F confidence intervals

switchability (or prescribability). The choice of method will depend on bioavailability characteristics of the drug or drug classes. Drugs that are highly variable will most likely require methods similar to those proposed for individual bioequivalence.

These concepts also will require more than the standard two-period crossover design. Determining the most appropriate three- or four-period crossover designs is an area of future research. The impact of these methods on sample size needs to be reviewed as well.

Progress is being made, but the whole process is likely to have many iterations; somewhat like "two steps forward and one step back." I say this, because of the linkage or interdependency between better defining the problem, defining the criteria, validating the methods, and deciding when a given method should be used. The next few years will be exciting as these problems are addressed.

References

Anderson, S. and Hauck, W.W. (1990). Consideration of individual bioequivalence. *Journal of Pharmacokinetics and Biopharmaceutics* 18, 259-273.

Chow, S.C. (1990). Alternative approaches for assessing bioequivalence regarding normality assumptions. *Drug Information Journal*,24, 753-762.

Ekbohm, G. and Melander, H. (1990). On variation, bioequivalence and interchangeability. Report #14, Department of Statistics, Swedish University of Agricultural Sciences, Uppsala.

Esinhart, J.D. and Chinchilli, V.M. (1991). Extension to the use of tolerance intervals for the assessment of individual bioequivalence. *Journal of Biopharmaceutical Statistics* (in press).

Schall, R. and Luus, H.G. (1993). On population and individual bioequivalence. *Statistics in Medicine*, 12, in press.

Sheiner, L.B. (1992). Bioequivalence revisited. *Statistics in Medicine* 11, 1777-1788.

Discussion

Carl M. Metzler

Nutwood Associates

For the past 15 years Sharon Anderson and Walter Hauck, individually and in collaboration, have been major contributors to the development of statistical methods for evaluating bioequivalence. I consider their proposal (1983) of the interval alternative hypothesis to be the best statistical tool on which to base a decision rule for average bioequivalence. The theoretical objections to it had no practical relevance; unfortunately it required everyone to completely reverse their thinking about acceptance and rejection regions, power and sample size. This may have been most difficult for statisticians. Perhaps for this reason it never received wide acceptance. In this paper Dr. Anderson reviews some of the current suggestions for changing the definitions of bioequivalence, and some proposed statistical tools to evaluate these new concepts. As she points out, all of the proposed tools still need some fixing. In my opinion the most important part of the paper is the Discussion section. To Sharon's question "...where should we be?" I would add the questions: Where have we been? and Where are we now? Twenty years ago *Biometrics* published my introductory paper on bioequivalence. Although I was listed as the sole author, this publication grew out of, and was indebted to, the discussions of an ASA committee of statisticians considering the then new subject of bioequivalence.

The definition then was that of average bioequivalence, and the accepted rule for declaring bioequivalence was an average bioequivalence of the test drug product that could be shown, with an acceptable risk of a wrong decision, of being not less than 80% nor more than 120% of the average of the standard drug product. With a very few exceptions that is still the rule. Have we not learned anything about pharmacology or biopharmaceutics of drugs in the last 20 years?

In an oral presentation at an FDA hearing in February of 1993 I looked at the top 11 drugs of 1992 (in world-wide dollar volume). For five of these drugs the Physicians Desk Reference gave a starting dose and then recommendations for titrating the dose to the needs of the individual. For the other six drugs a single dose was recommended. For three of the drugs something was said about reducing the dose in the presence of reduced kidney function. No other recommendations were given for adjusting dose, and certainly nothing was said about inter- or intra-subject variability in the absorption of the drug products. My point is this: If the top eleven drugs can be given to any patient, whether the little old 85-pound lady down the block or a young 280-pound football player, without regard to differences in volume of distribution, elimination, metabolism, etc., why should we get concerned about relative bioavailability of drug products?

Thus I strongly agree with Sharon that we should step back "...and let our regulatory and pharmacology colleagues decide what they need." Why have our regulatory colleagues and their academic consultants spent so many hours (day, weeks, months?) debating statistical points that have little importance and not addressed the pharmacologic and medical issues? Is it because they perceive the statistical issues to be easier? Is it because as statisticians we have allowed them to think that the statistical issues were really the important ones?

I submit that there are many non-statistical issues that need to be resolved before bioequivalence regulations need be changed: Is there any evidence that the present regulations are not serving well? If so, does this evidence point to the need for regulations that consider population values such as covariance structures, or do they point to the need for more discrimination among classes of drugs, with different criteria and various levels of risk? That is plus-or-minus 20% may not be appropriate for all drugs; a risk level of 5% may not be appropriate for all.

I don't mean to discourage statisticians from developing new methodology, but I do suggest that as statisticians we may be most useful if we can help regulators see which are the most important issues, and what is the proper role of statistics.

References

Anderson, S. and Hauck, W. W., 1983, A new procedure for testing equivalence in comparative bioavailability and other clinical trials. *Communication in Statistics Theory and Methods*, 12:2663-2692.

Metzler, C. M., 1974, Bioavailability - a problem in equivalence. *Biometrics* 30:309-317.

Discussion

Murray R. Selwyn, Ph.D.
Statistics Unlimited, Inc.

Introduction

Dr. Anderson has provided us with an interesting and informative article on "individual bioequivalence" and the problem of switchability. I would like to thank Dr. Cnaan and the *Biopharmaceutical Report* for the opportunity to comment on this topic.

Anderson motivates the question of assessing individual bioequivalence with the clinical maintenance of a patient who is successfully being treated with one formulation of a drug (the standard), but who is to be switched to a second, alternative formulation (the generic product). She argues that the current approach to bioequivalence testing (called average bioequivalence) is not necessarily satisfactory for a patient in this situation.

In discussing Anderson's paper and the ideas and issues with which it deals, I would like to separate my thoughts into three sections, as follows:

(1) General Issues: Is individual bioequivalence a consideration which should be investigated and statistically assessed?

(2) Clinical Issues: If so, what are the clinically relevant questions to be addressed and what would be the impact (if any) on a bioequivalence study design and other related studies?

(3) Statistical Issues: If we perform bioequivalence studies with the assessment of individual bioequivalence as one of their goals, how should we analyze the data from these studies? Further, how would current designs (e.g., the two period crossover) and typical sample sizes be affected?

General Issues

It is tempting for statisticians to pursue slight variations of standard problems to produce interesting statistical research. However, the problems themselves should be important, practical problems in need of pursuit and resolution. In considering "switchability," what are the potential reasons that a difference in the availability of the drug substance (typically measured through blood level AUCs of the active ingredient) is important to the individual patient? Suppose that the patient is already at a high drug level (high AUC) and that switching to the generic will result in an even higher, possibly toxic level. Conversely, suppose that the patient's drug level is toward the low end of the effective range. Will the generic formulation result in an even lower level, perhaps one that will not be efficacious for the patient's disease?

A further possibility that one can imagine is that the substitution of the generic drug for the standard results in a sudden change in the AUC or C_{max} and it is the suddenness of the change and its magnitude which causes a problem for the patient. How likely and clinically relevant are these and other possibilities? What studies have been performed in this regard? How much do we know about the seriousness and prevalence of this perceived problem?

Clinical Issues

I would like to review the purpose of bioequivalence studies: to demonstrate the approximate "blood level" equivalence of a new formulation (e.g., generic) to a standard formulation (e.g., currently approved and marketed product). The idea is that formulations which are equivalent in rate and extent of absorption of the same active ingredient will be therapeutically equivalent. That is, once the active ingredient enters the bloodstream, its subsequent actions do not depend on how it got there (whether generic or approved product). Instead of performing large and possibly difficult clinical equivalence studies in the target patient population, we conduct smaller bioequivalence studies, usually in healthy, normal volunteers. We assume that the findings from the bioequivalence study are representative and sufficient to make inference about the clinical situation.

In considering switchability for the individual patient, what do we know about that patient? Should the clinically relevant characteristics of that patient be considered in order to verify "switchability"? For example, are we dealing with an elderly patient, or one who is renally impaired, or one whose particular clinical situation is substantially different from the "typical" patient? It seems to me that when we are making clinical decisions about individual patients, we should know something about those patients.

I raise these issues not to be critical of Anderson's and other statisticians' methodological proposals, but only to suggest that the questions they consider transcend mere data analysis and statistical design considerations.

It seems to me that before we undertake the development and implementation of additional and perhaps imposing requirements for bioequivalence studies, particularly within the regulatory context, we should carefully consult with our medical colleagues to identify the types and sources of their concerns (with appropriate literature references of examples) and not rely on mere speculation about the clinical nature of the problem.

Statistical Issues

I generally agree with Anderson and Hauck's (1990) formulation of how to assess acceptable individual bioequivalence, i.e., a high probability that individuals' availability ratios will be between suitable limits. I was somewhat surprised, however, that Anderson and Hauck chose to collapse the quantitative information available from (AUC_T, AUC_R) into a simple binary variate indicating inclusion within such an interval (see step 2 of TIER). Instead, given the long history of the linear mixed model for assessing bioequivalence, I would take advantage of this formalism. Specifically, for the two period crossover, define as the model equation for AUC (Grizzle 1965, Selwyn et al. 1981):

$$Y_{ij} = \mu + S_i + P_j + F_k + e_{ij} \qquad (1)$$

for i=1,..., N; j=1,2; k=T,R, where μ is an overall mean, S_i represents the i-th subject effect, P_j is the j-th period effect, and F_T and F_R are the effects for the test and reference formulations, respectively, and is a term for unexplained variation. We further assume that the $\{Si\}\sim NI(0, \sigma_s^2)$ independent of the $\{eij\}\sim NI(0,\sigma_e^2)$ and impose the usual constraints on the fixed effects in the model ($P_1 + P_2 = F_T + F_R = 0$).

Because the period effect is a nuisance parameter inherent in the crossover design, we further define

$$\begin{aligned} W_{iT} &= \mu + S_i = F_T + e_i \\ W_{iR} &= \mu + S_i + F_R + e_i^* \end{aligned} \qquad (2)$$

for i=N+1,..., as unobservable AUCs for test and reference formulations, respectively, for future subjects N+1, ..., .

We can base assessment of individual bioequivalence on quantities derivable from the predictive density of $(W_{N+1,T}, W_{N+1,R})$ given the experimental data, and obtained from

$$g(W_{n+1,T}, W_{N+1,R}|y) = \int P(W_{N+1,T}, W_{N+1,R}|\theta)p(|\theta y)\partial\theta, \quad (3)$$

where $\theta^T = (\mu, P_1, F_T, \sigma_s^2, \sigma_\epsilon^2)$ is the vector of unknown parameters and $y = ((y_{11}, y_{12}),...,(y_{N1}, y_{N2}))$ is the observed data vector.

Given a suitable range (A,B) for relative availability, we would be interested in quantities such as $Pr[A \leq W_{N+1,T} / W_{N+1,R} \leq B]$ calculated from (3) (see Geisser 1982, Selwyn and Hall 1984). Similarly, one could compute the probability that at least $100(1-\gamma)\%$ of future patients would have relative availabilities between A and B (e.g., see Geisser 1982, equation 3.17) using (3) as the basis.

Returning to the question of specific patients or specific subsets of the patient population, we could quantify information about bioavailability for these individuals. For example, if a certain patient (#N+1) was known to have or was suspected of having an atypically low availability (AUC), say one which was near the border of the effective range [presumed to be (A',B'), we could compute probabilities such as

$$Pr[W_{N+1,T} \leq A'|A' \leq W_{N+1,R} \leq A''].$$

To do this, however, would generally require more knowledge (such as values for A' and B') and possibly differently designed bioequivalence studies than those we are now conducting.

I have chosen to base individual bioequivalence assessment on the Bayesian prediction distribution (3) and Bayesian tolerance intervals. One could alternatively consider the sampling distribution of $W_{N+1,T}/W_{N+1,R}$ or statistical tolerance intervals for such ratios (see Esinhart and Chinchilli 1994 for a frequentist analysis based on log ratios). Other modeling considerations would include use of log AUCs versus AUCs and generalizations of the form of the mixed linear model (1).

I would like to point out one practical consideration arising from individual bioequivalence assessments. It seems, out of necessity, that bioequivalence studies having the capability to make assessments at the individual level will need to be considerably larger than current studies (see Anderson and Hauck 1990 for TIER sample sizes, Esinhart and Chinchilli 1994a regarding those for frequentist tolerance intervals).

Concluding Remarks

The paper by Anderson introduces and discusses a potentially important problem, that of assessing individual rather than average bioequivalence. Certainly much of the early development in statistics has focused on problems involving mean values, e.g., the comparison of two means via Student's t-tests and more than two by ANOVA. The realization that mean values only are not sufficient to describe populations represents a more sophisticated attitude and possibly a better appreciation of the problem at hand.

In bioequivalence, we should ask ourselves to first identify the relevant clinical issues. While assessment of individual bioequivalence may be statistically challenging, is it clinically relevant? If so, let our medical colleagues identify, by providing actual data, the types of situations with which we as statisticians need to cope. I believe that we have the tools to mathematically formulate and resolve such technical problems. Bayesian and other inferential methods are certainly sufficient, once the specific issues have been defined.

Additional References

Geisser, S. (1982). Aspects of the Predictive and Estimative Approaches in the Determination of Probabilities, *Biometrics* Supplement: Current Topics in Biostatistics and Epidemiology, 75-85.

Grizzle, J.E. (1965). The Two-Period Change-Over Design and its Use in Clinical Trials, *Biometrics*, 21, 467-480.

Selwyn, M.R., Dempster, A.P., and Hall, N.R. (1981). A Bayesian Approach for the 2x2 Changeover Design, *Biometrics*, 37, 11-21.

Selwyn, M.R. and Hall, N.R. (1984). On Bayesian Methods for Bioequivalence, *Biometrics*, 40, 1103-1108.

Discussion

Jen-pei Liu

Biostatistics, Berlex Laboratories, Inc.

The views expressed in this discussion are those of the authors and are not necessarily of Berlex Laboratories, Inc.

I would like to congratulate Dr. Anderson for a comprehensive review of the concept of individual bioequivalence and a much-needed statistical critique of the current methods for evaluating individual bioequivalence.

Bioequivalence studies are surrogate trials for assessing equivalence without actually conducting clinical trials to establish similar effectiveness and safety of the test formulation because the fundamental bioequivalence assumption implies that bioequivalent formulations are therapeutic equivalents and can be used interchangeably (Metzler, 1974). Interchangeability for a naive or new patient means that similar and equivalent efficacy and safety will be achieved (or not achieved) no matter which formulation is prescribed to start treatment for the patient by the physician. The author used "prescribability" for this type of interchangeability. On the other hand, many diseases, such as hypertension, are required and can be controlled by chronic applications of medications. Interchangeability for the patients whose drug concentration has been titrated to a steady, efficacious and safe level actually requires that the drug concentration be maintained at the equivalent level of the reference formulation, if it is switched to the test formulation. The author coined "switchability" for interchangeability for this type of patients.

My additional comments start with both population and individual bioequivalence, followed by discussions on design and estimation.

Population Bioequivalence

As pointed out by the author, the assessment of bioequivalence, in fact, is an examination of the closeness between distributions. If the distributions of the pharmacokinetic (PK) responses for the test and reference formulations are obtained from a population of subjects, it is referred to as "population bioequivalence" (Chow and Liu, 1992). If the PK responses follow approximately a normal distribution, it then requires to establish bioequivalence of both averages and variabilities. Current applications of Schuirmann's two one-sided tests procedure (Schuirmann, 1987) to evaluating bioequivalence on average completely ignores the importance of the difference in intrasubject variabilities (Liu, 1991). For drug products with a narrow therapeutic window, bioinequivalence in intrasubject variabilities poses a serious

danger regarding drug interchangeability between the reference and test formulations based only on the evidence of bioequivalence for average bioavailability.

The parametric and nonparametric two one-sided Pitman-Morgan tests procedures were proposed by Liu and Chow (1992) for evaluating bioequivalence of intrasubject variabilities between two formulations. One important feature of the two one-sided Pitman-Morgan tests procedures is that the proposed test statistics for assessing bioequivalence in intrasubject variabilities are statistically independent of the test statistics of the Schuirmann's two one-sided tests procedure for average bioequivalence. Consequently, the individual nominal significance levels for average and variability can be predetermined based on the relative importance of the average to the intrasubject variability with respect to a certain drug class after an overall nominal significance level for the population bioequivalence is chosen. However, power properties and sample size determination of the two one-sided Pitman-Morgan tests procedures still are not clear and require further research.

Individual Bioequivalence

The statistical concept of individual bioequivalence is referred to as the comparison of the closeness between the two distributions of the PK responses from the same subject obtained under the repeated administrations of test and reference formulations. As indicated by the author, the current methods for evaluating individual bioequivalence, e.g., the test of individual equivalence ratios (TIER) by Anderson and Hauck (1990), tolerance interval approach by Esinhart and Chinchilli (1991) or use of ratios or differences of squared error loss by Sheiner (1992) and Schall and Luus (1993), are all not satisfactory. However, I would like to point out that Liu and Weng (1994), and Wellek (1993) have shown that, under the normality assumption of the log-scale for the PK responses, the hypothesis of individual bioequivalence by TIER can be reformulated in terms of the standardized average. In essence, individual bioequivalence using TIER is in fact evaluated through a bioavailability measure that combines average and intrasubject variability together. On the other hand, the measures proposed by Sheiner (1992) and Schall and Luus (1993) also combine both averages and variabilities together, but in a squared form. The danger of combining averages and variabilities is the possible masking effects. It is quite possible that two formulations are claimed bioequivalent based on a single measure which combines average and variability. The same two formulations, however, might not be bioequivalent with respect to other bioequivalence measures based on average or variability bioavailability alone. As an example, suppose that the average and intrasubject standard deviation of the $AUC0_{\infty}$ for the reference formulation are 100 µg x hr/mL and 20 µg x hr/mL, respectively, while for the test formulation they are 10 µg x hr/mL and 2 µg x hr/mL, respectively. Hence, the standardized average is 5 for both formulations even though the reference formulation is 10 times more bioavailable than that of the test formulation.

Wellek (1993) suggested another measure for individual bioequivalence. This parameter is the difference between the probability that for the same subject, the AUC of the test formulation is less than that of the reference formulation and 1/2. The optimal statistical testing procedure (uniformly most powerful invariant test) exists for this measure. However, Wellek's method suffers from the same drawbacks as the TIER. It is only valid in the absence of period and sequence effects and it is only applicable to the standard 2x2 crossover design. In addition to the drawbacks and flaws pointed out by the author, the exact distribution of any bioequivalence measure based on the functions of squared error loss, either under the null or alternative hypotheses is difficult to obtain analytically. Consequently, the power functions are not clear and no simple methods for sample size determination are available for those methods. Furthermore, the standard 2x2 crossover design, the most commonly employed for bioequivalence studies, is not able to provide necessary information (i.e., an identifiability problem) required for estimation of some measures based on squared error loss such as the one proposed by Sheiner (1992).

Comments

Another disadvantage of the current methods for evaluating individual bioequivalence under a standard 2x2 design is that for each individual subject, they fail to provide a description of the characteristics for the distributions of the PK responses under the two formulations. On the other hand, a repeated 2x2 crossover design (Liu, 1993) provides the multiple PK responses from the repeated administrations of the same formulation within each period. As a result, for each subject, not only the individualized test and reference averages can be obtained but also the individualized intrasubject variabilities for the test and reference formulations can be estimated. A repeated 2x2 crossover design both generates the data for comparing equivalence of the time to reach the steady state and also provides the information for assessing equivalence of pharmacokinetic profiles between the two formulations after the steady state is reached. This design is therefore an ideal design for testing the hypothesis of switchability.

The current trend for evaluating bioequivalence, either population or individual, tends to analyze the data on the logarithmic scale as shown in Table 1 of S. Anderson's paper. Hence, discussions of both population and individual bioequivalence ignore the average and variability on the original scale of PK responses. Caution is required for the routine use of logarithmic transformation in the bioequivalence problem (Chow and Liu, 1994). In particular, the lognormal distribution is not uniquely determined by its moments (Crow and Shimizu, 1988). Both the average and variability of a lognormal random variable are functions of the average and variability of its corresponding log-transformation. The between-subject, within-subject variabilities, or subject-by-formulation interaction on log-scale do not have the same meaning on the original scale. Any newly proposed methods and criteria for evaluating bioequivalence on the log-scale should consider their interpretations, the corresponding estimation problems and presentation of results on the original scale (Liu and Weng, 1992).

It is expected that one third of current innovative drugs on the market will lose their patents by the year 2000. Generic drugs will become a crucial component of cost reduction in health reform. Consequently, exchangeability between the test and reference formulations should be considered in terms of prescribability and switchability for assessment of bioequivalence. Consumers should be also given the information of prescribability and switchability for generic copies of innovative drugs. Development of meaningful, interpretable, and valid statistical methods for evaluation of prescribability and switchability remains a tremendous challenge for us.

References

Chow S.C., and Liu J.P. (1992) *Design and Analysis of Bioavailability and Bioequivalence Studies.* Marcel Dekker, New York.

Chow S.C., and Liu, J.P. (1994) Recent statistical developments in bioequivalence trials - a review of the FDA guidance. *Drug Information Journal*. to appear in No. 2 of Vol. 28.

Crow, E.L. and Shimizu, K. (1988) *Lognormal Distributions*, Marcel Dekker, New York.

Liu, J.P. (1991). Bioequivalence and intrasubject variability. *Journal of Biopharmaceutical Statistics*, 2:205-219.

Liu, J.P. (1993) Use of the repeated crossover designs to assessing bioequivalence. Presented at the Second International Meeting for Statistical Methods in Biopharmacy, Paris France, September 7, 1993.

Liu J.P., and Weng C.S. (1992) Estimation of direct formulation effect under lognormal distribution in bioavailability/bioequivalence studies. *Statistics in Medicine*, 11, 881-896.

Liu J.P., and Chow S.C. (1992) On assessment of bioequivalence in variability of bioavailability. *Communications in Statistics, Theory and Methods*, 21, 2591-2607.

Liu J.P. and Weng C.S. (1994) Evaluation of log-transformation in assessing bioequivalence. *Communications in Statistics - Theory and Methods*, (in press).

Metzler, C.M. (1974) Bioavailability: A problem in equivalence. *Biometrics*, 30, 309-317.

Schuirmann D.J. (1987) A comparison of the two one-sided tests procedure and power approach for assessing the equivalence of average bioavailability. *Journal of Pharmacokinetics and Biopharmaceutics*, 15, 657-680.

Wellek S. (1993) Basing the analysis of comparative bioavailability trials on an individualized statistical definition of equivalence. *Biometrical Journal*, 35, 47-55.

Discussion

Daniel J. Holder

Merck Research Laboratories

Dr. Anderson's characteristic clarity and insight always make her articles a pleasure to read. In this article she has given an excellent overview of current ideas on individual and population bioequivalence. In my comments I would like to focus on her discussion of individual bioequivalence by supplying some details and pointing out some important issues regarding criteria for individual bioequivalence.

I was quite pleased to see that Dr. Anderson separated her discussion of the motivation and criteria for individual bioequivalence from her discussion of proposed testing methods. Lack of distinction between criterion and testing method has led to much confusion in the area of bioequivalence. The 75/75 rule is an example of a decision rule which was employed for testing bioequivalence without reference to a specific set of hypotheses or criterion. It is important to clarify what we mean by terms such as individual bioequivalence and state the hypotheses before we propose tests.

Although I do not disagree with the description of individual bioequivalence given in Table 1, I would like to formulate the statistical notion of individual bioequivalence in terms I find easier to understand. Each subject, j, has a mean difference of the log of the bioavailability measure (Y), which, using the notation of Table 1, we call $\delta_j = \mu_{Tj} - \mu_{Rj}$. The parameter δ_j has a distribution, F, with mean δ and variance σ_δ^2 ($= \sigma_{BT}^2 + \sigma_{BR}^2 - 2r\sigma_{BT}\sigma_{BR}$) over the population of possible subjects. Note that σ_δ^2 is essentially the variance component for a subject-by-formulation interaction.

Average bioequivalence has to do with how close δ is to zero. Individual bioequivalence is concerned not only with whether δ is close to zero, but how tightly the δ_j are clustered around zero. Anderson and Hauck (1990) argue that an important measure of individual bioequivalence or switchability is the proportion of individuals for which T and R are bioequivalent; that is the proportion of δ_j contained in some interval around 0, say $[b_0,b_1]$.This leads to the definition that T and R are individual bioequivalent if and only if

$$\text{pr}\{\delta_j \in [b_0, b_1]\} \geq p^*, \qquad (1)$$

where $b_0 > b_1$, and p^* are determined by regulatory and pharmacological considerations. The constant p^* should be large, maybe 0.75 or greater, since we want to insure that T and R are bioequivalent for a large proportion of the subject population. The definition above is intuitive since it is simply a translation of the notion of switchability for a large proportion of the population into statistical language. An important property of the definition is that it involves only the distribution of the δ_j and does not involve the within-subject error variances. This is advantageous since the within-subject error variance can be study dependent. Another consequence of this definition is that drugs which are highly variable with respect to within-subject variation are measured against precisely the same criterion as drugs which are less variable.

By framing the concept of individual bioequivalence as above, it is clear that the methods that Dr. Anderson describes as "based on derived statistics" in Table 3, test something different than criterion (1), since all of these methods measure the magnitude of the difference between formulations relative to the within-subject variance of the reference formulation. This should be regarded as a reflection of the philosophies of these individual authors towards individual bioequivalence and not taken as evidence that use of derived statistics necessarily implies rejection of (1) as a useful definition. Holder and Hsuan (1993) have shown for bioequivalence intervals that are symmetric about 0 (i.e., [-b,b]), that by making assumptions about the shape of F, one can choose a c, so that the criterion $\delta^2 + \sigma_\delta^2 \leq cb^2$ implies (1). Thus, individual bioequivalence in terms of (1) can be established by showing that an upper confidence limit for $\delta^2 + \sigma_\delta^2$ is less than or equal to cb^2.

Note that determination of individual bioequivalence requires information not only on means but between subject variances as well. Therefore, as Dr. Anderson points out, the standard two period crossover design is inadequate for determination of individual bioequivalence. The reluctance of experimenters to abandon this design has been an impediment to the investigation of individual bioequivalence.

Lastly, I would like to emphasize that individual bioequivalence is a relevant and important concept. Although consensus on a statistical method for assessing individual bioequivalence or even defining a suitable criterion has yet to be reached, the days of average bioequivalence as the sole criterion for bioequivalence are probably numbered.

Additional Reference

Holder, D.J. and Hsuan, F. (1993). Moment-based criteria for determining bioequivalence. *Biometrika* 80, (to appear in December).

Discussion

Vern Chinchilli
Penn State Center for Biostatistics & Epidemiology
Hershey Medical Center

Sharon Anderson should be congratulated for a timely article, which hopefully will spur further research and discussion in the area of bioequivalence testing. I will begin my commentary by making some general remarks about individual bioequivalence and follow it with some specific remarks about Sharon Anderson's article.

My impression is that the typical prescription-drug consumer does not understand the distinction between population and individual bioequivalence. When asked about his/her understanding of bioequivalence, such a person is unsure what bioequivalence means unless it is placed within the context of generic drug substitution. Then the standard reply to this question is something analogous to Sharon Anderson's definition of switchability, i.e., it does not matter whether the user takes the pioneer-developed drug or a generic version because the delivered dose will be approximately the same. The consumer is quite surprised when he/she learns that the FDA approval process for generic drugs is based on average bioequivalence instead of individual bioequivalence.

Therefore, the issue for debate is whether the FDA should require a company to establish individual bioequivalence of pharmaceutical formulations, because this is what the general public expects. However, many pharmacists feel that the requirements for establishing individual bioequivalence are unnecessarily rigid and that the current FDA process based on average bioequivalence provides adequate efficacy and safety for generic drug substitution. My personal opinion is that this may be true for many drug classes. However, it may not be appropriate for certain drugs with moderate-to-high intra-subject variability especially if the disease is life-threatening. I am ignorant of the field of pharmacoepidemiology and there may exist epidemiological studies that have investigated this issue. If not, a series of epidemiological studies in diseased patients across a broad spectrum of disease categories and drug types may answer the question of whether the FDA should base approval on the establishment of individual bioequivalence.

Some specific remarks in response to Sharon Anderson's article are listed below. The distinction between prescribability and switchability is important, but I would like to add that if a formulation is approved for use because it satisfies average bioequivalence criteria, then the consequences could be less dire for prescribability than switchability. When a physician prescribes a particular drug for a patient, there is usually a titration phase at the onset, in which the physician monitors the patient's reactions to the drug and adjusts the dose accordingly. On the other hand, the physician may not be aware of the patient switching to a different formulation at a later stage, so that efficacy and/or toxicity within that patient may be altered and go undetected by the physician.

Figure 1 and Table 1 presented by Sharon Anderson succinctly represent the distinctions among average bioequivalence, population bioequivalence, and individual bioequivalence. Although some biostatisticians may quibble over the listing in Table 1 because of slight differences in interpretation, my opinion is that the figure and table illustrate the basic concepts well enough to be understood by pharmaceutical scientists.

Analogous to Sharon Anderson's example in which average bioequivalence was established but individual bioequivalence was not, Esinhart and Chinchilli (1994) observed the same result in all three of their examples (they use tolerance intervals for investigating individual bioequivalence). It is very likely that this is true for most formulations that have been approved using average bioequivalence criteria. This is not surprising because individual bioequivalence is a more stringent requirement and the sample sizes in current studies are designed for establishing average bioequivalence. Esinhart and Chinchilli (1994a) investigate the sample size issue for individual bioequivalence (again based on tolerance intervals) and the standard 24-subject bioequivalence trial may need to be doubled in size in order to have any chance of establishing individual bioequivalence.

Sharon Anderson states that if the subject-by-formulation interaction is null ($\sigma_{WT}^2 + \sigma_{WR}^2 - 2R\sigma_{WT}\sigma_{WT} = 0$ in her notation), then the requirement of average bioequivalence may be sufficient. I do not necessarily agree with this conjecture. In this situation individual bioequivalence still could depend upon within-subject variability. For example, in a two-period crossover design in which it is determined that the subject-by-formulation interaction is null, the test and reference formulations could be so highly variable within each subject that the test and reference observations within each subject could be so different from each other that one questions whether the definition of switchability could be satisfied.

Sharon Anderson concludes her article by discussing the various methodologies that have been proposed for determining individual bioequivalence. I agree that much more statistical work is needed because none of the proposed methods is ideal. However, I would not dismiss any of them so quickly. A number of statisticians and pharmaceutical scientists are working on these problems and refinements to some of these procedures may soon appear in the literature and become well-accepted. I do wish she would have elaborated more on some of her criticisms, such as her claims that (1) the tolerance interval approach is inconsistent, and (2) the derived statistics are flawed. Hopefully, she or other researchers will start to investigate these claims about the current methodologies for individual bioequivalence in more detail.

Additional Reference

Esinhart, J.D. and Chinchilli, V.M. (1994a). Sample size considerations for assessing individual bioequivalence based on the method of tolerance intervals. International *Journal of Clinical Pharmacology* (in press).

Rejoinder

Sharon Anderson

When Walter and I defined individual and population bioequivalence in our 1990 paper, we never expected that these concepts would stimulate the amount of research that they have in the relatively short time period of three years. I would like to thank Tuli for the opportunity to discuss these concepts and the Discussants for their comments. In an effort

to be brief, I will highlight what are, I believe, the most salient comments.

While it is exciting to develop new statistical methods, the point made by Carl Metzler needs to be underscored. Namely, in order to successfully tackle the concepts of individual and population equivalence we need the input of our regulatory, pharmacology, and clinical colleagues. As statisticians we can continue to publish papers but we should not continue to be the driving force. We need to step back.

Murray Selwyn asked for input from our clinical colleagues, specifically to provide "actual data." Some data does exist in the literature regarding treatment failures upon substitution, for example for psychoactive and anticonvulsant drugs. Systematic data, however, does not exist for a variety of reasons. First, the lack of efficacy may not be as obvious as it is for psychoactive or anticonvulsant drugs. Second, there is no national reporting system for treatment failures, only for safety. Couple this with the fact that both physician and patient may be ignorant of any substitutions. Finally, the use of the standard two-period crossover design has resulted in little available data to explore within-subject variation. The FDA is presently reviewing the data they have, based on 3 and 4 period designs, but this is minimal. This is a situation where we may never have what would be considered "sufficient" data. To overcome this issue, simulations are being done to better understand where the use of average bioequivalence will be insufficient to assure individual or population bioequivalence, for various classes of drugs.

One issue that will need to be addressed was mentioned by Jen-pei Liu. Namely, the interpretation of methods and equivalence criteria based on the log scale. As he points out, "the between-subject, within-subject and subject-by-formulation interaction on the log scale do not have the same meaning on the original scale." Whatever measures are finally adopted must be interpretable to a variety of audiences.

Daniel Holder raises an interesting argument for developing a method that does not involve the within-subject variability: the within-subject variability is study dependent. The approval to market a generic drug may be granted on the basis of one bioequivalence study. The within-subject reference variation will, therefore, be determined by the subjects the generic firm enrolls in this one study. The concern is whether the within-subject variability on the reference formulation that is seen in the study, is representative. Information from the developer of the reference formulation is generally unavailable. Since ignoring the within-subject variability is contrary to what I understand is desired by the FDA, more discussion of this approach would be interesting.

Finally, Vern Chinchilli asked for more details concerning the inconsistency of the tolerance interval approach as well as the flaws of the derived statistics. The tolerance interval method (as stated in a 1993 unpublished manuscript), because it did not take into account the within-subject variability suffered the same problem as TIER. The "flaws" in the derived statistics are (1) interpretability; (2) ability to set meaningful criteria; (3) in the case of Sheiner's method, as he states in his paper, it is biased; and (4) in the case of Schall and Luus' method, a standardized ratio is more appropriate as the authors have concluded in later work.

As I concluded in the main text, this is an exciting and important area of research because of the changes in our health care system. It is also hoped that the work done for bioequivalence testing will be extended into positive control clinical trials. The future should be interesting!

Section News

Letter to Members of the Biopharmaceutical Section

Bruce Rodda
Immediate Past Chair

As you read this, a new chair and a new Executive Committee will be directing the path of the Biopharmaceutical Section through 1994. Bob Starbuck will be chairing the section for the coming year and Lilliam Kingsbury will be aiding him as chair-elect. Lilliam will assume the responsibility for the section on January 1, 1995. Ken Koury is this year's program chair and has an outstanding set of programs planned. Helping him in this effort will be next year's program chair, Joe Heyse. Bob Davis will continue his able administration of the section's financial and secretarial duties.

1993 was a very challenging and exciting year for the section, a year in which we realized a substantial number of significant accomplishments. Early in the year we decided to restructure the section's budget. In the past, section finances were administered on a more or less ad hoc basis. Under Bob Davis' guidance and in concert with Penny Young and others at the ASA offices, we created a more formal mechanism for planning and dispersing section funds. This has resulted in a much more knowledgeable and coordinated financial approach to the section's activities.

While examining the budget, we noted that there was a small number of corporate members who were paying $500 a year for the honor. The Executive Committee decided that it would be much more effective to lower the dues and encourage broader representation of various potential corporate members. This was accomplished at the end of 1993 and a 40% reduction in individual corporate dues will be implemented in 1994. The section anticipates that the reduced dues will result in enough additional corporate members to offset the lower dues.

Under Gary Neidert's leadership, we updated and finalized the manual of operations for the section. This was heroic effort on Gary's part and really formalized all various activities of the section.

It has been several years since the Biopharmaceutical Section has searched for potential members of FDA Advisory Committees. Beginning in 1993, Vern Chinchilli has been re-initiating an effort to update a list of potential candidates to serve on these committees. An ad has been published in the *Amstat News* soliciting information from statisticians who might be interested. These names and their qualifications will be reviewed by the section, compiled into a summary document and forwarded to Bob O'Neil and Susan Ellenberg at the FDA for their use in selecting statisticians to serve on future FDA Advisory Committees.

The Biopharmaceutical Section has always had a firm commitment to education. During 1993, we continued our commitment to continuing education by sponsoring several workshops, training sessions, and by expanding the section's involvement in the quantitative literacy program. In addition, we awarded plagues to three outstanding papers at the 1993 Annual Meetings. These were awarded to Ronald Helms, University of North Carolina; Joe Heyse, Merck; and Carolin and Michael Frey, Indiana University of Pennsylvania.

To the Editor, *Biopharmaceutical Report*

In response to a book review by Dr. C.M. Metzler on our book entitled "Design and Analysis of Bioavailability and Bioequivalence Studies" which appeared in Biopharmaceutical Report, Vol 1(3), 1992, we wish to make the following comments:

For assessment of bioequivalence, estimation is at least as important as hypothesis testing. This is the reason why more than half of Chapter 3 is devoted to the point and interval estimation procedures of formulation, period, and other effects under the additive model. Moreover, the whole of Chapter 6 is devoted to the point and estimation procedures under the multiplicative model (actually lognormal linear model).

On pages 75 and 123, we present our viewpoints on the use of the classical confidence interval for assessment of average bioequivalence. The coverage probability is for the unknown true formulation effect which has nothing to do with the probability of the random interval being within the fixed bioequivalence limits. Our viewpoint on this subject might be different from that of Dr. Metzler, it is *correct*.

We agree with Dr. Metzler that it is crucial to examine the residuals for the adequacy of the selected model. However, Dr. Metzler's viewpoint is somewhat misleading. In his review, he indicated that "...the authors repeat the common mistake of justifying the log-transform by the skewness of the observed data (e.g. AUC)...". However, in our book, we did not justify the possible use of logarithmic transformation mainly based on the skewness of the observed data. The importance of examining the model residuals has, in fact, been repeatedly emphasized. In particular, there are eight figures of intra-subject or inter-subject residuals in Chapter 8 alone.

Our criticism of the Anderson-Hauck procedure is valid when the logarithmic transformation of nonnegative pharmaceutical responses is used.

In summary, our book presents a comprehensive and unified summarization of statistical design and analysis for bioavailability and bioequivalence studies from which readers will benefit.

Shein-Chung Chow and Jen-pei Liu

Although we have used the awards program to encourage people to present papers in our sessions, we felt that a greater commitment to developing students in the biopharmaceutical area is critical to the future of the section. To provide tangible support for this philosophy, the Executive Committee authorized the awarding of 5 (five) $1,000 student travel grants to attend the annual meeting in Toronto. These grants will be awarded to students contributing papers to the annual meeting. To be eligible, a student must be attending a full time program and be the primary author on the manuscript. We feel that this program, which will be administered on an annual basis, will encourage much more student participation in section activities and will result in a broader interest in biopharmaceutical topics by statistics students.

Dr. Mark Scott was the 1993 program chair, and under his able leadership we sponsored 5 (five) sessions at the Biometric Society ENAR meetings in Philadelphia, co-sponsored the mid-west Biopharmaceutical Statistics Workshop, and co-sponsored the Applied Statistics Conference in Atlantic City. In addition, the section sponsored 3 (three) invited sessions and 10 contributed paper sessions at the annual meeting in Toronto. Nick Teoh coordinated 8 (eight) round tables at these meetings. These continue to be very successful by providing an informal opportunity for discussion of various topics of interest to section members.

The section continued to publish all manuscripts presented at the annual meeting and the proceedings of the Biopharmaceutical Section is one of the most popular of the proceedings published by the ASA. Chris Gennings continues to direct this effort.

One of the most exciting accomplishments of the section during the year was the request to sponsor the 1995 Winter meetings. Earlier in the year, Lianng Yuh suggested that we consider sponsoring the winter meetings. We then approached Stu Hunter about the possibility of the section's sponsoring these meetings. In the past, we have co-sponsored sessions at the winter meetings and have had minor success. Stu was very receptive to our proposal, and we received official approval from Mike O'Fallon at our meeting in San Francisco. Ken Koury is the 1994 Program Chair and will be coordinating this as well as the other meetings we sponsor. He will aided in this effort by Joe Heyse, the program chair-elect for 1995. The next winter meetings will be held in January of next year in the research triangle area. We will be working very closely with the North Carolina chapter of the ASA to make these a success. Considerations are underway for publishing the proceedings of the entire meeting and making them available for distribution.

The Biopharmaceutical Section has well over 1,000 members, yet its activities are directed by a small group of individuals. Growth and vigor in the section require that different people from different disciplines participate in the complete variety of activities in which the section is involved. I encourage each member of the section to contact Bob Starbuck, Lilliam Kingsbury, Bob Davis, Ken Koury, or any member of the Executive Committee with suggestions, ideas, or any thoughts you might have which would make the section more effective and responsive to its membership and to the membership of the ASA. We cannot have too many people involved in the activities of Biopharmaceutical Section. The section belongs to its members and is there to serve them. To do this properly, it needs participation by all.

The last year has been a very challenging one for me personally and for the section. We have accomplished a lot and for that I thank all the members of the Executive Committee. We could not have accomplished what we did without the commitment and hard work provided by these people. These include our past chair Camellia Brooks; John Schmaltz who helped in the finance considerations; Nick Teoh who

Editorial Board

Avital Cnaan
University of Pennsylvania
Editor

Thomas Bradstreet
Merck Research Laboratories
Associate Editor

Eric Sampson & Alison Stern-Dunyak
American Statistical Association
Layout and Design

coordinated all our work groups; Pat O'Meara who chaired the Midwest Biopharmaceutical Statistics Workshop; the ever present Karl Peace who was instrumental in the coordination of the Applied Statistics Conference; our Council of Sections representatives, Ed Nevius and Janet Begun; Nguyen Dat for his help with the continuing education subcommittee; John Lambert who guided the student travel grant program; Akbar Zaidi for coordinating the membership survey that will be conducted the coming year; Mike Boyd for his contribution to quantitative literacy and continuing education; and Tuli Cnaan for her untiring effort in editing and publishing the *Biopharmaceutical Report*. These members of the Executive Committee and the other members of the Executive Committee mentioned earlier in this letter, all deserve the appreciation of the membership for helping the Biopharmaceutical Section grow and advance during 1993. It has been a pleasure working with them and I look forward to working with them in the future. I wish Bob Starbuck the best as he assumes the chair of the section; he has an outstanding committee with which to work and I know the 1994 will be even more successful than 1993.

Minutes of ASA Biopharmaceutical Section Executive Committee Meeting, August 9, 1993

Attendees:

Bruce Rodda	Bob Starbuck	Bob Davis
Mark Scott	Ken Koury	Dick Bittman
Nick Teoh	Lianng Yuh	Mike Boyd
Nguyen Dat	Tuli Cnaan	Anna Nevius
John Lambert	Akbar Zaidi	

Lee Decker (ASA Office)
Mike O'Fallon (Chairman of Committee on Meetings)

Bruce Rodda opened the meeting by announcing the winners of the recent Section elections: Lilliam Kingsbury for Section Chairperson and Joe Heyse for Program Chair for 1995.

1995 Winter Meeting

Mike O'Fallon and Ken Koury announced that the ASA Committee on Meetings had authorized the Section as the sponsor of the 1995 Winter Meeting. The theme of the meeting will be "Interface of Statistical Science with Other Scientific Disciplines". Ken noted that we need to work with Lee Decker to select a site for the meeting. Raleigh/Durham seems to be the first choice but concerns were expressed about the uncertain weather in that area in early January. The Biometrics Section was invited to co-sponsor some sessions at the meeting but they appeared somewhat reluctant to participate actively due to their own planning requirements for the 1994 IBC Meeting.

Mike O'Fallon reminded the committee that the Winter Conference will be a major effort requiring the support of many people. Nick Teoh, Joe Heyse, Bob Starbuck and Mike Boyd were appointed to help Ken with the planning.

Assignment: The North Carolina Chapter will appoint academic and FDA Committee members to the Planning Committee.

Lee Decker noted that the Winter Conference can be quite flexible, with any combination of sessions possible. Short courses are another option and should be set up through Bob Mason of Continuing Education. The outline of the invited session needs to be in place in 1993 followed by a call for contributed papers in 1994. A session set up by Gladys Reynolds and a Health Economics session by Joe Heyse were suggested. Lee suggested that we consider having companies sponsor the coffee breaks. Four hundred registrants is the break-even point, although non-member invited speakers do not pay registration fees. We should get announcements of the conference in each issue of Amstat News.

Assignment: Ken Koury will apprise the Executive Committee of progress.

1993 Business Meeting

Bruce announced that the Business Meeting would be held Wednesday, August 11 at 6:00 pm. Judy Goldberg of the Biometrics Section had asked that we try not to conflict with that section's meeting.

Assignment: Bob Starbuck will schedule the 1994 meetings to not overlap with Biometrics.

1994 Winter Meetings

The Section will sponsor sessions organized by Bob Small and Joe Heyse at the 1994 Winter Meeting in Atlanta.

Secretary and Treasurer Report

The March Executive Committee minutes were approved. Bob Davis announced that the Section had $54,170.44 cash on hand as of June 30. The proposed Section 1994 budget was approved. The Section's projected income for 1994 is $24,100. with projected expenses of $23,500.

Assignment: Bob Davis will submit the budget to the ASA office council.

Several suggestions for expenditures were made. Tuli Cnaan proposed that the Section's projected interest income ($1,500.00 in 1994) be used to fund a special invited speaker. Lee Decker noted that unless this session were properly structured, it would count as one of the Sections invited sessions allocated by ASA. She suggested that if the Section always paid an honorarium for the speaker the proposal might be acceptable. Realistically, the 1995 Annual Meeting is the earliest it could be implemented.

Assignment: Tuli Cnaan will draft a proposal for an invited speaker. Ken Koury will present it at the January meeting of the Committee on Meetings if the Executive Committee decides to pursue.

The idea of sponsoring students to present papers at the 1994 Annual Meeting was revisited.

Assignment: John Lambert will place announcements and application forms in the *Amstat News*.

Students should write on their abstract from that they wish to be considered for the Biopharmaceutical Section competition. The student must be the presenter and first author. The abstracts will be due at the ASA by February and the final paper by April 1. Up to five winners will be selected, each receiving a $1,000.00 travel award and a certificate.

Assignment: Ken Koury will forward all abstracts and final papers to Mark Scott, Nick Teoh, Bob Starbuck and John Lambert or their designees for review.

The committee agreed that there will be no change in Section dues for an individual but corporate membership will be reduced from $500.00 to $300.00. Each corporate member will be listed in the masthead of the *Biopharmaceutical Report*.

Assignment: Bruce Rodda will write all relevant corporate representatives announcing the reduced membership rate.

1993 Meeting

Mark Scott noted that the room size for the Section-sponsored session continues to be inadequate.

Assignment: Mark Scott will gather attendance information from session chairs and forward to Lee Decker.

1994 Midwest Statistics Conference

Dick Bittman reported that there were 140 registrants and 25 speakers at the 1993 conference. Lianng Yuh noted that Brad Efron will be the plenary speaker at the 1994 meeting, co-chaired by Earl Nordbrock and Tony Segreti.

Work Groups

Nick Teoh reported that the only active work group is the Population Pharmacokinetics group chaired by Lianng Yuh, who will become the new coordinator for the work groups. Nick urged the Section to encourage the younger statisticians to get involved with the work groups.

Roundtables

Nick Teoh announced that the Section was sponsoring eight roundtables luncheon discussions, all fully subscribed. He suggested that there be more tables, perhaps at other times of the day.

ENAR Meeting (1994)

As noted by Ken Koury, there is little progress on the Section's session for the 1994 meeting in Cleveland. He had received no proposals for sessions.

Post Meeting Notes:

With the assistance of Lianng Yuh and Nick Teoh, we have obtained commitments for five invited paper sessions at the 1994 ENAR meetings. They are listed elsewhere in this issue.

We will also be sponsoring a one-day course on "Resampling-based Multiple Testing" given by Peter Westfall and Stanley Young.

Annual Meeting 1994

Ken Koury reported that five proposals have been received for consideration as an invited paper session at the 1994 ASA meeting in Toronto:

1. *An Individual Bioequivalence: Statistical Issues and Clinical Impact*, proposed by James Esinhart.
2. *Nonlinear Mixed Effects Models in Drug Development*, proposed by Demissie Alemayeh
3. *Invited Paper Session on AIDS Clinical Trials*, proposed by Neil Dubin (also submitted to Biometrics, ENAR, WNAR).
4. *Pharmacoeconomic Issues in Clinical Trial Drug Development*, proposed by Christopher Barker (also submitted to Business and Economics).
5. *Multiple Endpoints in Clinical Trials*, proposed by Ji Zhang.

Ken may negotiate with other sections to sponsor some of these, such as pharmacoeconomic session.

Assignment: Bruce Rodda will convene a subset of the Executive Committee to decide the rank order of these sessions and to make other plans for 1994. (Note: Meeting has been scheduled for November 2 at Bristol-Myers Squibb).

Training

Mike Boyd updated his proposal for a "Training Workshop for New Biopharmaceutical Statisticians" to be run in Toronto at the 1994 Annual Meeting. The tentative schedule follows:

1:00 pm	Role of Statistics in Drug Development - Bob Starbuck and Bruce Rodda
2:15 pm	Break
2:30 pm	FDA Guidelines for "The Format and Content of the Full Integrated Clinical and Statistical Report of a Controlled Clinical Study" - Gordon Pledger
3:45 pm	Break
4:00 pm	Technical Writing - Howard Smith (medical writer at PRA)
5:00 pm	Adjourn

The idea behind the workshop is for experienced Section members to interact with the participants. The workshop is not meant to compete with existing PMA courses. Following the Executive Committee meeting and after consultation with ASA, Mike Boyd and Bob Starbuck established that the workshop would be limited to 40 attendees, with a fee of $50.00 for members, $20.00 for students. ASA would take care of the finances, room and snacks.

Assignment: Mike Boyd will talk to Bob Mason and Marti Hearron of Continuing Education to complete plans for the workshop

In other Continuing Education business, Nguyen Dat noted that Lilliam

Kingsbury is still encouraging Joe Heyse to organize a Health Economics course in Toronto.

Assignment: Bruce Rodda and Joe Heyse will decide whether to make a proposal for a HEcon course. We will aim for 1995 for this course.

Applied Statistics Conference

Bruce Rodda reported for Karl Peace that the Atlantic City conference will feature the following sessions:

A. **Session 1:** "Interim Analyses of Repeated Measures Designs", Harji Patel, Berlex. David Reboussins, Wake Fores
B. **Session 2:** "Population PD/PK Models: an FDA Perspective", Stella Machado, FDA; Tom Ludden, FDA
C. **Session 3:** "Problems in Multiple Arm Trials", Nancy Geller, NHLBI; Michael Proschan, NHLBI
D. **Two-day Short Course:** "Population PD/PK Models, Analysis and Applications", Nick Holford, BRCI; Tom Ludden, FDA; Stella Machado, FDA; Steve Olson, Parke-Davis

ASA Fellows

Bruce announced that John Schmaltz of Upjohn was elected Fellow for 1993.

Assignment: All Section members should send any proposed Fellow nominations to Bruce.

FDA Advisory Committees

There was no progress or recommendation for the committees.

Assignment: Bruce will review any progress with Vern Chinchilli.

Biopharmaceutical Report

Tuli Cnaan reported that the second newsletter of 1993 would be published imminently and the third newsletter is in progress.

Assignment: Bruce Rodda and Bob Starbuck will appoint a new Editor and Associate Editor of the newsletter by August, 1994.

Publications

Chris Jennings reported that as of mid-July over 260 issues of the 1992 Biopharmaceutical Proceedings had been purchased. The number of copies run to date is 770, up 4% from last year. The price per volume (set at $25.00 for pre-publication, $30.00 for members and $45.00 for non-members) has not changed since 1990. The average cost per volume is $9.90. To date we have a surplus from the production of the proceedings of $5,975.00, an increase of 21% from last year and 69% from 1991. The 1992 Proceedings includes 49 papers with an average length of 6.5 pages per paper.

The organization for the 1993 Proceedings is underway. We sent mailing labels to the ASA office of all invited speakers in Biopharm-sponsored sessions from ENAR in Philadelphia, The Applied Statistics Conference in Atlantic City, and the Midwest Biopharmaceutical Statistics Workshop in Muncie. Lists already exist for invited speakers in Biopharm-sponsored sessions at the Joint Meetings. ASA sent information for paper submission to the authors on these lists on August 1. The papers are due back to ASA October 15, 1993...

Bruce noted that the Editor of *STATS* Magazine requested from the Biopharmaceutical Section a contributing editor to solicit one featured article each year

Assignment: Bruce has named Steve Ruberg as the contributing editor.

Council of Sections

Anna Nevius, filling in for family member Ed, reported that the Council reviewed the issue of certification of statisticians. If certification proceeds, the Section may need to send representatives to an ASA committee on job analysis.

Quantitative Literacy

Assignment: Mike Boyd will submit to the Biopharmaceutical Report a small write-up on the Section's quantitative literacy activities.

Awards

Bruce announced that the Section would present three awards at the Business Meeting for the best papers presented in Biopharmaceutical sections sponsored contributed paper sessions. The recipients are Ron Helms, Joe Heyse and, Carolin and Michael Frey (co-authors).

Membership Activities

John Lambert plans to send a highlighted Operations Manual to each Section member. Akbar Zaidi reported that the membership survey questionnaire has been completed and will be mailed to the Section through the ASA office. The "Hot Pink" Section flyer will be included in the mailing. John Lambert has received an offer from Steve Albrecht of Clintrials to provide the data entry for the survey at no charge to the Section.

Call for Statisticians

Committee for Recommending Statisticians to FDA Advisory Committees (CRSFAC)

The U.S. Food and Drug Administration (FDA) maintains a number of advisory committees which provide expertise and guidance on scientific issues. The committees within the FDA's Center for Drug Evaluation and Research are as follows:

- Anesthetic & Life Support
- Anti-Infective
- Antiviral
- Arthritis
- Cardiovascular and Renal
- Dermatology
- Drug Abuse
- Endocrinologic and Metabolic
- Fertility and Maternal Health
- Gastrointestinal
- Generic
- Medical Imaging
- Nonprescription
- Oncology
- Peripheral and Central Nervous System
- Psychopharmacologic
- Pulmonary-Allergy

In addition, there may be vacancies for statisticians on advisory committees for the Center for Biologics Evaluation and Research and the Center for Devices and Radiological Health.

At least one statistician serves on each of these committees. The Biopharmaceutical Section of the ASA formed a Committee for Recommending Statisticians to FDA Advisory Committees (CRSFAC) whose function is to solicit interest from qualified statisticians and make recommendations to the FDA as to appointments.

At this time, the CRSFAC needs to update its list of qualified statisticians. The qualifications for a statistician to serve on an FDA advisory committee are:

1. Sound training in statistics;
2. considerable experience in clinical trials in the appropriate drug specialty;
3. well-proven abilities and skills to make persuasive arguments on important issues in a committee forum.

Individuals who are interested in serving should be aware that all advisory committee members are subject to government conflict of interest regulations. Therefore, candidates with extensive involvements with regulated industry on matters which will come before their committees frequently will be recused from participation.

Any qualified statistician who would like to be considered for an appointment to an FDA advisory committee should submit a C.V., prior to March 31, 1994, with a cover letter indicating areas of interest to the chair of the CRSFAC at the following address: Vernon M. Chinchilli, Ph.D., Chair, CRSFAC, Center for Biostatistics & Epidemiology, Penn State University, Hershey, PA 17033

Book Review

Cross-over Trials in Clinical Research. Stephen Senn
John Wiley & Sons Ltd., Chichester, England (1993)

Reviewed by James A. Bolognese
Associate Director
Biometrics Research
Merck Research Labs, Rahway, NJ

This book provides a user-friendly, work-sheet approach to the analysis of crossover studies. It is intended for (1) the scientist using cross-over trials who either has to analyze them himself or needs to interpret their analyses by others, and (2) the applied statistician with no particular experience with cross-overs. The author presents many helpful tips on crossovers and clinical trials, in addition to a self-admitted biased viewpoint on carryover effect.

Chapter 1 provides useful descriptions of cross-overs, discusses their advantages and disadvantages, and describes the mathematical level (heuristic arguments with little algebra) and general attitudes taken in the book. Among the attitudes are a ban on pre-testing of factors and model reduction based on data from the current trial, and the recommendation to design cross-over trials to avoid carry-over and ignore it in their subsequent analysis. Nearly all computations described in the book can be achieved with a hand calculator, but SAS® examples are also included. Chapter 2 describes the statistical level assumed: concepts of random variables, estimators and SE's confidence intervals, significance levels, t-tests, F-tests, ANOVA, and some computer package knowledge of linear regression. A review of linear combinations of random variables, associated variance, and their use in estimation completes the Chapter.

The AB/BA design with normally distributed data is extensively discussed in Chapter 3. The computational approach taken is to assess treatment differences blocked by sequence group; this is expanded with a discussion of why carry-over cannot be purely assessed. Incorporation of adjustment for a covariate is skillfully included in the author's straight-forward spreadsheet-type approach to the analysis. This basic approach ought to be easily understood by the non-statistician. Chapter 4 continues on the analysis of AB/BA design, but centers on data transformations, non-parametric approaches, and binary outcomes. This chapter contains an excellent intuitive description of the sign test, the signed-rank test, and associated confidence intervals which are adjusted for period effect. The author presents a very nice progression through non-parametric rank-based methods and their application to cross-overs.

In Chapter 5, designs with ≥ 3 treatments are assessed in pairs of treatments blocked by sequence group using methods described in Chapter 2 for the AB/BA design. Balancing for period effect, but not for carry-over effect is recommended, because the author feels that the latter can only be dealt with by an adequate washout period. Non-parametric analyses for these designs are discussed in Chapter 6; included are Cochran-Mantel-Haenzel statistics, Hodges-Lehman estimators, and Mantel-Haenzel statistics for stratified binary outcomes. As with previous chapters, these two chapters are also skillfully presented and should be easily understood by a mathematically sophisticated non-statistician. However, this reviewer wishes the author had cautioned the practitioner employing the recommended pairwise treatment comparison approaches of the multiplicity and correlation issues.

"Special Designs" are discussed in Chapter 7; they include factorial, incomplete block, n=1 trials, and bioequivalence studies. The discussion of single-patient trials is very informative, worthwhile, and insightful regarding the associated probability of type I error. The author highlights well the problem with relying on t-tests from n=1 trials, pointing out the proper interpretation based on randomization tests. Chapter 8 describes some basic graphical and tabular presentations to which non-statisticians should pay close attention; however, there is nothing new here for the statistician. This reviewer was surprised at the omission of the usual response-over-period plots of treatment-by-group means; they were not even referenced.

The following design issues were addressed in Chapter 9: parallel versus cross-over, use of washout to eliminate carry-over, a cursory look at choices of sequences, sample-size considerations, and a discussion of missing data. This chapter contains a very useful and clear description of the difference between intra- and inter- subject variance, and their relationship to the correlation coefficient. Use of a covariate is also skillfully tied to this discussion. A handy SAS® program for computing power is included.

Having alluded to it throughout the book, the author fires five salvos against analyzing for carry-over effect in Chapter 10.

(1) "If it applies then the investigator can design a trial which eliminates it." But this reviewer feels that such designs may be impractically long to carry out, especially for large numbers of treatments.

(2) "It is implausible given elementary pharmacokinetic (modeled by sum of exponentials) and pharmacodynamic (modeled by the Hill equation) theory." Persuasive mathematical arguments are presented, but psychological carry-over is not addressed, and the author claims never to have seen a constant carryover.

(3) "The models which incorporate it are self-contradicting." Using a Williams square for the 4x4 crossover involving treatments PP, AP, PB, and AB, the author states that while the carryover of AB interaction is accounted for, the interaction of main effect of A with carryover of B is not. He feels that these should be equally important, therefore, the design is self-contradicting. This reviewer feels that the importance issue is subjective, not necessarily self-contradicting.

(4) "The estimators based on it are inefficient" (compared to unadjusted-for-carryover estimates). But the author does not say that the latter are biased if "simple" carryover is present, an event the author contends never occurs.

(5) "The designs associated with it are not necessarily better than others." This depends on the assumptions about the true underlying conditions.

These arguments are clearly and persuasively presented with counter arguments to many issues, but not to those raised above by this reviewer. Following these salvos is a further 10+ pages presenting the analysis adjusted for carryover effects, "if the reader is not persuaded by these arguments." The analysis is presented in a nicely intuitive and understandable fashion involving the derivation of weights for linear combinations of cell means to estimate pairwise treatment differences adjusted for carryover.

The book contains many clearly presented, useful tips about clinical trials, among which are the following:

- clinical trials don't really represent random samples from populations, rather, results are interpreted/ assumed to represent that which is expected;
- concentrate on estimation, and avoid over-emphasis on "p<.05";
- use of baselines and covariance analysis can improve precision;
- guidance on interpreting interaction; assessing p-values for hypothesis generation in borderline cases;
- examining variances to justify assumptions and signal their effect by treatment; and
- the t-statistic is generally robust except in extreme cases.

In general, regarding style, there is a gross lack of commas throughout the book, some of which made reading sentences difficult. The prevalence of typos and grammatical errors indicated a lack of professional proof-reading. The choice of fonts for SAS® example program statements and output match too closely those used for regular text. This author's pet peeve was the incorrect citation of the reviewer's bible for design as "Cox (1957)", instead of "Cochran & Cox (1957)"; maybe "Cox (1958)" was intended.

Other particular problems worth noting are the following. The statement on page 80 about excluding, as uninformative, patients who are missing 1 of 2 periods in a 2x2 crossover, should have included a caution about informative censoring. The author rightly does not approve of power calculations as an aid to interpret non-significant results, and suggests looking at likelihood under the alternative, but states that this is beyond the scope of the book. This reviewer would have liked to see some reference to the use of confidence intervals, which are not beyond the scope.

With the above reservations, this book is recommended as a guide to a straight-forward approach to the analysis of crossover trials, or as a reference in support of ignoring carryover effect in the choice of treatment sequences in crossover designs and their subsequent analysis, if anyone would want to take that approach.

Book Review

Multiple Comparisons, Selection, and Applications in Biometry
Edited by Fred M. Hoppe
Marcel Dekker, 1993

Reviewed by Dror M. Rom
Rhone-Poulenc Rorer

This book consists of a collection of papers presented at a Symposium on Biostatistics held at McMaster University, Hamilton, Canada in honor of Charles Dunnett.

As its title indicates, the book is divided into three sections: Multiple Comparisons, Selection, and Biometry & Design.

The first chapter is a most interesting conversation with Professor Dunnett about his military, industrial, and academic

1994 International Research Conference on Lifetime Data Models in Reliability and Survival Analysis

Boston 15-17 June 1994

This research conference will be held in Boston, MA on June 15-17, 1994. The conference is co-sponsored by the Statistics Department of Harvard University, the Boston Chapter of the American Statistical Association, Kluwer Academic Publishers and Pfizer, Inc. The conference has been organized to bring together specialists and practitioners from all fields who have an interest in lifetime data analysis, including biostatistics, the natural sciences, engineering, business, and the social sciences. The following list indicates the wide range of conference topics that are of interest:

Accelerated failure rate models, Bayesian lifetime models, censoring and truncation, classes of lifetime distributions, competing risk models, counting processes, degradation processes, inequalities for reliability bounds, maintenance policies and replacement models, meta-analysis of life data, models for multiple states, models for noncompliance, multivariate failure models, network reliability models, nonparametric estimation of survival functions, nonproportional hazards models, parametric estimation and predictive inference, parametric regression models, proportional hazards models, quality-of-life models, random effects models, rank tests for comparing lifetime distributions, and surrogate marker processes.

Registration fee is $150
Student registration fee is $30
Thursday night dinner ticket(s) $35 x (# of tickets)

The registration fee covers one mixer ticket, meeting schedule, abstract booklet and a copy of the Conference Proceedings, which will be published after the conference. The Thursday night dinner ticket is not included.

The student registration fee is for full-time students only. This reduced fee includes the meeting schedule and abstract booklet, but not the mixer ticket, Proceedings, or dinner ticket.

Contact
Dr. Mei-Ling Ting Lee for registration forms at:
Channing Laboratory, Harvard Medical School
180 Longwood Avenue, Boston, MA 02115
email: stmei@gauss.med.harvard.edu

careers, from his early work on radar in the Royal Navy and Air Force to his pioneering work in drug screening.

The second chapter is a discussion on past, present, and future of Biometry by Professor David Finney. Professor Finney brings up some important issues that will effect the future advancement in Biometry, such as software development.

The sections on Multiple Comparisons and Selection consist of a nice mixture of theory and application, and both review papers as well as new developments.

The article by John Tukey "Where Should Multiple Comparisons Go Next" can serve as a starting point for future research. Professor Tukey emphasizes some fundamental aspects of multiple comparisons:

"Purposes for the use of multiple comparison vary widely, and techniques may need to vary widely as a consequence."

"Multiple comparisons are somewhat complicated—as a result, graphical presentation of multiple comparisons results is even more important than graphical presentation of simpler results."

The section on Selection features several interesting articles which cover both new methods and review of existing methods. I particularly liked the papers of Stefan Driessen "A note on Selection Procedures and Selection Constants" and the paper by Manfred Horn and Rudiger Vollandt "Sharpening Subset Selection of Treatments Better than a Control." These two papers present the parallels between Multiple Comparisons and Selection procedures. Statisticians who work primarily in one these two areas will find it useful to relate their work to similar issues in the other areas.

The selection on Biometry and Design consists of several articles of importance to clinical statisticians. Those who occasionally face the problem of "Interim Analyses" will find interest in the review article by Peter Armitage 'Interim Analyses in Clinical Trials'. Of particular interest and somewhat controversial approach in this area is the incorporation of Bayesian methods. To this end, Professor Armitage states: "I hope we can regard these differences of approach as reflecting legitimate differences in the way we chose to look at data, rather than as exemplifying moral rectitude or turpitude, as sometimes seems to be implied by our discussions".

In summary, while this is not a typical textbook on multiple comparisons and selection procedures, it certainly would be a good source for those who want to stay current in these fields. The only negative point I could find about this book is its price: $135 seems a little high.

ENAR Meeting Schedule

Monday, April 11, 1994
3:30 - 5:15 pm
19. Sequential Designs in Clinical Trials
Sponsor: ASA, Biopharmaceutical Section
Organizer: C.F. Jeff, Wu, University of Michigan
Chair: Dan Anbar, Schering-Plough Research Institute

3:30 Two-stage design of bioessays in pharmaceutical studies: An overview. C.F. Jeff Wu, University of Michigan
4:00 Practical experience using a two stage study design. L. Mellars, D. Anbar, Schering-Plough Research Institute
4:30 Some recent experiences in two-arm and multi-arm adaptive clinical trials. Roy N. Tamura, Eli Lilly and Company Incorporated
5:00 Floor discussion

Tuesday, April 12, 1994
9:30 - 10:15 am
25. Multiple Endpoints in Clinical Trials
Sponsor: ASA, Biopharmaceutical Section
Organizer/Chair: Ji Zhang, Merck Research Laboratories

8:30 Testing the hypothesis that matters. Thomas Capizzi, Ji Zhang, Merck Research Laboratories
8:55 Improving some methods for multiple endpoints. Dei-In Tang, Nathan S. Kline Institute for Psychiatric Research
9:20 Using multiple endpoints to answer clinically relevant questions. David S. Salsburg, Pfizer Central Research
9:45 Discussants. Abdul J. Sankoh, FDA and Bruce W. Turnbull, Cornell University
10:05 Floor discussion

Tuesday, April 12, 1994
3:30 - 5:15 pm
38. FDA/Industry Session: Analysis of Longitudinal Data in Clinical Trials
Sponsor: ASA, Biopharmaceutical Section
Organizers: Satya D. Dubey, FDA, Nick K.W. Teoh, Schering-Plough
Chair: Samuel M. Heft, Schering-Plough

3:30 Overview of methodology for longitudinal data analysis within the regulatory context. Masahiro Takeuchi, FDA
3:50 Application of longitudinal data analysis methodology to account for dropouts. Corste Dating Sanders, Shu-Yen Ho, Lingshi Tan, Schering-Plough Research Institute
4:10 Longitudinal data analysis for heartburn trials. Mohannad F. Huque, Abdual J. Sankoh, Ferrin, D. Harrison, Satya D. Dubey, FDA
4:30 Application of generalized estimating equations (GEE) in the analysis of repeated ordinal data. David Shaw, Bristol-Myers Squibb (Brussels), Mike Kenward, Rothamsted Experimental Station, Luc Biknens, Jean Senden, Bristol-Myers Squibb (Brussels)
5:00 Discussants. Bruce E. Rodda, Bristol-Myers Squibb, H.M. James Eung, FDA

Wednesday, April 13, 1994
9:30 - 10:15 am
44. Methods for Handling Dropouts in Comparative Efficacy Trials
Sponsor: ASA, Biopharmaceutical Section
Organizer/Chair: Chuck Davis, University of Iowa

Wednesday, April 13, 1994
10:30 - 12:15 pm
48. Analyzing Survival Data: Recent Advances in Methodology
Sponsor: ASA, Biopharmaceutical Section
Organizer/Chair: Robert Strawderman, University of Michigan

10:30 Unbiased estimation in the Cox proportional hazards model with missing covariate data. Marian Pugh, Stuart Lipsitz, David Harrington, Harvard School of Public Health, Dana Farber Cancer Institute
10:55 Evaluating surrogate markers of clinical outcome when measured with error. Urania G. Dafni, Anastasios A. Tsiatis, Harvard School of Public Health
11:20 Semiparametric analysis of general hazard-based survival models. D.Y. Lin, S. Ying, University of Washington
11:45 Discussant. Robert Wolfe, University of Michigan
12:00 Floor discussion

ASA Biopharmaceutical Section Executive Committee—1994

Immediate Past Chair

Bruce E. Rodda, Ph.D.
Vice President, Biostatistics & Data Management
Bristol-Myers Squibb
Pharmaceutical Research Inst.
PO Box 4000
Princeton, NJ 08543-4000
(609) 252-5776
(609) 252-6060 fax

Chair

Robert R. Starbuck, Ph.D.
Assistant Vice-President
Clinical Biostatistics and Data Management
Wyeth-Ayerst Research
145 King of Prussia Road, B-2
Radnor, PA 19087-4517
(215) 341-2070
(215) 341-2092 Fax

Chair Elect

Lilliam Kingsbury, Ph.D.
Director of Biostatistics
Bio-Pharm Clinical Services
512 Township Line Road
Blue Bell, PA 19422
(215) 283-0770
(215) 283-0733 fax

Secretary - Treasurer

Robert L. Davis, Ph.D.
Director, Biostatistics
The Astra/Merck Group of
Merck & Co., Inc.
725 Chesterbrook Blvd.
Wayne, PA 19087-5677
(215) 695-1070
(215) 889-1288 Fax

Program Chair

Kenneth J. Koury, Ph.D.
Dept. Head, Clinical Statistics
American Cyanamid Co.
Lederle Laboratories
Building 60, Room 203
North Middletown Road
Pearl River, NY 10965
(914) 732-3827
(914) 732-5518 Fax

Program Chair Elect

Joseph F. Heyse, Ph.D.
Director, Health Economics Statistics
Merck Research Laboratories, BL-32
Sumneytown Pike
West Point, PA 19486
(610) 397-2334
(610) 397-2931 Fax

Executive Committee Member

Michael N. Boyd, Ph.D.
Director, Biostatistical Services
Pharmaceutical Research Associates
2400 Old Ivy Road
Charlottesville, VA 22903-4826
(804) 977-2772
(804) 293-7084 Fax

Executive Committee Member

Charles S. Davis, Ph.D.
Associate Professor
Dept. of Preventive Medicine
University of Iowa
2837 Steindler Bldg.
Iowa City, IA 52242-1176
(319) 335-9625
(319) 335-9200 Fax

Executive Committee Member

Nguyen V. Dat, Ph.D.
Vice President, Project Operations
Biometrics Research Institute
1300 North 17th Street
Arlington, VA 22209
(703) 276-0400
(703) 243-9746 Fax

Executive Committee Member

Sally A. Greenberg, Ph.D.
Senior Statistical Research Scientist
Syntex Development Research
3401 Hillview Avenue, A6-100
Palo Alto, CA 94804-1397
(415) 813-4888
(415) 813-4844 Fax

Executive Committee Member

C.S. Wayne Weng, Ph.D.
Statistics Manager
Shering Laboratories
2000 Galloping Hill Road
Kenilworth, NJ 07033
(908) 298-5457
(908) 298-5700 Fax

Executive Committee Member

Work Group Coordinator
Chair of Midwest Biopharm. Meeting
Lianng Yuh
Senior Manager
Biometrics Department
Warner-Lambert/Parke-Davis
2800 Plymouth Road
Ann Arbor, MI 48105-2430
(313) 996-7854
(313) 996-1796 Fax

Representative, Applied Statistics Conference

Karl E. Peace, Ph.D., FASA
President, Biopharmaceutical
Research Consultants, Inc.
4600 Stein Road, Suite B
Ann Arbor, MI 48105
(313) 663-4440
(313) 663-7797 Fax

Publications Officer

Chris Gennings, Ph.D.
Biostatistics Department
Medical College of Virginia
Box 32
MCV Station
Richmond, VA 23298-0032
(804) 786-9824
(804) 371-8482 fax

Biopharmaceutical Report *Editor*

Avital Cnaan, Ph.D.
Division of Biostatistics, Department of Pediatrics
University of Pennsylvania
The Children's Hospital of Philadelphia
34th Street and Civic Center Boulevard
Philadelphia, PA 19104-4399
(215) 590-4486
(215) 590-4487 Fax

Council of Sections Representative

Harji I. Patel, Ph.D.
Biostatistics & RIS
Berlex Laboratories, Inc.
300 Fairfield Road
Wayne, NJ 07470-7358
(201) 305-5386
(201) 694-9093 Fax

Council of Sections Representative

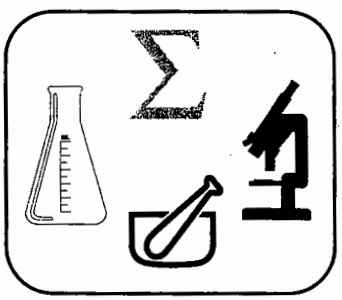
Denise J. Roe, Dr.P.H.
Assistant Professor
University of Arizona
Arizona Cancer Center
1515 North Campbell Avenue
Tucson, AZ 85724
(602) 626-2281
(602) 626-2284 Fax

Let's Hear from You!

If you have any comments or contributions, contact:
Dr. Avital Cnaan, Editor, Biopharmaceutical Report, *Division of Biostatistics, The Children's Hospital of Philadelphia, 34th Street and Civic Center Boulevard Philadelphia, Pa 19104-4399, telephone: (215) 590-4486 Fax (215) 590-4487*

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

© 1994 The American Statistical Association
Printed in the United States of America



Biopharmaceutical Report
c/o American Statistical Association
1429 Duke Street
Alexandria, VA 22314-3402
USA

FIRST-CLASS MAIL
U.S. POSTAGE
PAID
WASHINGTON, D.C.
PERMIT NO. 9959

FIRST CLASS POSTAGE