Glossary

a	calculated intercept in regression
ANCOVA	analysis of covariance
ANOVA	analysis of variance
b	calculated slope in regression
BMS	between mean square
BSS	between sum of squares
C. T.	correction term
CI	confidence interval
CV	coefficient of variation; relative error; relative standard deviation
CXR	column × row interaction
df	degrees of freedom
E	expected number in chi-square table
F	*F* value for *F* distribution
Ha	alternative hypothesis
Ho	null hypothesis
In	natural log
LSD	least significant difference
O	observed number in chi-square table
p	estimated proportion (binomial)
p (A)	probability that event will occur
p (A|B)	conditional probability of A given B
Po	true or hypothesized proportion
q	probability of failure in binomial
R	range
r	calculated correlation coefficient
r (Dixon)	computation for outlier analysis
r^2	square of correlation coefficient
RSD	relative standard deviation
S	sample standard deviation
S^2	sample variance
$S^2y.x$	estimated variance from line fitting
t	*t* value for *t* distribution
Tn	test for outlier
σ	true standard deviation of distribution
w	weight in weighted least squares
WSS	within sum of squares
X_i	*i*th observation
Z	normal standard deviate
X^2	chi square
Δ	delta, true change or difference
N	sample size
Σ	sum of observations

α	alpha level or error for null hypothesis; error of first kind
β	beta error (1-power)
δ	observed change or difference
μ	true mean of distribution

Appendix I
Some Properties of the Variance

I.1 POOLING VARIANCES

In many statistical procedures, an estimate of the variance is obtained by "averaging" or *pooling* the variances from more than one group of observations. The pooling of variances is appropriate in cases where samples from separate groups or different experiments provide estimates of the *same* variance. Note that we do not pool or average standard deviations. As we have previously noted, the sample variance, $\sum (X - \bar{X})^2/(N-1)$ [Eq. (1.5)], is an unbiased estimate of the true population variance. The standard deviation, estimated from a *sample*, is a *biased estimate* of the true *population* standard deviation. On the average, the sample standard deviation underestimates the population standard deviation. Estimation and properties of the variance are important considerations in both theoretical and applied statistics.

A common example of a procedure where variance estimates from different groups are pooled is the two-sample independent-groups t test for comparison of means discussed in chapter 5. In this test, the average results of two treatments* (e. g., active drug versus placebo; dissolution behavior of two tablet formulations) are compared. An estimate of the variance of the observations is needed in order to compare the two treatment groups statistically. An important assumption underlying this test is that the variances for each group are equal. The variance is first calculated for each treatment group separately. The variance is more precisely estimated from samples with a larger number of observations, and the pooled variance from both treatment groups is the best estimate of the common variance. For example, suppose that the following variances were observed in a comparative experiment:

Placebo group: $N = 25$ and the variance $(S^2) = 10$
Drug group: $N = 20$ and the variance $(S^2) = 15$

Although we assume that the true variance (the population variance) is the same for each group, different variances are observed in the two groups. If the two groups truly have equal variance, the difference in the observed variance is a consequence of random variation, due in part to the particular samples which were chosen, and measurement errors. The pooling procedure, in general, uses a *weighted average*, where the weights are equal to the degrees of freedom [see Eq. (1.2)].

$$S^2 \text{ pooled} = S_p^2 = \frac{(24)(10) + (19)(15)}{24 + 19} = 12.21.$$

The standard deviation is 3.49 ($\sqrt{12.21}$). The numbers 24 and 19 are the degrees of freedom for the two groups. If variances are to be pooled from more than two groups, the procedure is the same. Use a weighted average of the group variances, weighting the variance in each group by its number of degrees of freedom.

I.2 COMPONENTS OF VARIANCE

Variability of observations usually arise from more than one source. Hence, the variability of observations can often be expressed as the sum of independent sources of error that comprise the

* The word "treatment" in statistics does not necessarily mean treatment in the medical sense. Treatments are conditions or combinations of conditions whose effects on an experimental outcome are to be assessed.

total variation. This notion is presented in more detail under the topic of *components of variance* in section 12.4.1. The variance of the average of assay results for three tablets obtained by selecting a single tablet from each of three batches and assaying each tablet is as follows: [*variance* due to mean potency differences among batches (i.e., the batch averages are not identical) + *variance* due to tablet differences within batches† + *variance* due to drug assay]/3. Note that this is the variance of a mean of three results (a total of three tablets have been assayed from the three batches). This accounts for the number 3 in the denominator ($S^2 = S^2/N$).

Similarly, the variability of individual cholesterol changes, derived from a group of patients, such as shown in Table 1.1, is the sum of the components that contribute to the overall variability: (a) biological variation as reflected in inherent differences between patients, (b) the day-to-day variability within patients (a single person's cholesterol varies from day to day), and (c) the analytical error, among other sources of error.

I.3 VARIANCE OF LINEAR COMBINATIONS OF INDEPENDENT VARIABLES

The variance of linear combinations of variables, where the variables are independent, can be shown to be

$$\text{Variance}(mX_1 \pm nX_2) = m^2 \,\text{variance}(X_1) + n^2 \,\text{variance}(X_2), \tag{I.1}$$

where m and n are constants. This important result can be used to derive the variance of the mean of n independent observations, for example. Consider m observations of the variable X. We can represent the observations as X_1, X_2, X_3,. . ., X_{m}. The mean is

$$\frac{\sum X_i}{m} = \frac{X_1 + X_2 + X_3 + \cdots + X_m}{m}.$$

The variance of each X is σ^2. Therefore, the variance of the mean is

$$\frac{\sigma_1^2 + \sigma_2^2 + \sigma_3^2 + \cdots \sigma_m^2}{m^2} = \frac{m(\sigma^2)}{m^2} = \frac{\sigma^2}{m}$$

Equation (I.1) also demonstrates that the variance of the difference of two independent observations is the *sum* of their variances. An example noted by Mandel [1] that illustrates this concept is the timing of a reaction. A stopwatch is started at the initiation of the reaction and stopped at some end point. The time depends on both the initial and final readings. If errors in the times are independent, the variance of $t_2 — t_1$, the difference between final and initial readings, is the sum of the variances; that is, the error of the difference of the two readings is larger than the error of either reading alone. Consider another example where a procedure calls for 10 mL of solution to be removed from a beaker containing 30 mL. Only 10-mL pipettes are available. The original 30 mL of solution is prepared by pipetting three 10-mL portions into a beaker. A total of 10 mL is then removed. The variance of the volume remaining in the solution is calculated as follows:

$$\text{Variance}(P_1 + P_2 + P_3 - P_4) = \sigma^2 P_1 + \sigma^2 P_2 + \sigma^2 P_3 + \sigma^2 P_4,$$

where P_{i} ($i = 1, 2, 3, 4$) represents the four pipetting steps. If the variance of a pipetting step is 0.01, the total variance of the remaining solution (with an expected volume of 20 mL) is (4)(0.01) = 0.04.

REFERENCE

1. Mandel J. The Statistical Analysis of Experimental Data, New York: Interscience, 1964.

† Variation resulting from differences in tablet potency in a randomly chosen sample of tablets which is due to the inherent variability of tablets (a result of the heterogeneity of the tableting process) is also known as "sampling error."

Appendix II
Comparison of Slopes and Testing of Linearity: Determination of Relative Potency

A common problem in bioassay, or when comparing the potency of compounds such as in drug screening programs, is the assessment of the relative potency of the comparative drugs. The problems in this analysis consist of (a) obtaining a function of dose and response that is linear, (b) testing the lines for each compound for parallelism (i.e., equality of slopes), and (c) determining the relative potency. We will discuss some elementary concepts for a comparison of two anti-inflammatory compounds, a standard drug (St) and an experimental compound (Ex). The experiment consists of measuring the reduction in volume after treatment of initially inflamed paws of two animals at each of three doses for each compound. The results are shown in Table II.1 and plotted in Figure II.1. The figure shows that the plot of *log* dose versus response is approximately linear. A *transformation* of dose and/or response is often necessary to achieve linearity in dose-response relationships. The response is usually considered to be a linear function of *log* dose (see chap. 10). Transformations to obtain linearity are desirable because straight-line relationships are more easily analyzed and interpreted than are more complex functions.

How does one determine if the data are represented by a linear function such as a straight line? A known theoretical relationship between X and Y may be sufficient to answer the question. From a statistical point of view, replicate measurements at fixed values of X are needed to test for linearity. Replicate measurements of Y at a fixed X represent $S^2{}_y$ only, a variance estimate which is independent of the functional form of X and Y. If X and Y are truly related by a straight-line function, deviations of the observed values of Y from the fitted line should be due only to the variability of Y. If the relationship between X and Y is not a straight line, the variance as measured by the deviations of Y from the fitted line will be increased due to "nonlinearity" (see Fig. 7.4b). To test for linearity, we compare the variance due to deviations of Y from the fitted line (deviations from regression) to the variation due only to Y (the pooled error from the Y replicates, the within mean square). The "deviations" mean square is the mean square due to deviations of the averages of Y (at each X) from the fitted line. The statistical test is an F test obtained from an analysis of variance. The concept of this test is illustrated in Figure II.2.

To perform the test, a one-way ANOVA is first performed on the data (Table II.2), duplicate determinations for three doses in the present example. The ANOVA is computed for each of both the standard and experimental drugs. For example, the calculations for the ANOVA for the standard drug are as follows:

$$\text{Total SS} = \sum Y^2 - \frac{\left(\sum Y^2\right)}{N} = 1.674 - 1.4406 = 0.2334$$

$$\text{Between-doses SS} = \frac{0.49^2 + 1.00^2 + 1.45^2}{2} - 1.4406 = 0.2307.$$

The within SS is the difference between the total SS and the between SS (see sec. 8.1).

The between-doses SS is the sum of two components: (a) the SS due to the slope (regression SS) and (b) the SS due to *deviations of the mean values (at each X) of Y from the fitted line. The deviation SS* has been discussed above and is shown in Figure II.2. The easiest way to compute the deviation SS is to divide the between-doses SS into its components as follows. The "regression" SS has 1 degree of freedom and is defined as

$$\text{Regression SS} = b^2 \sum (X - \overline{X})^2. \tag{II.1}$$

Table II.1 Results of the Experiment Comparing Potencies of Two Compounds[a]

	Dose (mg)		
Compound	**5**	**15**	**45**
Standard (St)	0.22	0.51	0.70
	0.27	0.49	0.75
Experimental (Ex)	0.29	0.55	0.76
	0.26	0.54	0.83

[a]Data are relative reduction in paw volume from baseline value.

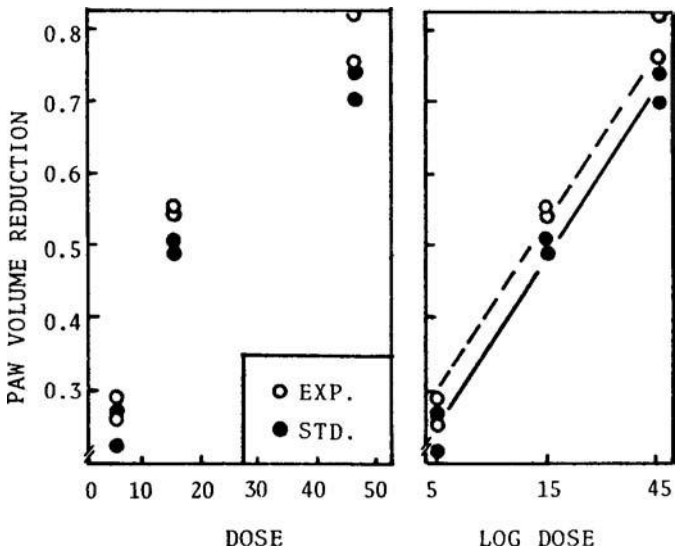


Figure II.1 Plot of dose response data for anti-inflammatory study.

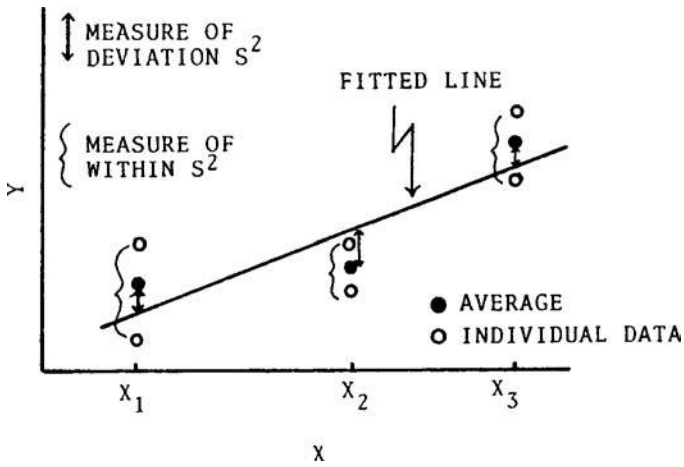


Figure II.2 ANOVA test for linearity.

Table II.2 One-way ANOVA for Data from Standard and Experimental Drugs

	Standard drug			Experimental drug		
Source	**d.f.**	**SS**	**MS**	**d.f.**	**SS**	**MS**
Between doses	2	0.2307	0.1154	2	0.27053	0.1353
Within (doses)	3	0.0027	0.0009	3	0.00295	0.00098
Total	5	0.2334		5	0.27348	

This SS, a result of the slope of the line, will be zero for a line of zero slope ($b = 0$), and will be large for a line with a steep positive or negative slope. For the standard drug, the regression sum of squares is calculated as follows (remember, we are using log dose = X):

$$b = 0.503$$
$$b^2 = \sum (X - \overline{X})^2 = 0.503^2(0.9106) = 0.2304.$$

The deviation SS (sometimes called "lack of fit" SS) is equal to the between-doses SS minus the regression SS. Therefore, the deviation SS = 0.2307–0.2304 = 0.0003.

The results of this calculation for both standard and experimental drugs are shown in Table II.3.

The test for linearity is an F test (deviation MS)/(within MS). For the standard drug, for example, the F ratio is 0.0003/0.0009 = 0.33, with 1 and 3 d.f., which is not significant (within MS = 0.0009, Table II.2). There is no evidence for lack of linearity for both lines.

Usually, in these assays, the deviation mean squares are pooled from both products and compared to the pooled error (within MS), testing linearity of both lines simultaneously. The pooled deviation MS is (0.000433)/2 with 2 degrees of freedom. The pooled within **MS** is 0.000942 with 6 degrees of freedom. The F test for linearity is 0.000217/ 0.00094 = 0.23 (2 and 6 d.f.), which is clearly not significant. The pooling assumes that the error for both drugs is the same, and that both drugs show a linear response versus log dose.

Another assumption in the analysis of the parallel-line assay is that the two lines are parallel. A test of parallelism is equivalent to a test of equality of slopes. The common slope, calculated from all the data combined, is

$$b = \frac{\sum XY - (\sum X \sum Y)/N}{\sum (X - \overline{X})^2} = 0.5240.$$

The regression SS due to the common slope is

$$b^2 \sum (X - \overline{X})^2 = (0.5240)^2(1.8212) = 0.500.$$

The regression SS of the common slope is subtracted from the pooled *regression* SS for the two drugs to obtain the SS attributed to lack of parallelism of the lines. The pooled regression SS is

Table II.3 Regression and Deviations Sum of Squares for Standard and Experimental Drugs[a]

	Standard drug		Experimental drug	
Source	**d.f.**	**SS**	**d.f.**	**SS**
Regression	1	0.2304	1	0.2704
Deviations	1	0.0003	1	0.000133
Between doses	2	0.2307	2	0.270533

[a]Degrees of freedom for "regression" in the simple linear regression case is always equal to 1. Degrees of freedom for "deviations" is equal to (number of doses – 2).

0.2304 + 0.2704 = 0.5008. The SS for "parallelism" is 0.0008 (0.5008 – 0.5000). The F test has 1 and 6 d.f., using the pooled error term:

$$F_{1,6} = \frac{0.0008}{0.00094} = 0.851.$$

Since the F value shows lack of significance at the 5% level, we conclude that the lines appear to be parallel within "experimental error."

The test for parallelism for *two* lines can also be done by using a t test with the same results as the F test. (For the case of two lines, the t is the square root of the F value.) For the t test, we compare the two slopes, using the standard deviation of the difference of the two slopes in the denominator of the t ratio. The slopes are 0.5030 and 0.5449 for the standard and experimental drugs, respectively. The variances in both groups are assumed to be equal.

$$t = \frac{|b_1 - b_2|}{\sqrt{S^2\left[1/\sum_1 (X - \overline{X})^2 + 1\sum_2 (X - \overline{X})^2\right]}}$$

$$t = \frac{|0.5030 - 0.5449|}{\sqrt{0.00094\left[1/\sum_1 (X - \overline{X})^2 + 1\sum_2 (X - \overline{X})^2\right]}}, \tag{II.2}$$

where $\sum_i (X - \overline{X})^2$ represents the sum of squares of the X's for the respective groups. [Note that the variance of a slope equals $S^2/\sum (X - \overline{X})^2$.]

Having satisfied ourselves that the assumptions of the assay have been met (i.e., particularly, linearity and parallelism), we can now estimate the relative potency. The relative potency is the ratio of the comparative drugs that will give the same response. If the lines are parallel, we can choose any response (Y) to estimate the relative potency; the answer will be the same (Fig. II.3).

One can show that the log of the relative potency (log R) is equal to

$$\log R = \log\left[\frac{\text{experimental}}{\text{standard}}\right] = \frac{a_e - a_d}{b},$$

where a_e and a_d are the intercepts for the experimental drug and the standard drug, respectively; b is the common slope (0.524, in our example); and (experimental/standard) is the inverse ratio of doses that gives equal response. For the data of Table II.1,

$$a_d = -0.1262 \quad a_e = -0.0779$$

$$\log R = \frac{-0.0779 - (-0.1262)}{0.5240} = 0.092.$$

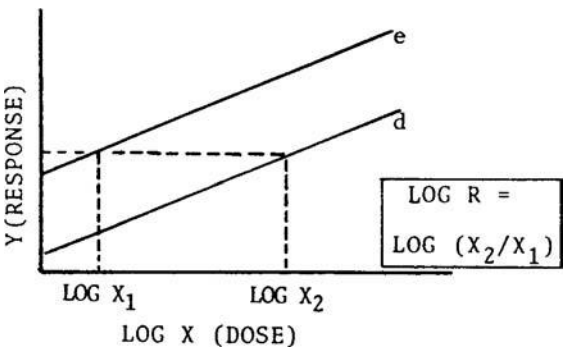


Figure II.3 Relative potency estimation using parallel dose–response lines; doses equivalent to log X_1 and log X_2 give the same response for products *e* and *d*, respectively.

The relative potency is 1.24; that is, the experimental drug is 1.24 times as potent as the standard. This means that 124 mg of the standard is needed to give the same response as 100 mg of the experimental drug, for example.

Confidence limits can be put on the relative potency based on Fieller's theorem (similar to confidence limits for X at a given Y; see chap. 7). The procedure is complicated, and the interested reader is referred to the book by Finney, *Statistical Methods in Biological Assay* [1], for details of the computations.

REFERENCE

1. Finney DJ. Statistical Methods in Biological Assay. New York: Hafner, 1964.

Appendix III
Multiple Regression

Multiple regression is a topic of utmost importance in statistics, analysis of variance being a special case of the more general regression techniques. Multiple regression is an extension of linear regression, in which we wish to relate a response, Y (dependent variable), to more than one independent variable, X_i.

Linear regression: $Y = A + BY$
Multiple regression: $Y = B_0 + B_1X_1 + B_2X_2 + ...$

The independent variables, X_1, X_2, and so on, generally represent factors that we believe influence the response. Usually, the purpose of multiple regression analysis is to quantitate the relationship between Y and the X_i's by means of an equation, the multiple regression equation. For example, tablet dissolution may be measured as a function of several variables, such as level of disintegrant, lubricant, and drug. In this case, a multiple regression equation would be useful to predict dissolution, at given levels of the independent variables.

$$Y = B_0 + B_1X_1 + B_2X_2 + B_3X_3, \tag{III.1}$$

where Y is the some measure of dissolution, X_i is ith independent variable, and B_i the regression coefficient for the ith independent variable.

Here, X_1, X_2, and X_3 refer to the level of disintegrant, lubricant, and drug. B_1, B_2, and B_3 are the coefficients relating the X_i to the response. These coefficients correspond to the slope (B) in linear regression. B_0 is the intercept. This equation cannot be simply depicted, graphically, as in the linear regression case. With two independent variables (X_1 and X_2), the response surface is a plane (Fig. III.1). With more than two independent variables, it is not possible to graph the response in two dimensions.

Data suitable for multiple regression analysis can be obtained in different ways. Optimal efficiency and interpretation are obtained by using data from "designed" experiments. In designed experiments, the independent variables are carefully chosen and deliberately controlled at preassigned levels. For example, in the dissolution experiment noted above, we may be able to fix the levels of disintegrant, lubricant, and drug according to a factorial design (as described in chap. 9). Table III.1 illustrates a 2^3 factorial design. These data correspond to the eight combinations in the 2^3 design that can be used to construct a multiple regression equation. The procedure for fitting data from a factorial design to a regression equation is given in section 16.2.

The form of the equation and the number of independent variables necessary to define the response adequately depend on a knowledge of the system being investigated. In the example above, there are three independent variables (factors), but interactions of factors may also be needed to define the response. In multiple regression equations, interactions may be represented by "cross-product" terms, such as (X_1X_2) or ($X_1X_2X_3$). We usually include only those terms in the equation that probably have a meaningful effect on the response. Suppose, in our example, that the three factors and the lubricant X drug interaction are related to the response, dissolution. We would include terms for X_1, X_2, X_3, and X_2X_3 in the model.

$$Y = B_0 + B_1X_1 + B_2X_2 + B_3X_3 + B_{23}X_2X_3.$$

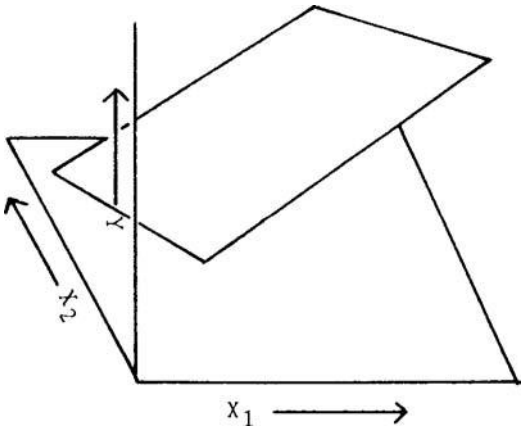


Figure III.1 Representation of the multiple regression equation response, $Y = B_0 + B_1 \times_1 + B_2 X_2$, as a plane.

Data for multiple regression fits are often obtained from undesigned experiments where the levels of the independent variables are not controlled. This less desirable alternative is often a consequence of convenience or cost considerations. Sometimes, the circumstances are such that we have no choice; we get the data in any way that we can. For example, suppose that tableting pressure, temperature, and humidity all affect some particular quality of a finished tablet. Tablets may be conveniently selected for inspection during the manufacturing process, at which time measurements of the pressure, temperature, and humidity are made. After collecting a sufficient quantity of data, these variables may be related to tablet quality using multiple regression techniques.

$$Y = B_0 + B_1(\text{tablet press pressure}) + B_2(\text{temperature}) + B_3(\text{humidity}).$$

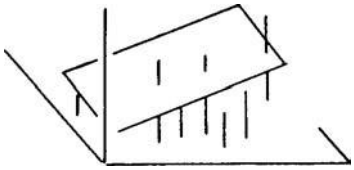
In this example, we have no control of the variables; their values are a matter of "happenstance." We take the values as they come. A significant disadvantage of making conclusions based on data of this sort is that a correlation exists among the independent variables, which can be eliminated (or controlled) in a designed experiment. The result of this correlation is that the effects of the variables cannot be clearly separated. What we attribute to one variable, temperature for example, has a component due to humidity and pressure as well. With data derived from a designed experiment, such as the factorial design noted above, the regression equation can be constructed so that the effects of different factors and interactions are represented by the coefficients (B_i) and are independent of other factors.

The computations to determine the coefficients in multiple regression analysis are very tedious, and without the use of computers, analysis of undesigned experiments of reasonable size are virtually impossible. Manipulations of large matrices are often performed in the solution of these problems. Regression equations for orthogonal (designed) factors are much easier to compute. However, with easy access to computers, hand analysis should be done only as a learning tool to gain insight into the analytical process. We will not discuss computational methods in the general multiple regression model. However, because of the importance of multiple regression in optimization procedures discussed in chapter 16, some further introductory concepts will be presented here.

Table III.1 Factorial Design to Be Used as the Source for a Multiple Regression Equation

		Disintegrant low level		Disintegrant high level	
		Drug		Drug	
		Low level	High level	Low level	High level
Lubricant	Low level				
	High level				

The technique of fitting a linear model to data consisting of N observations of a response, Y, and one or more independent variables, X_i, is applicable when the number of observations is equal to or greater than the number of parameters to be estimated (the coefficients are the parameters in multiple regression). In simple linear regression, we estimate two parameters in the usual case, the intercept and the slope. Given two X, Y points, the line (slope and intercept) is unambigously fixed. With more than two points, the best straight line is considered to be the line that minimizes the sum of the squared deviations of the observed values from the fitted least squares line. Multiple regression is just an extension of this procedure. If there are N parameters (coefficients) in the regression model, N observations will result in an exact fit to the model. For example, an equation with six coefficients will be exactly fit to six appropriate experimental values (with certain mathematical restrictions). With more than N observations, the coefficients, B_i, are calculated to minimize the squared deviations of the observations from the least squares regression fit (the same concept as in simple linear regression).



The relationship of the independent variables and the dependent variable in the multiple regression model must be *linear in the coefficients*, B_i, in order to obtain the regression equation by the usual procedures [1]. The general form of the regression equation is given by Eq. (III.1).

$$Y = B_0 + B_1 X_1 + B_2 X_2 + B_3 X_3. \tag{III.1}$$

The X_i's can be "nonlinear" functions such as X^2, log X, or 10^x. However, the coefficients, B_i, cannot be in this nonlinear form. Thus

$$Y = B_1 X_1 + B_2 X_2 + B_3 X_1^2 + B_4 X_1 X_2 \quad \text{is linear in } B_i$$
$$Y = B_0 + B_1 X_1 + X_1^{B_2} \quad \text{is not linear in } B_i.$$

The basic problems in multiple regression analysis are concerned with estimation of the error and the coefficients (parameters) of the regression model. Statistical tests can then be performed for the significance of the coefficient estimates.

When many independent variables are candidates to be entered into a regression equation, one may wish to use only those variables that contribute "significantly" to the relationship with the dependent variable. In designed experiments (e. g., factorial designs) the significance of each factor can be determined using analysis of variance, or, equivalently, by testing the regression coefficients for significance. In an undesigned experiment, where the data come from "uncontrolled" combinations of the variables, the independent variables will inevitably be more or less correlated. Thus, if dissolution is to be related to tablet weight, drug content, and tablet hardness, based on production records, we are obliged to fit an equation with the available data, and some correlation will exist between drug content and weight, for example. This lack of independence presents special problems when deciding which variables are relevant, contributing significantly to the regression relationship. If two of the X variables, X_i and X_j, are highly correlated, inclusion of both in the regression equation will be redundant. Therefore, there may be some X variables that appear to contribute to the regression but which are correlated to other X variables. We must then make a choice regarding their inclusion in the final regression equation. Draper and Smith note: "There is no unique statistical procedure for doing this," and some degree of arbitrariness must be used in making choices [1]. Two methods used to help make such decisions are made possible through the use of computers. One method involves regression fits using all possible combinations of the independent variables (2^k regressions,

where k is the number of independent variables). For two independent variables, X_1 and X_2, the four possible regressions are

1. $Y = B_0$
2. $Y = B_0 + B_1X_1$
3. $Y = B_0 + B_2X_2$
4. $Y = B_0 + B_1X_1 + B_2X_2$

The best equation may then be selected based on the fit and the number of variables needed for the fit. The multiple correlation coefficient, R^2, is a measure of the fit. R^2 is the sum of squares due to regression divided by the sum of squares without regression. For example, if R^2 is 0.85 when three variables are used to fit the regression equation, and R^2 is equal to 0.87 when six variables are used, we probably would be satisfied using the equation with three variables, other things being equal. The inclusion of more variables in the regression equation cannot result in a decrease of R^2.

Another method of selecting variables to be included in the regression equation is the popular stepwise procedure, which is considered a better method than the "all possible regressions" approach. Independent variables (X_i) are entered into the equation, one at a time, starting with the independent variable that is most highly correlated to the dependent variable, Y. As each new variable is considered, its inclusion is based on a preassigned statistical test related to its correlation with the dependent variable, as well as its correlation to those independent variables already included in the regression equation.

Probably the biggest pitfall in multiple regression techniques lies in the interpretation of the coefficients. Draper and Smith discuss this problem, and the answer is by no means simple [1].

Interpretation of the meaning of the coefficients in multiple regression equations is much more clear in a designed (orthogonal) experiment. As we have noted previously, in a factorial experiment, the levels of the factors can be controlled, so that the effects of the factors can be independently evaluated. Techniques to describe and optimize pharmaceutical systems by fitting experimental data to regression models using designed experiments are discussed in chapter 16.

An application of regression analysis to physical properties of finished tablets, with compression pressure and various tablet components as independent variables can be found in Ref. [2]. In this paper, the authors considered five independent variables for inclusion in the regression equation. They suggested the following equation as a predictor of dissolution:

$$Y = 69.91 - 37.3X_5 - 17.48X_2 + 4.24X_3, \tag{III.2}$$

where Y is the dissolution, X_5 the magnesium stearate level, X_2 the compression pressure, and X_3 the starch disintegrant.

Magnesium stearate and compression pressure decrease dissolution (negative coefficient). Starch increases dissolution. The authors discuss possible mechanisms for these effects.

Multiple regression equations that relate variables such as those described above are empirical relationships. We do not encounter real systems that can be described so simply, theoretically. The multiple regression equation is a "model" of a real system that must be recognized as being only an approximation of reality. How good an approximation the equation is can be evaluated only by seeing how the equation performs as a predictor of the response in new situations, where the levels of the independent variables are changed. Also, particularly in undesigned systems, placing physical interpretation on the signs and magnitude of the coefficients can be hazardous. As noted previously, the coefficients can give insights into the mechanisms of a process, but great caution is needed before making definitive judgments on this basis. Problems similar to those discussed for prediction in linear regression apply here as well. Error (variability) in the estimation of the coefficients, extrapolating to areas outside the levels of the variables in the experiment, and the choice of an incorrect model all adversely affect the reliability of the predicted value.

In addition to its use as a predictive equation, the regression equation may also be used to help obtain combinations of ingredients that will give a desired (e. g., optimum) response.

This process is discussed in chapters 9 and 16. For those readers who are interested in a more advanced, in-depth discussion of regression, the excellent book by Draper and Smith, *Applied Regression Analysis*, is recommended [1].

REFERENCES

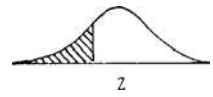
1. Draper NR, Smith H. Applied Regression Analysis, 2 nd ed. New York: Wiley, 1981.
2. Bohidar NR, Restaino FA., Schwartz JB. Selecting Key Pharmaceutical Formulation Factors by Regression Analysis. Drug Dev Ind Pharm 1979; 5: 175.

Appendix IV
Tables

Table IV.1 Random Numbers

44	17	50	92	09	79	27	71	05	07	76	21	95	93	04
83	50	39	13	89	83	45	72	40	94	78	62	93	55	62
28	79	77	81	43	04	54	23	14	80	49	98	32	70	27
55	29	62	11	00	62	65	76	31	83	08	22	02	35	53
88	93	30	81	50	24	43	07	88	45	96	24	60	78	89
46	00	76	13	83	31	98	15	30	74	17	76	73	31	40
99	05	78	83	75	79	52	47	39	12	70	33	42	30	45
24	88	59	45	16	73	64	63	03	16	04	43	81	66	97
14	90	27	33	43	46	37	68	94	35	12	72	70	43	54
50	27	98	87	19	20	15	73	00	94	52	85	80	22	26
55	47	03	77	04	44	22	78	84	26	04	33	46	09	52
59	29	97	68	60	71	91	38	67	54	13	58	18	24	76
48	55	90	65	72	96	57	69	36	10	96	46	92	42	45
66	37	32	20	30	77	84	57	03	29	10	45	65	04	26
68	49	69	10	82	53	75	91	93	30	34	25	20	57	27
83	62	64	11	12	67	19	00	71	74	60	47	21	92	86
06	90	91	47	68	25	49	33	74	02	16	29	35	65	16
33	23	97	78	26	78	26	45	40	19	61	29	53	73	09
47	15	40	15	02	82	06	93	20	01	67	38	02	37	90
79	65	14	62	16	34	96	02	75	82	46	75	43	89	36

Table IV.2 Cumulative Normal Distribution: Cumulative Area Under the Normal Distribution (Less Than or Equal to Z)



Z	Area	Z	Area	Z	Area	Z	Area
−3.25	0.0006	−1.50	0.0668	0.25	0.5987	2.00	0.9772
−3.20	0.0007	−1.45	0.0735	0.30	0.6179	2.05	0.9798
−3.15	0.0008	−1.40	0.0808	0.35	0.6368	2.10	0.9821
−3.10	0.0010	−1.35	0.0885	0.40	0.6554	2.15	0.9842
−3.05	0.0011	−1.30	0.0968	0.45	0.6736	2.20	0.9861
−3.00	0.0013	−1.25	0.1056	0.50	0.6915	2.25	0.9878
−2.95	0.0016	−1.20	0.1151	0.55	0.7088	2.30	0.9893
−2.90	0.0019	−1.15	0.1251	0.60	0.7257	2.35	0.9906
−2.85	0.0022	−1.10	0.1357	0.65	0.7422	2.40	0.9918
−2.80	0.0026	−1.05	0.1469	0.70	0.7580	2.45	0.9929
−2.75	0.0030	−1.00	0.1587	0.75	0.7734	2.50	0.9938
−2.70	0.0035	−0.95	0.1711	0.80	0.7881	2.55	0.9946
−2.65	0.0040	−0.90	0.1841	0.85	0.8023	2.60	0.9953
−2.60	0.0047	−0.85	0.1977	0.90	0.8159	2.65	0.9960
−2.55	0.0054	−0.80	0.2119	0.95	0.8289	2.70	0.9965
−2.50	0.0062	−0.75	0.2266	1.00	0.8413	2.75	0.9970
−2.45	0.0071	−0.70	0.2420	1.05	0.8531	2.80	0.9974
−2.40	0.0082	−0.65	0.2578	1.10	0.8643	2.85	0.9978
−2.35	0.0094	−0.60	0.2743	1.15	0.8749	2.90	0.9981
−2.30	0.0107	−0.55	0.2912	1.20	0.8849	2.95	0.9984
−2.25	0.0122	−0.50	0.3085	1.25	0.8944	3.00	0.9987
−2.20	0.0139	−0.45	0.3264	1.30	0.9032	3.25	0.9994
−2.15	0.0158	−0.40	0.3446	1.35	0.9115		
−2.10	0.0179	−0.35	0.3632	1.40	0.9192		
−2.05	0.0202	−0.30	0.3821	1.45	0.9265		
−2.00	0.0228	−0.25	0.4013	1.50	0.9332		
−1.95	0.0256	−0.20	0.4207	1.55	0.9394		
−1.90	0.0287	−0.15	0.4404	1.60	0.9452		
−1.85	0.0322	−0.10	0.4602	1.65	0.9505		
−1.80	0.0359	−0.05	0.4801	1.70	0.9554		
−1.75	0.0401	0	0.5000	1.75	0.9599		
−1.70	0.0446	0.05	0.5199	1.80	0.9641		
−1.65	0.0495	0.10	0.5398	1.85	0.9678		
−1.60	0.0548	0.15	0.5596	1.90	0.9713		
−1.55	0.0606	0.20	0.5793	1.95	0.9744		

Z	Area
1.282	0.90
1.645	0.95
1.960	0.975
2.326	0.99
2.576	0.995
3.090	0.999

Table IV.3 Individual Terms of the Binomial Distribution for $N = 2$ to 10 and $P = 0.2$, 0.5, and 0.7[a]

					$P = 0.2$				
					N				
X	2	3	4	5	6	7	8	9	10
0	0.64	0.512	0.410	0.328	0.262	0.210	0.168	0.134	0.107
1	0.32	0.384	0.410	0.410	0.393	0.367	0.336	0.302	0.268
2	0.04	0.096	0.154	0.205	0.246	0.275	0.294	0.302	0.302
3		0.008	0.026	0.051	0.082	0.115	0.147	0.176	0.201
4			0.002	0.006	0.015	0.029	0.046	0.066	0.088
5				*	0.002	0.004	0.009	0.017	0.026
6					*	*	0.001	0.003	0.006
7						*	*	*	0.001
8							*	*	*
9								*	*
10									*
					$P = 0.5$				
					N				
X	2	3	4	5	6	7	8	9	10
0	0.250	0.125	0.0625	0.031	0.016	0.008	0.004	0.002	0.001
1	0.500	0.375	0.250	0.156	0.094	0.055	0.031	0.018	0.010
2	0.250	0.375	0.375	0.313	0.234	0.164	0.109	0.070	0.044
3		0.125	0.250	0.313	0.313	0.273	0.219	0.164	0.117
4			0.0625	0.156	0.234	0.273	0.273	0.246	0.205
5				0.031	0.094	0.164	0.219	0.246	0.246
6					0.016	0.055	0.109	0.164	0.205
7						0.008	0.031	0.070	0.117
8							0.004	0.018	0.044
9								0.002	0.010
10									0.001
					$P = 0.7$				
					N				
X	2	3	4	5	6	7	8	9	10
0	0.090	0.027	0.008	0.002	0.001	*	*	*	*
1	0.420	0.189	0.076	0.028	0.010	0.004	0.001	*	*
2	0.490	0.441	0.265	0.132	0.060	0.025	0.010	0.004	0.001
3		0.343	0.412	0.309	0.185	0.097	0.047	0.021	0.009
4			0.240	0.360	0.324	0.227	0.136	0.074	0.037
5				0.168	0.303	0.318	0.254	0.172	0.103
6					0.118	0.247	0.296	0.267	0.200
7						0.082	0.198	0.267	0.267
8							0.058	0.156	0.233
9								0.040	0.121
10									0.028

*$P < 0.0005$.

[a]These tables may be used for $P = 0.8$ and $P = 0.3$ as follows. Use the table with $P = 0.2$ to obtain terms for $P = 0.8$; and use the table with $P = 0.7$ to obtain terms for $P = 0.3$. For example, for the probability of 5 ($x' = 5$) successes in 8 trials ($N = 8$) for $P = 0.8$, look in the table for $P = 0.2$, $N = 8$, and $X = N - X' = 8 - 5 = 3$. This is equal to 0.147.

Table IV.4 *t* Distributions

Two-sided:	**40%**	**20%**	**10%**	**5%**	**1%**
One-sided:	**20%**	**10%**	**5%**	**2.50%**	**0.50%**
d.f.:	$t_{0.80}$	$t_{0.90}$	$t_{0.95}$	$t_{0.975}$	$t_{0.995}$
1	1.376382	3.077684	6.313752	12.7062	63.65674
2	1.06066	1.885618	2.919986	4.302653	9.924843
3	0.978472	1.637744	2.353363	3.182446	5.840909
4	0.940965	1.533206	2.131847	2.776445	4.604095
5	0.919544	1.475884	2.015048	2.570582	4.032143
6	0.905703	1.439756	1.94318	2.446912	3.707428
7	0.89603	1.414924	1.894579	2.364624	3.499483
8	0.88889	1.396815	1.859548	2.306004	3.355387
9	0.883404	1.383029	1.833113	2.262157	3.249836
10	0.879058	1.372184	1.812461	2.228139	3.169273
11	0.87553	1.36343	1.795885	2.200985	3.105807
12	0.872609	1.356217	1.782288	2.178813	3.05454
13	0.870152	1.350171	1.770933	2.160369	3.012276
14	0.868055	1.34503	1.76131	2.144787	2.976843
15	0.866245	1.340606	1.75305	2.13145	2.946713
16	0.864667	1.336757	1.745884	2.119905	2.920782
17	0.863279	1.333379	1.739607	2.109816	2.898231
18	0.862049	1.330391	1.734064	2.100922	2.87844
19	0.860951	1.327728	1.729133	2.093024	2.860935
20	0.859964	1.325341	1.724718	2.085963	2.84534
21	0.859074	1.323188	1.720743	2.079614	2.83136
22	0.858266	1.321237	1.717144	2.073873	2.818756
23	0.85753	1.31946	1.713872	2.068658	2.807336
24	0.856855	1.317836	1.710882	2.063899	2.796939
25	0.856236	1.316345	1.708141	2.059539	2.787436
26	0.855665	1.314972	1.705618	2.055529	2.778715
27	0.855137	1.313703	1.703288	2.05183	2.770683
28	0.854647	1.312527	1.701131	2.048407	2.763262
29	0.854192	1.311434	1.699127	2.04523	2.756386
30	0.853767	1.310415	1.697261	2.042272	2.749996
31	0.85337	1.309464	1.695519	2.039513	2.744042
32	0.852998	1.308573	1.693889	2.036933	2.738481
33	0.852649	1.307737	1.69236	2.034515	2.733277
34	0.852321	1.306952	1.690924	2.032244	2.728394
35	0.852012	1.306212	1.689572	2.030108	2.723806
36	0.85172	1.305514	1.688298	2.028094	2.719485
37	0.851444	1.304854	1.687094	2.026192	2.715409
38	0.851183	1.30423	1.685954	2.024394	2.711558
39	0.850935	1.303639	1.684875	2.022691	2.707913
40	0.8507	1.303077	1.683851	2.021075	2.704459
41	0.850476	1.302543	1.682878	2.019541	2.701181
42	0.850263	1.302035	1.681952	2.018082	2.698066
43	0.85006	1.301552	1.681071	2.016692	2.695102
44	0.849867	1.30109	1.68023	2.015368	2.692278
45	0.849682	1.300649	1.679427	2.014103	2.689585
46	0.849505	1.300228	1.67866	2.012896	2.687013
47	0.849336	1.299825	1.677927	2.01174	2.684556
48	0.849174	1.299439	1.677224	2.010635	2.682204
49	0.849018	1.299069	1.676551	2.009575	2.679952
50	0.848869	1.298714	1.675905	2.008559	2.677793
75	0.84644	1.292941	1.665425	1.992102	2.642983
100	0.84523	1.290075	1.660234	1.983971	2.625891
500	0.842341	1.283247	1.647907	1.96472	2.585698
infinity	0.841621	1.281552	1.644855	1.959966	2.575834

Table IV.5 Chi-Square Distributions

Degrees of Freedom	Probability								
	0.01	0.025	0.05	0.1	0.2	0.8	0.9	0.95	0.99
1	6.634897	5.023886	3.841459	2.705544	1.642375	0.064185	0.015791	0.003932	0.000157
2	9.21034	7.377759	5.991465	4.60517	3.218876	0.446287	0.210721	0.102587	0.020101
3	11.34487	9.348404	7.814728	6.251388	4.641628	1.005174	0.584374	0.351846	0.114832
4	13.2767	11.14329	9.487729	7.77944	5.988617	1.648777	1.063623	0.710723	0.297109
5	15.08627	12.8325	11.0705	9.236357	7.289276	2.342534	1.610308	1.145476	0.554298
6	16.81189	14.44938	12.59159	10.64464	8.55806	3.070088	2.204131	1.635383	0.87209
7	18.47531	16.01276	14.06714	12.01704	9.80325	3.822322	2.833107	2.16735	1.239042
8	20.09024	17.53455	15.50731	13.36157	11.03009	4.593574	3.489539	2.732637	1.646497
9	21.66599	19.02277	16.91898	14.68366	12.24215	5.380053	4.168159	3.325113	2.087901
10	23.20925	20.48318	18.30704	15.98718	13.44196	6.179079	4.865182	3.940299	2.558212
11	24.72497	21.92005	19.67514	17.27501	14.63142	6.988674	5.577785	4.574813	3.053484
12	26.21697	23.33666	21.02607	18.54935	15.81199	7.807328	6.303796	5.226029	3.570569
13	27.68825	24.7356	22.36203	19.81193	16.9848	8.633861	7.041505	5.891864	4.106915
14	29.14124	26.11895	23.68479	21.06414	18.15077	9.467328	7.789534	6.570631	4.660425
15	30.57791	27.48839	24.99579	22.30713	19.31066	10.30696	8.546756	7.260944	5.229349
16	31.99993	28.84535	26.29623	23.54183	20.46508	11.15212	9.312236	7.961646	5.812213
17	33.40866	30.19101	27.58711	24.76904	21.61456	12.00227	10.08519	8.67176	6.40776
18	34.80531	31.52638	28.8693	25.98942	22.75955	12.85695	10.86494	9.390455	7.014911
19	36.19087	32.85233	30.14353	27.20357	23.90042	13.71579	11.65091	10.11701	7.63273
20	37.56623	34.16961	31.41043	28.41198	25.03751	14.57844	12.44261	10.85081	8.260398
21	38.93217	35.47888	32.67057	29.61509	26.1711	15.44461	13.2396	11.59131	8.897198
22	40.28936	36.78071	33.92444	30.81328	27.30145	16.31404	14.04149	12.33801	9.542492
23	41.6384	38.07563	35.17246	32.0069	28.42879	17.18651	14.84796	13.09051	10.19572
24	42.97982	39.36408	36.41503	33.19624	29.55332	18.0618	15.65868	13.84843	10.85636
25	44.3141	40.64647	37.65248	34.38159	30.6752	18.93975	16.47341	14.61141	11.52398
26	45.64168	41.92317	38.88514	35.56317	31.79461	19.82019	17.29189	15.37916	12.19815
27	46.96294	43.19451	40.11327	36.74122	32.91169	20.70298	18.1139	16.1514	12.8785
28	48.27824	44.46079	41.33714	37.91592	34.02657	21.58797	18.93924	16.92788	13.56471
29	49.58788	45.72229	42.55697	39.08747	35.13936	22.47505	19.76774	17.70837	14.25645
30	50.89218	46.97924	43.77297	40.25602	36.25019	23.36412	20.59923	18.49266	14.95346
31	52.19139	48.23189	44.98534	41.42174	37.35914	24.25506	21.43356	19.28057	15.65546
32	53.48577	49.48044	46.19426	42.58475	38.46631	25.14779	22.27059	20.07191	16.36222
33	54.77554	50.72508	47.39988	43.74518	39.57179	26.04222	23.1102	20.86653	17.07351
34	56.06091	51.966	48.60237	44.90316	40.67565	26.93827	23.95225	21.66428	17.78915
35	57.34207	53.20335	49.80185	46.05879	41.77796	27.83587	24.79666	22.46502	18.50893
36	58.61921	54.43729	50.99846	47.21217	42.8788	28.73496	25.6433	23.26861	19.23268
37	59.8925	55.66797	52.19232	48.36341	43.97822	29.63547	26.49209	24.07494	19.96023
38	61.16209	56.89552	53.38354	49.51258	45.07628	30.53734	27.34295	24.8839	20.69144
39	62.42812	58.12006	54.57223	50.65977	46.17303	31.44052	28.19579	25.69539	21.42616
40	63.69074	59.34171	55.75848	51.80506	47.26854	32.34495	29.05052	26.5093	22.16426
41	64.95007	60.56057	56.94239	52.94851	48.36283	33.2506	29.90709	27.32555	22.90561
42	66.20624	61.77676	58.12404	54.0902	49.45597	34.15741	30.76542	28.14405	23.65009
43	67.45935	62.99036	59.30351	55.23019	50.54799	35.06534	31.62545	28.96472	24.3976
44	68.70951	64.20146	60.48089	56.36854	51.63892	35.97435	32.48713	29.78748	25.14803
45	187.5299	180.2291	174.101	167.2074	159.1036	130.5082	123.6489	118.1714	108.3451
46	71.2014	66.61653	62.82962	58.64054	53.8177	37.79548	34.21517	31.439	26.65724
47	72.44331	67.82065	64.00111	59.77429	54.90561	38.70752	35.08143	32.26762	27.41585
48	73.68264	69.02259	65.17077	60.90661	55.99258	39.62051	35.94913	33.09808	28.17701
49	74.91947	70.22241	66.33865	62.03754	57.07863	40.53442	36.81822	33.93031	28.94065
50	76.15389	71.4202	67.50481	63.16712	58.1638	41.44921	37.68865	34.76425	29.70668
51	77.38596	72.61599	68.66929	64.2954	59.24811	77.38596	38.56038	35.59986	30.47505
52	78.61576	73.80986	69.83216	65.42241	60.33158	78.61576	39.43339	36.43709	31.24567
53	79.84334	75.00186	70.99345	66.5482	61.41425	79.84334	40.30762	37.27589	32.01849
54	81.06877	76.19205	72.15322	67.67279	62.49613	81.06877	41.18304	38.11622	32.79345
55	82.29212	77.38047	73.31149	68.79621	63.57724	82.29212	42.05962	38.95803	33.57048
56	83.51343	78.56716	74.46832	69.91851	64.65762	83.51343	42.93734	39.80128	34.34952
57	84.73277	79.75219	75.62375	71.03971	65.73727	84.73277	43.81615	40.64593	35.13053
58	85.95018	80.93559	76.7778	72.15984	66.81621	85.95018	44.69603	41.49195	35.91346
59	87.16571	82.11741	77.93052	73.27893	67.89448	87.16571	45.57695	42.33931	36.69825
60	88.37942	83.29768	79.08194	74.39701	68.97207	88.37942	46.45889	43.18796	37.48485
80	112.3288	106.6286	101.8795	96.5782	90.40535	112.3288	64.27785	60.39148	53.54008
100	135.8067	129.5612	124.3421	118.498	111.6667	135.8067	82.35814	77.92947	70.0649
500	576.4928	563.8515	553.1268	540.9303	526.4014	576.4928	459.9261	449.1468	429.3875

Table IV.6A1 Upper 5% Values of the F Distribution

Degrees of freedom in denominator	Degrees of freedom in numerator																											
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	25	30	40	50	60	80	100	inf
1	161.448	199.500	215.707	224.583	230.162	233.986	236.768	244.690	240.543	241.882	242.983	243.906	244.690	245.364	245.950	244.690	246.918	247.323	247.686	248.013	249.260	250.095	251.143	251.774	252.196	252.724	253.041	254.314
2	18.513	19.000	19.164	19.247	19.296	19.330	19.353	19.371	19.385	19.396	19.405	19.413	19.419	19.424	19.429	19.433	19.437	19.440	19.443	19.446	19.456	19.462	19.471	19.476	19.479	19.483	19.486	19.496
3	10.128	9.552	9.277	9.117	9.013	8.941	8.887	8.845	8.812	8.786	8.763	8.745	8.729	8.715	8.703	8.692	8.683	8.675	8.667	8.660	8.634	8.617	8.594	8.581	8.572	8.561	8.554	8.526
4	7.709	6.944	6.591	6.388	6.256	6.163	6.094	6.041	5.999	5.964	5.936	5.912	5.891	5.873	5.858	5.844	5.832	5.821	5.811	5.803	5.769	5.746	5.717	5.699	5.688	5.673	5.664	5.628
5	6.608	5.786	5.409	5.192	5.050	4.950	4.876	4.818	4.772	4.735	4.704	4.678	4.655	4.636	4.619	4.604	4.590	4.579	4.568	4.558	4.521	4.496	4.464	4.444	4.431	4.415	4.405	4.365
6	5.987	5.143	4.757	4.534	4.387	4.284	4.207	4.147	4.099	4.060	4.027	4.000	3.976	3.956	3.938	3.922	3.908	3.896	3.884	3.874	3.835	3.808	3.774	3.754	3.740	3.722	3.712	3.669
7	5.591	4.737	4.347	4.120	3.972	3.866	3.787	3.726	3.677	3.637	3.603	3.575	3.550	3.529	3.511	3.494	3.480	3.467	3.455	3.445	3.404	3.376	3.340	3.319	3.304	3.286	3.275	3.230
8	5.318	5.318	4.066	3.838	3.687	3.581	3.500	3.438	3.388	3.347	3.313	3.284	3.259	3.237	3.218	3.202	3.187	3.173	3.161	3.150	3.108	3.079	3.043	3.020	3.005	2.986	2.975	2.928
9	5.117	4.256	3.863	3.633	3.482	3.374	3.293	3.230	3.179	3.137	3.102	3.073	3.048	3.025	3.006	2.989	2.974	2.960	2.948	2.936	2.893	2.864	2.826	2.803	2.787	2.768	2.756	2.707
10	4.965	4.103	3.708	3.478	3.326	3.217	3.135	3.072	3.020	2.978	2.943	2.913	2.887	2.865	2.845	2.828	2.812	2.798	2.785	2.774	2.730	2.700	2.661	2.637	2.621	2.601	2.588	2.538
11	4.844	3.982	3.587	3.357	3.204	3.095	3.012	2.948	2.896	2.854	2.818	2.788	2.761	2.739	2.719	2.701	2.685	2.671	2.658	2.646	2.601	2.570	2.531	2.507	2.490	2.469	2.457	2.404
12	4.747	3.885	3.490	3.259	3.106	2.996	2.913	2.849	2.796	2.753	2.717	2.687	2.660	2.637	2.617	2.599	2.583	2.568	2.555	2.544	2.498	2.466	2.426	2.401	2.384	2.363	2.350	2.296
13	4.667	3.806	3.411	3.179	3.025	2.915	2.832	2.767	2.714	2.671	2.635	2.604	2.577	2.554	2.533	2.515	2.499	2.484	2.471	2.459	2.412	2.380	2.339	2.314	2.297	2.275	2.261	2.206
14	4.600	3.739	3.344	3.112	2.958	2.848	2.764	2.699	2.646	2.602	2.565	2.534	2.507	2.484	2.463	2.445	2.428	2.413	2.400	2.388	2.341	2.308	2.266	2.241	2.223	2.201	2.187	2.131
15	4.543	3.682	3.287	3.056	2.901	2.790	2.707	2.641	2.588	2.544	2.507	2.475	2.448	2.424	2.403	2.385	2.368	2.353	2.340	2.328	2.280	2.247	2.204	2.178	2.160	2.137	2.123	2.066
16	4.494	3.634	3.239	3.007	2.852	2.741	2.657	2.591	2.538	2.494	2.456	2.425	2.397	2.373	2.352	2.333	2.317	2.302	2.288	2.276	2.227	2.194	2.151	2.124	2.106	2.083	2.068	2.010
17	4.451	3.592	3.197	2.965	2.810	2.699	2.614	2.548	2.494	2.450	2.413	2.381	2.353	2.329	2.308	2.289	2.272	2.257	2.243	2.230	2.181	2.148	2.104	2.077	2.058	2.035	2.020	1.960
18	4.414	3.555	3.160	2.928	2.773	2.661	2.577	2.510	2.456	2.412	2.374	2.342	2.314	2.290	2.269	2.250	2.233	2.217	2.203	2.191	2.141	2.107	2.063	2.035	2.017	1.993	1.978	1.917
19	4.381	3.522	3.127	2.895	2.740	2.628	2.544	2.477	2.423	2.378	2.340	2.308	2.280	2.256	2.234	2.215	2.198	2.182	2.168	2.155	2.106	2.071	2.026	1.999	1.980	1.955	1.940	1.878
20	4.351	3.493	3.098	2.866	2.711	2.599	2.514	2.447	2.393	2.348	2.310	2.278	2.250	2.225	2.203	2.184	2.167	2.151	2.137	2.124	2.074	2.039	1.994	1.966	1.946	1.922	1.907	1.843
21	4.325	3.467	3.072	2.840	2.685	2.573	2.488	2.420	2.366	2.321	2.283	2.250	2.222	2.197	2.176	2.156	2.139	2.123	2.109	2.096	2.045	2.010	1.965	1.936	1.916	1.891	1.876	1.812
22	4.301	3.443	3.049	2.817	2.661	2.549	2.464	2.397	2.342	2.297	2.259	2.226	2.198	2.173	2.151	2.131	2.114	2.098	2.084	2.071	2.020	1.984	1.938	1.909	1.889	1.864	1.849	1.783
23	4.279	3.422	3.028	2.796	2.640	2.528	2.442	2.375	2.320	2.275	2.236	2.204	2.175	2.150	2.128	2.109	2.091	2.075	2.061	2.048	1.996	1.961	1.914	1.885	1.865	1.839	1.823	1.757
24	4.260	3.403	3.009	2.776	2.621	2.508	2.423	2.355	2.300	2.255	2.216	2.183	2.155	2.130	2.108	2.088	2.070	2.054	2.040	2.027	1.975	1.939	1.892	1.863	1.842	1.816	1.800	1.733
25	4.242	3.385	2.991	2.759	2.603	2.490	2.405	2.337	2.282	2.236	2.198	2.165	2.136	2.111	2.089	2.069	2.051	2.035	2.021	2.007	1.955	1.919	1.872	1.842	1.822	1.796	1.779	1.711
26	4.225	3.369	2.975	2.743	2.587	2.474	2.388	2.321	2.265	2.220	2.181	2.148	2.119	2.094	2.072	2.052	2.034	2.018	2.003	1.990	1.938	1.901	1.853	1.823	1.803	1.776	1.760	1.691
27	4.210	3.354	2.960	2.728	2.572	2.459	2.373	2.305	2.250	2.204	2.166	2.132	2.103	2.078	2.056	2.036	2.018	2.002	1.987	1.974	1.921	1.884	1.836	1.806	1.785	1.758	1.742	1.672
28	4.196	3.340	2.947	2.714	2.558	2.445	2.359	2.291	2.236	2.190	2.151	2.118	2.089	2.064	2.041	2.021	2.003	1.987	1.972	1.959	1.906	1.869	1.820	1.790	1.769	1.742	1.725	1.654
29	4.183	3.328	2.934	2.701	2.545	2.432	2.346	2.278	2.223	2.177	2.138	2.104	2.075	2.050	2.027	2.007	1.989	1.973	1.958	1.945	1.891	1.854	1.806	1.775	1.754	1.726	1.710	1.638
30	4.171	3.316	2.922	2.690	2.534	2.421	2.334	2.266	2.211	2.165	2.126	2.092	2.063	2.037	2.015	1.995	1.976	1.960	1.945	1.932	1.878	1.841	1.792	1.761	1.740	1.712	1.695	1.622
31	4.160	3.305	2.911	2.679	2.523	2.409	2.323	2.255	2.199	2.153	2.114	2.080	2.051	2.026	2.003	1.983	1.965	1.948	1.933	1.920	1.866	1.828	1.779	1.748	1.726	1.699	1.681	1.608
32	4.149	3.295	2.901	2.668	2.512	2.399	2.313	2.244	2.189	2.142	2.103	2.070	2.040	2.015	1.992	1.972	1.953	1.937	1.922	1.908	1.854	1.817	1.767	1.736	1.714	1.686	1.669	1.594
33	4.139	3.285	2.892	2.659	2.503	2.389	2.303	2.235	2.179	2.133	2.093	2.060	2.030	2.004	1.982	1.961	1.943	1.926	1.911	1.898	1.844	1.806	1.756	1.724	1.702	1.674	1.657	1.581
34	4.130	3.276	2.883	2.650	2.494	2.380	2.294	2.225	2.170	2.123	2.084	2.050	2.021	1.995	1.972	1.952	1.933	1.917	1.902	1.888	1.833	1.795	1.745	1.713	1.691	1.663	1.645	1.569
35	4.121	3.267	2.874	2.641	2.485	2.372	2.285	2.217	2.161	2.114	2.075	2.041	2.012	1.986	1.963	1.942	1.924	1.907	1.892	1.878	1.824	1.786	1.735	1.703	1.681	1.652	1.635	1.558
36	4.113	3.259	2.866	2.634	2.477	2.364	2.277	2.209	2.153	2.106	2.067	2.033	2.003	1.977	1.954	1.934	1.915	1.899	1.883	1.870	1.815	1.776	1.726	1.694	1.671	1.643	1.625	1.547
37	4.105	3.252	2.859	2.626	2.470	2.356	2.270	2.201	2.145	2.098	2.059	2.025	1.995	1.969	1.946	1.926	1.907	1.890	1.875	1.861	1.806	1.768	1.717	1.685	1.662	1.633	1.615	1.537
38	4.098	3.245	2.852	2.619	2.463	2.349	2.262	2.194	2.138	2.091	2.051	2.017	1.988	1.962	1.939	1.918	1.899	1.883	1.867	1.853	1.798	1.760	1.708	1.676	1.653	1.624	1.606	1.527
39	4.091	3.238	2.845	2.612	2.456	2.342	2.255	2.187	2.131	2.084	2.044	2.010	1.981	1.954	1.931	1.911	1.892	1.875	1.860	1.846	1.791	1.752	1.700	1.668	1.645	1.616	1.597	1.518
40	4.085	3.232	2.839	2.606	2.449	2.336	2.249	2.180	2.124	2.077	2.038	2.003	1.974	1.948	1.924	1.904	1.885	1.868	1.853	1.839	1.783	1.744	1.693	1.660	1.637	1.608	1.589	1.509
50	4.034	3.183	2.790	2.557	2.400	2.286	2.199	2.130	2.073	2.026	1.986	1.952	1.921	1.895	1.871	1.850	1.831	1.814	1.798	1.784	1.727	1.687	1.634	1.599	1.576	1.544	1.525	1.438
60	4.001	3.150	2.758	2.525	2.368	2.254	2.167	2.097	2.040	1.993	1.952	1.917	1.887	1.860	1.836	1.815	1.796	1.778	1.763	1.748	1.690	1.649	1.594	1.559	1.534	1.502	1.481	1.389
80	3.960	3.111	2.719	2.486	2.329	2.214	2.126	2.056	1.999	1.951	1.910	1.875	1.845	1.817	1.793	1.772	1.752	1.734	1.718	1.703	1.644	1.602	1.545	1.508	1.482	1.448	1.426	1.325
100	3.936	3.041	2.696	2.463	2.305	2.191	2.103	2.032	1.975	1.927	1.886	1.850	1.819	1.792	1.768	1.746	1.726	1.708	1.691	1.676	1.616	1.573	1.515	1.477	1.450	1.415	1.392	1.283
200	3.888	3.041	2.650	2.417	2.259	2.144	2.056	1.985	1.927	1.878	1.837	1.801	1.769	1.742	1.717	1.694	1.674	1.656	1.639	1.623	1.561	1.516	1.455	1.415	1.386	1.346	1.321	1.189
infinity	3.842	3.912	2.605	2.372	2.214	2.099	2.010	1.939	1.880	1.831	1.789	1.752	1.720	1.692	1.666	1.644	1.623	1.604	1.587	1.571	1.506	1.459	1.394	1.350	1.318	1.274	1.244	1.000

Table IV.6A2 Upper 10% Values of the F Distribution

Degrees of freedom in denominator	Degrees of freedom in numerator																											
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	25	30	40	50	60	80	100	inf
1	39.863	49.500	53.593	55.833	57.240	58.204	58.906	60.903	59.858	60.195	60.473	60.705	60.903	61.073	61.220	60.903	61.464	61.566	61.658	61.740	62.055	62.265	62.529	62.688	62.794	62.927	63.007	63.328
2	8.526	9.000	9.162	9.243	9.293	9.326	9.349	9.367	9.381	9.392	9.401	9.408	9.415	9.420	9.425	9.429	9.433	9.436	9.439	9.441	9.451	9.458	9.466	9.471	9.475	9.479	9.481	9.491
3	5.538	5.462	5.391	5.343	5.309	5.285	5.266	5.252	5.240	5.230	5.222	5.216	5.210	5.205	5.200	5.196	5.193	5.190	5.187	5.184	5.175	5.168	5.160	5.155	5.151	5.147	5.144	5.134
4	4.545	4.325	4.191	4.107	4.051	4.010	3.979	3.955	3.936	3.920	3.907	3.896	3.886	3.878	3.870	3.864	3.858	3.853	3.849	3.844	3.828	3.817	3.804	3.795	3.790	3.782	3.778	3.761
5	4.060	3.780	3.619	3.520	3.453	3.405	3.368	3.339	3.316	3.297	3.282	3.268	3.257	3.247	3.238	3.230	3.223	3.217	3.212	3.207	3.187	3.174	3.157	3.147	3.140	3.132	3.126	3.105
6	3.776	3.463	3.289	3.181	3.108	3.055	3.014	2.983	2.958	2.937	2.920	2.905	2.892	2.881	2.871	2.863	2.855	2.848	2.842	2.836	2.815	2.800	2.781	2.770	2.762	2.752	2.746	2.722
7	3.589	3.257	3.074	2.961	2.883	2.827	2.785	2.752	2.725	2.703	2.684	2.668	2.654	2.643	2.632	2.623	2.615	2.607	2.601	2.595	2.571	2.555	2.535	2.523	2.514	2.504	2.497	2.471
8	3.458	3.458	2.924	2.806	2.726	2.668	2.624	2.589	2.561	2.538	2.519	2.502	2.488	2.475	2.464	2.455	2.446	2.438	2.431	2.425	2.400	2.383	2.361	2.348	2.339	2.328	2.321	2.293
9	3.360	3.006	2.813	2.693	2.611	2.551	2.505	2.469	2.440	2.416	2.396	2.379	2.364	2.351	2.340	2.329	2.320	2.312	2.305	2.298	2.272	2.255	2.232	2.218	2.208	2.196	2.189	2.159
10	3.285	2.924	2.728	2.605	2.522	2.461	2.414	2.377	2.347	2.323	2.302	2.284	2.269	2.255	2.244	2.233	2.224	2.215	2.208	2.201	2.174	2.155	2.132	2.117	2.107	2.095	2.087	2.055
11	3.225	2.860	2.660	2.536	2.451	2.389	2.342	2.304	2.274	2.248	2.227	2.209	2.193	2.179	2.167	2.156	2.147	2.138	2.130	2.123	2.095	2.076	2.052	2.036	2.026	2.013	2.005	1.972
12	3.177	2.807	2.606	2.480	2.394	2.331	2.283	2.245	2.214	2.188	2.166	2.147	2.131	2.117	2.105	2.094	2.084	2.075	2.067	2.060	2.031	2.011	1.986	1.970	1.960	1.946	1.938	1.904
13	3.136	2.763	2.560	2.434	2.347	2.283	2.234	2.195	2.164	2.138	2.116	2.097	2.080	2.066	2.053	2.042	2.032	2.023	2.014	2.007	1.978	1.958	1.931	1.915	1.904	1.890	1.882	1.846
14	3.102	2.726	2.522	2.395	2.307	2.243	2.193	2.154	2.122	2.095	2.073	2.054	2.037	2.022	2.010	1.998	1.988	1.978	1.970	1.962	1.933	1.912	1.885	1.869	1.857	1.843	1.834	1.797
15	3.073	2.695	2.490	2.361	2.273	2.208	2.158	2.119	2.086	2.059	2.037	2.017	2.000	1.985	1.972	1.961	1.950	1.941	1.932	1.924	1.894	1.873	1.845	1.828	1.817	1.802	1.793	1.755
16	3.048	2.668	2.462	2.333	2.244	2.178	2.128	2.088	2.055	2.028	2.005	1.985	1.968	1.953	1.940	1.928	1.917	1.908	1.899	1.891	1.860	1.839	1.811	1.793	1.782	1.766	1.757	1.718
17	3.026	2.645	2.437	2.308	2.218	2.152	2.102	2.061	2.028	2.001	1.978	1.958	1.940	1.925	1.912	1.900	1.889	1.879	1.870	1.862	1.831	1.809	1.781	1.763	1.751	1.735	1.726	1.686
18	3.007	2.624	2.416	2.286	2.196	2.130	2.079	2.038	2.005	1.977	1.954	1.933	1.916	1.900	1.887	1.875	1.864	1.854	1.845	1.837	1.805	1.783	1.754	1.736	1.723	1.707	1.698	1.657
19	2.990	2.606	2.397	2.266	2.176	2.109	2.058	2.017	1.984	1.956	1.932	1.912	1.894	1.878	1.865	1.852	1.841	1.831	1.822	1.814	1.782	1.759	1.730	1.711	1.699	1.683	1.673	1.631
20	2.975	2.589	2.380	2.249	2.158	2.091	2.040	1.999	1.965	1.937	1.913	1.892	1.875	1.859	1.845	1.833	1.821	1.811	1.802	1.794	1.761	1.738	1.708	1.690	1.677	1.660	1.650	1.607
21	2.961	2.575	2.365	2.233	2.142	2.075	2.023	1.982	1.948	1.920	1.896	1.875	1.857	1.841	1.827	1.815	1.803	1.793	1.784	1.776	1.742	1.719	1.689	1.670	1.657	1.640	1.630	1.586
22	2.949	2.561	2.351	2.219	2.128	2.060	2.008	1.967	1.933	1.904	1.880	1.859	1.841	1.825	1.811	1.798	1.787	1.777	1.768	1.759	1.726	1.702	1.671	1.652	1.639	1.622	1.611	1.567
23	2.937	2.549	2.339	2.207	2.115	2.047	1.995	1.953	1.919	1.890	1.866	1.845	1.827	1.811	1.796	1.784	1.772	1.762	1.753	1.744	1.710	1.686	1.655	1.636	1.622	1.605	1.594	1.549
24	2.927	2.538	2.327	2.195	2.103	2.035	1.983	1.941	1.906	1.877	1.853	1.832	1.814	1.797	1.783	1.770	1.759	1.748	1.739	1.730	1.696	1.672	1.641	1.621	1.607	1.590	1.579	1.533
25	2.918	2.528	2.317	2.184	2.092	2.024	1.971	1.929	1.895	1.866	1.841	1.820	1.802	1.785	1.771	1.758	1.746	1.736	1.726	1.718	1.683	1.659	1.627	1.607	1.593	1.576	1.565	1.518
26	2.909	2.519	2.307	2.174	2.082	2.014	1.961	1.919	1.884	1.855	1.830	1.809	1.790	1.774	1.760	1.747	1.735	1.724	1.715	1.706	1.671	1.647	1.615	1.594	1.581	1.562	1.551	1.504
27	2.901	2.511	2.299	2.165	2.073	2.005	1.952	1.909	1.874	1.845	1.820	1.799	1.780	1.764	1.749	1.736	1.724	1.714	1.704	1.695	1.660	1.636	1.603	1.583	1.569	1.550	1.539	1.491
28	2.894	2.503	2.291	2.157	2.064	1.996	1.943	1.900	1.865	1.836	1.811	1.790	1.771	1.754	1.740	1.726	1.715	1.704	1.694	1.685	1.650	1.625	1.592	1.572	1.558	1.539	1.528	1.478
29	2.887	2.495	2.283	2.149	2.057	1.988	1.935	1.892	1.857	1.827	1.802	1.781	1.762	1.745	1.731	1.717	1.705	1.695	1.685	1.676	1.640	1.616	1.583	1.562	1.547	1.529	1.517	1.467
30	2.881	2.489	2.276	2.142	2.049	1.980	1.927	1.884	1.849	1.819	1.794	1.773	1.754	1.737	1.722	1.709	1.697	1.686	1.676	1.667	1.632	1.606	1.573	1.552	1.538	1.519	1.507	1.456
31	2.875	2.482	2.270	2.136	2.042	1.973	1.920	1.877	1.842	1.812	1.787	1.765	1.746	1.729	1.714	1.701	1.689	1.678	1.668	1.659	1.623	1.598	1.565	1.543	1.529	1.509	1.498	1.446
32	2.869	2.477	2.263	2.129	2.036	1.967	1.913	1.870	1.835	1.805	1.780	1.758	1.739	1.722	1.707	1.694	1.682	1.671	1.661	1.652	1.616	1.590	1.556	1.535	1.520	1.501	1.489	1.437
33	2.864	2.471	2.258	2.123	2.030	1.961	1.907	1.864	1.828	1.799	1.773	1.751	1.732	1.715	1.700	1.687	1.675	1.664	1.654	1.645	1.608	1.583	1.549	1.527	1.512	1.493	1.480	1.428
34	2.859	2.466	2.252	2.118	2.024	1.955	1.901	1.858	1.822	1.793	1.767	1.745	1.726	1.709	1.694	1.680	1.668	1.657	1.647	1.638	1.601	1.576	1.541	1.520	1.505	1.485	1.473	1.419
35	2.855	2.461	2.247	2.113	2.019	1.950	1.896	1.852	1.817	1.787	1.761	1.739	1.720	1.703	1.688	1.674	1.662	1.651	1.641	1.632	1.595	1.569	1.535	1.513	1.497	1.478	1.465	1.411
36	2.850	2.456	2.243	2.108	2.014	1.945	1.891	1.847	1.811	1.781	1.756	1.734	1.715	1.697	1.682	1.669	1.656	1.645	1.635	1.626	1.589	1.563	1.528	1.506	1.491	1.471	1.458	1.404
37	2.846	2.452	2.238	2.103	2.009	1.940	1.886	1.842	1.806	1.776	1.751	1.729	1.709	1.692	1.677	1.663	1.651	1.640	1.630	1.620	1.583	1.557	1.522	1.500	1.484	1.464	1.452	1.397
38	2.842	2.448	2.234	2.099	2.005	1.935	1.881	1.838	1.802	1.772	1.746	1.724	1.704	1.687	1.672	1.658	1.646	1.635	1.624	1.615	1.578	1.551	1.516	1.494	1.478	1.458	1.445	1.390
39	2.839	2.444	2.230	2.095	2.001	1.931	1.877	1.833	1.797	1.767	1.741	1.719	1.700	1.682	1.667	1.653	1.641	1.630	1.619	1.610	1.573	1.546	1.511	1.488	1.473	1.452	1.439	1.383
40	2.835	2.440	2.226	2.091	1.997	1.927	1.873	1.829	1.793	1.763	1.737	1.715	1.695	1.678	1.662	1.649	1.636	1.625	1.615	1.605	1.568	1.541	1.506	1.483	1.467	1.447	1.434	1.377
50	2.809	2.412	2.197	2.061	1.966	1.895	1.840	1.796	1.760	1.729	1.703	1.680	1.660	1.643	1.627	1.613	1.600	1.588	1.578	1.568	1.529	1.502	1.465	1.441	1.424	1.402	1.388	1.327
60	2.791	2.393	2.177	2.041	1.946	1.875	1.819	1.775	1.738	1.707	1.680	1.657	1.637	1.619	1.603	1.589	1.576	1.564	1.553	1.543	1.504	1.476	1.437	1.413	1.395	1.372	1.358	1.291
80	2.769	2.370	2.154	2.016	1.921	1.849	1.793	1.748	1.711	1.680	1.653	1.629	1.609	1.590	1.574	1.559	1.546	1.534	1.523	1.513	1.472	1.443	1.403	1.377	1.358	1.334	1.318	1.245
100	2.756	2.329	2.139	2.002	1.906	1.834	1.778	1.732	1.695	1.663	1.636	1.612	1.592	1.573	1.557	1.542	1.528	1.516	1.505	1.494	1.453	1.423	1.382	1.355	1.336	1.310	1.293	1.214
200	2.731	2.329	2.111	1.973	1.876	1.804	1.747	1.701	1.663	1.631	1.603	1.579	1.558	1.539	1.522	1.507	1.493	1.480	1.468	1.458	1.414	1.383	1.339	1.310	1.289	1.261	1.242	1.144
infinity	2.706	3.912	2.084	1.945	1.847	1.774	1.717	1.670	1.632	1.599	1.571	1.546	1.524	1.505	1.487	1.471	1.457	1.444	1.432	1.421	1.375	1.342	1.295	1.263	1.240	1.207	1.185	1.000

Table IV.6B Upper 1% Values of the F Distribution

Degrees of freedom in denominator	Degrees of Freedom in numerator												
	1	2	3	4	5	6	7	8	9	10	11	12	13
1	4052.181	4999.500	5403.352	5624.583	5763.650	5858.986	6125.865	6125.865	6022.473	6055.847	6083.317	6106.321	6125.865
2	98.503	99.000	99.166	99.249	99.299	99.333	99.422	99.374	99.388	99.399	99.408	99.416	99.422
3	34.116	30.817	29.457	28.710	28.237	27.911	26.983	27.489	27.345	27.229	27.133	27.052	26.983
4	21.198	18.000	16.694	15.977	15.522	15.207	14.307	14.799	14.659	14.546	14.452	14.374	14.307
5	16.258	13.274	12.060	11.392	10.967	10.672	9.825	10.289	10.158	10.051	9.963	9.888	9.825
6	13.745	10.925	9.780	9.148	8.746	8.466	7.657	8.102	7.976	7.874	7.790	7.718	7.657
7	12.246	9.547	8.451	7.847	7.460	7.191	6.410	6.840	6.719	6.620	6.538	6.469	6.410
8	11.259	11.259	7.591	7.006	6.632	6.371	5.609	6.029	5.911	5.814	5.734	5.667	5.609
9	10.561	8.022	6.992	6.422	6.057	5.802	5.055	5.467	5.351	5.257	5.178	5.111	5.055
10	10.044	7.559	6.552	5.994	5.636	5.386	4.650	5.057	4.942	4.849	4.772	4.706	4.650
11	9.646	7.206	6.217	5.668	5.316	5.069	4.342	4.744	4.632	4.539	4.462	4.397	4.342
12	9.330	6.927	5.953	5.412	5.064	4.821	4.100	4.499	4.388	4.296	4.220	4.155	4.100
13	9.074	6.701	5.739	5.205	4.862	4.620	3.905	4.302	4.191	4.100	4.025	3.960	3.905
14	8.862	6.515	5.564	5.035	4.695	4.456	3.745	4.140	4.030	3.939	3.864	3.800	3.745
15	8.683	6.359	5.417	4.893	4.556	4.318	3.612	4.004	3.895	3.805	3.730	3.666	3.612
16	8.531	6.226	5.292	4.773	4.437	4.202	3.498	3.890	3.780	3.691	3.616	3.553	3.498
17	8.400	6.112	5.185	4.669	4.336	4.102	3.401	3.791	3.682	3.593	3.519	3.455	3.401
18	8.285	6.013	5.092	4.579	4.248	4.015	3.316	3.705	3.597	3.508	3.434	3.371	3.316
19	8.185	5.926	5.010	4.500	4.171	3.939	3.242	3.631	3.523	3.434	3.360	3.297	3.242
20	8.096	5.849	4.938	4.431	4.103	3.871	3.177	3.564	3.457	3.368	3.294	3.231	3.177
21	8.017	5.780	4.874	4.369	4.042	3.812	3.119	3.506	3.398	3.310	3.236	3.173	3.119
22	7.945	5.719	4.817	4.313	3.988	3.758	3.067	3.453	3.346	3.258	3.184	3.121	3.067
23	7.881	5.664	4.765	4.264	3.939	3.710	3.020	3.406	3.299	3.211	3.137	3.074	3.020
24	7.823	5.614	4.718	4.218	3.895	3.667	2.977	3.363	3.256	3.168	3.094	3.032	2.977
25	7.770	5.568	4.675	4.177	3.855	3.627	2.939	3.324	3.217	3.129	3.056	2.993	2.939
26	7.721	5.526	4.637	4.140	3.818	3.591	2.904	3.288	3.182	3.094	3.021	2.958	2.904
27	7.677	5.488	4.601	4.106	3.785	3.558	2.871	3.256	3.149	3.062	2.988	2.926	2.871
28	7.636	5.453	4.568	4.074	3.754	3.528	2.842	3.226	3.120	3.032	2.959	2.896	2.842
29	7.598	5.420	4.538	4.045	3.725	3.499	2.814	3.198	3.092	3.005	2.931	2.868	2.814
30	7.562	5.390	4.510	4.018	3.699	3.473	2.789	3.173	3.067	2.979	2.906	2.843	2.789
31	7.530	5.362	4.484	3.993	3.675	3.449	2.765	3.149	3.043	2.955	2.882	2.820	2.765
32	7.499	5.336	4.459	3.969	3.652	3.427	2.744	3.127	3.021	2.934	2.860	2.798	2.744
33	7.471	5.312	4.437	3.948	3.630	3.406	2.723	3.106	3.000	2.913	2.840	2.777	2.723
34	7.444	5.289	4.416	3.927	3.611	3.386	2.704	3.087	2.981	2.894	2.821	2.758	2.704
35	7.419	5.268	4.396	3.908	3.592	3.368	2.686	3.069	2.963	2.876	2.803	2.740	2.686
36	7.396	5.248	4.377	3.890	3.574	3.351	2.669	3.052	2.946	2.859	2.786	2.723	2.669
37	7.373	5.229	4.360	3.873	3.558	3.334	2.653	3.036	2.930	2.843	2.770	2.707	2.653
38	7.353	5.211	4.343	3.858	3.542	3.319	2.638	3.021	2.915	2.828	2.755	2.692	2.638
39	7.333	5.194	4.327	3.843	3.528	3.305	2.624	3.006	2.901	2.814	2.741	2.678	2.624
40	7.314	5.179	4.313	3.828	3.514	3.291	2.611	2.993	2.888	2.801	2.727	2.665	2.611
50	7.171	5.057	4.199	3.720	3.408	3.186	2.508	2.890	2.785	2.698	2.625	2.562	2.508
60	7.077	4.977	4.126	3.649	3.339	3.119	2.442	2.823	2.718	2.632	2.559	2.496	2.442
80	6.963	4.881	4.036	3.563	3.255	3.036	2.361	2.742	2.637	2.551	2.478	2.415	2.361
100	6.895	4.713	3.984	3.513	3.206	2.988	2.313	2.694	2.590	2.503	2.430	2.368	2.313
200	6.763	4.713	3.881	3.414	3.110	2.893	2.220	2.601	2.497	2.411	2.338	2.275	2.220
infinity	6.635	3.912	3.782	3.319	3.017	2.802	2.130	2.511	2.408	2.321	2.248	2.185	2.130

14	15	16	17	18	19	20	25	30	40	50	60	80	100	inf
6142.674	6157.285	6125.865	6181.435	6191.529	6200.576	6208.730	6239.825	6260.649	6286.782	6302.517	6313.030	6326.197	6334.110	6365.861
99.428	99.433	99.437	99.440	99.444	99.447	99.449	99.459	99.466	99.474	99.479	99.482	99.487	99.489	99.499
26.924	26.872	26.827	26.787	26.751	26.719	26.690	26.579	26.505	26.411	26.354	26.316	26.269	26.240	26.125
14.249	14.198	14.154	14.115	14.080	14.048	14.020	13.911	13.838	13.745	13.690	13.652	13.605	13.577	13.463
9.770	9.722	9.680	9.643	9.610	9.580	9.553	9.449	9.379	9.291	9.238	9.202	9.157	9.130	9.020
7.605	7.559	7.519	7.483	7.451	7.422	7.396	7.296	7.229	7.143	7.091	7.057	7.013	6.987	6.880
6.359	6.314	6.275	6.240	6.209	6.181	6.155	6.058	5.992	5.908	5.858	5.824	5.781	5.755	5.650
5.559	5.515	5.477	5.442	5.412	5.384	5.359	5.263	5.198	5.116	5.065	5.032	4.989	4.963	4.859
5.005	4.962	4.924	4.890	4.860	4.833	4.808	4.713	4.649	4.567	4.517	4.483	4.441	4.415	4.311
4.601	4.558	4.520	4.487	4.457	4.430	4.405	4.311	4.247	4.165	4.115	4.082	4.039	4.014	3.909
4.293	4.251	4.213	4.180	4.150	4.123	4.099	4.005	3.941	3.860	3.810	3.776	3.734	3.708	3.602
4.052	4.010	3.972	3.939	3.909	3.883	3.858	3.765	3.701	3.619	3.569	3.535	3.493	3.467	3.361
3.857	3.815	3.778	3.745	3.716	3.689	3.665	3.571	3.507	3.425	3.375	3.341	3.298	3.272	3.165
3.698	3.656	3.619	3.586	3.556	3.529	3.505	3.412	3.348	3.266	3.215	3.181	3.138	3.112	3.004
3.564	3.522	3.485	3.452	3.423	3.396	3.372	3.278	3.214	3.132	3.081	3.047	3.004	2.977	2.868
3.451	3.409	3.372	3.339	3.310	3.283	3.259	3.165	3.101	3.018	2.967	2.933	2.889	2.863	2.753
3.353	3.312	3.275	3.242	3.212	3.186	3.162	3.068	3.003	2.920	2.869	2.835	2.791	2.764	2.653
3.269	3.227	3.190	3.158	3.128	3.101	3.077	2.983	2.919	2.835	2.784	2.749	2.705	2.678	2.566
3.195	3.153	3.116	3.084	3.054	3.027	3.003	2.909	2.844	2.761	2.709	2.674	2.630	2.602	2.489
3.130	3.088	3.051	3.018	2.989	2.962	2.938	2.843	2.778	2.695	2.643	2.608	2.563	2.535	2.421
3.072	3.030	2.993	2.960	2.931	2.904	2.880	2.785	2.720	2.636	2.584	2.548	2.503	2.475	2.360
3.019	2.978	2.941	2.908	2.879	2.852	2.827	2.733	2.667	2.583	2.531	2.495	2.450	2.422	2.305
2.973	2.931	2.894	2.861	2.832	2.805	2.781	2.686	2.620	2.535	2.483	2.447	2.401	2.373	2.256
2.930	2.889	2.852	2.819	2.789	2.762	2.738	2.643	2.577	2.492	2.440	2.403	2.357	2.329	2.211
2.892	2.850	2.813	2.780	2.751	2.724	2.699	2.604	2.538	2.453	2.400	2.364	2.317	2.289	2.169
2.857	2.815	2.778	2.745	2.715	2.688	2.664	2.569	2.503	2.417	2.364	2.327	2.281	2.252	2.131
2.824	2.783	2.746	2.713	2.683	2.656	2.632	2.536	2.470	2.384	2.330	2.294	2.247	2.218	2.097
2.795	2.753	2.716	2.683	2.653	2.626	2.602	2.506	2.440	2.354	2.300	2.263	2.216	2.187	2.064
2.767	2.726	2.689	2.656	2.626	2.599	2.574	2.478	2.412	2.325	2.271	2.234	2.187	2.158	2.034
2.742	2.700	2.663	2.630	2.600	2.573	2.549	2.453	2.386	2.299	2.245	2.208	2.160	2.131	2.006
2.718	2.677	2.640	2.606	2.577	2.550	2.525	2.429	2.362	2.275	2.220	2.183	2.135	2.106	1.980
2.696	2.655	2.618	2.584	2.555	2.527	2.503	2.406	2.340	2.252	2.198	2.160	2.112	2.082	1.956
2.676	2.634	2.597	2.564	2.534	2.507	2.482	2.386	2.319	2.231	2.176	2.139	2.090	2.060	1.933
2.657	2.615	2.578	2.545	2.515	2.488	2.463	2.366	2.299	2.211	2.156	2.118	2.070	2.040	1.911
2.639	2.597	2.560	2.527	2.497	2.470	2.445	2.348	2.281	2.193	2.137	2.099	2.050	2.020	1.891
2.622	2.580	2.543	2.510	2.480	2.453	2.428	2.331	2.263	2.175	2.120	2.082	2.032	2.002	1.872
2.606	2.564	2.527	2.494	2.464	2.437	2.412	2.315	2.247	2.159	2.103	2.065	2.015	1.985	1.854
2.591	2.549	2.512	2.479	2.449	2.421	2.397	2.299	2.232	2.143	2.087	2.049	1.999	1.968	1.837
2.577	2.535	2.498	2.465	2.434	2.407	2.382	2.285	2.217	2.128	2.072	2.034	1.984	1.953	1.820
2.563	2.522	2.484	2.451	2.421	2.394	2.369	2.271	2.203	2.114	2.058	2.019	1.969	1.938	1.805
2.461	2.419	2.382	2.348	2.318	2.290	2.265	2.167	2.098	2.007	1.949	1.909	1.857	1.825	1.683
2.394	2.352	2.315	2.281	2.251	2.223	2.198	2.098	2.028	1.936	1.877	1.836	1.783	1.749	1.601
2.313	2.271	2.233	2.199	2.169	2.141	2.115	2.015	1.944	1.849	1.788	1.746	1.690	1.655	1.494
2.265	2.223	2.185	2.151	2.120	2.092	2.067	1.965	1.893	1.797	1.735	1.692	1.634	1.598	1.427
2.172	2.129	2.091	2.057	2.026	1.997	1.971	1.868	1.794	1.694	1.629	1.583	1.521	1.481	1.279
2.082	2.039	2.000	1.965	1.934	1.905	1.878	1.773	1.697	1.592	1.523	1.473	1.404	1.358	1.000

Table IV.7A Upper 5% Points in the Studentized Range

	Number of treatments, *k*										
d.f. (error)	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**15**	**20**
2		8.33	9.80	10.89	11.73	12.43	13.03	13.54	13.99	15.65	16.77
4		5.04	5.76	6.29	6.71	7.06	7.35	7.60	7.83	8.67	9.24
5	3.64	4.60	5.22	5.67	6.03	6.33	6.58	6.80	6.99	7.72	8.21
6	3.46	4.34	4.90	5.31	5.63	5.89	6.12	6.32	6.49	7.14	7.59
8	3.26	4.04	4.53	4.89	5.17	5.40	5.60	5.77	5.92	6.48	6.87
10	3.15	3.88	4.33	4.66	4.91	5.12	5.30	5.46	5.60	6.12	6.47
12	3.08	3.77	4.20	4.51	4.75	4.95	5.12	5.27	5.40	5.88	6.21
14	3.03	3.70	4.11	4.41	4.64	4.83	4.99	5.13	5.25	5.72	6.03
16	3.00	3.65	4.05	4.34	4.56	4.74	4.90	5.03	5.15	5.59	5.90
18	2.97	3.61	4.00	4.28	4.49	4.67	4.83	4.96	5.07	5.50	5.79
20	2.95	3.58	3.96	4.24	4.45	4.62	4.77	4.90	5.01	5.43	5.71
24	2.92	3.53	3.90	4.17	4.37	4.54	4.68	4.81	4.92	5.32	5.59
30	2.89	3.48	3.84	4.11	4.30	4.46	4.60	4.72	4.83	5.21	5.48
40	2.86	3.44	3.79	4.04	4.23	4.39	4.52	4.63	4.74	5.11	5.36
60	2.83	3.40	3.74	3.98	4.16	4.31	4.44	4.55	4.65	5.00	5.24
120	2.80	3.36	3.69	3.92	4.10	4.24	4.36	4.47	4.56	4.90	5.13
∞	2.77	3.32	3.63	3.86	4.03	4.17	4.29	4.39	4.47	4.80	5.01

Table IV.7B Values of t' for Dunnett's Comparison of Several Treatments and a Control ($\alpha = 0.05$)

	Number of treatments					
d.f.	**2**	**3**	**4**	**5**	**6**	**7**
5	3.03	3.39	3.66	3.88	4.06	4.22
6	2.86	3.18	3.41	3.60	3.75	3.85
7	2.75	3.04	3.24	3.41	3.54	3.66
8	2.67	2.94	3.13	3.28	3.40	3.51
9	2.61	2.86	3.04	3.18	3.29	3.39
10	2.57	2.81	2.97	3.11	3.21	3.31
11	2.53	2.76	2.92	3.05	3.15	3.24
12	2.50	2.72	2.88	3.00	3.10	3.18
13	2.48	2.69	2.84	2.96	3.06	3.14
14	2.46	2.67	2.81	2.93	3.02	3.10
15	2.44	2.64	2.79	2.90	2.99	3.07
20	2.38	2.57	2.70	2.81	2.89	2.96
24	2.35	2.53	2.66	2.76	2.84	2.91
30	2.32	2.50	2.62	2.72	2.79	2.86
40	2.29	2.47	2.58	2.67	2.75	2.81
60	2.27	2.43	2.55	2.63	2.70	2.76
120	2.24	2.40	2.51	2.59	2.66	2.71
∞	2.21	2.37	2.47	2.55	2.62	2.67

Table IV.8 Dixon's Criteria for Rejecting Outliers

		Significance level	
k		**5%**	**1%**
3	$r_{10} = (X_2 - X_1)/(X_k - X_1)$ if smallest value is suspected;	0.941	0.988
4		0.765	0.889
5	$= (X_k - X_{k-1})/(X_k - X_1)$ if largest value is suspected	0.642	0.780
6		0.560	0.698
7		0.507	0.637
8	$r_{11} = (X_2 - X_1)/(X_{k-1} - X_1)$ if smallest value is suspected;	0.554	0.683
9		0.512	0.635
10	$= (X_k - X_{k-1})/(X_k - X_2)$ if largest value is suspected	0.477	0.597
11	$r_{21} = (X_3 - X_1)/(X_{k-1} - X_1)$ if smallest value is suspected;	0.576	0.679
12		0.546	0.642
13	$= (X_k - X_{k-2})/(X_k - X_2)$ if largest value is suspected	0.521	0.615
14	$r_{22} = (X_3 - X_1)/(X_{k-2} - X_1)$ if smallest value is suspected;	0.546	0.641
15		0.525	0.616
16	$= (X_k - X_{k-2})/(X_k - X_3)$ if largest value is suspected	0.507	0.595
17		0.490	0.577
18		0.475	0.561
19		0.462	0.547
20		0.450	0.535
21		0.440	0.524
22		0.430	0.514
23		0.421	0.505
24		0.413	0.497
25		0.406	0.489

Table IV.9 Critical Values of T for a Two-Sided Test at the 5% Level of Significance (Test for Outliers)

Sample size	***T***
3	1.155
4	1.481
5	1.715
6	1.887
7	2.020
8	2.126
9	2.215
10	2.290
11	2.355
12	2.412
13	2.462
14	2.507
15	2.549
16	2.585
17	2.620
18	2.651
19	2.681
20	2.709
25	2.822
30	2.908
35	2.979
40	3.036
50	3.128
100	3.383

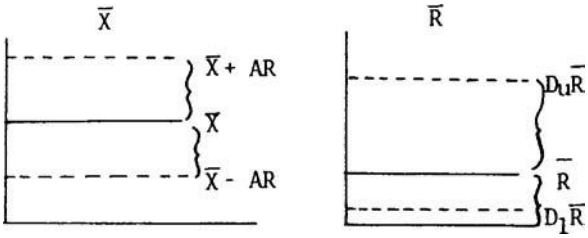
Table IV.10 Factors for Determining Upper and Lower 3σ Limits for Mean ($\overline{X}$) and Range (R) Charts, and for Estimating σ from $\overline{R}$

		Factors for range chart		
Sample size of subgroup, *N*	***A*: Factor for $\overline{X}$ chart**	**D_L for lower limit**	**D_U for upper limit**	**$\sigma = \frac{\overline{R}}{d_2}$ d_2**
2	1.88	0	3.27	1.128
3	1.02	0	2.57	1.693
4	0.73	0	2.28	2.059
5	0.58	0	2.11	2.326
6	0.48	0	2.00	2.534
7	0.42	0.08	1.92	2.704
8	0.37	0.14	1.86	2.847
9	0.34	0.18	1.82	2.970
10	0.31	0.22	1.78	3.078
15	0.22	0.35	1.65	3.472
20	0.18	0.41	1.59	3.735

Example: If $\overline{X} = 100$ and $\overline{R}$ (the average range) $= 5$, and $N = 6$, the upper and lower limits for the $\overline{X}$ chart are

$\overline{X} \pm A\overline{R} = 100 \pm 0.48(5) = 100 \pm 2.4 = (102.4, 97.6)$.

The upper limit for the range chart is $D_U\overline{R} = 2.0(5) = 10$. The lower limit for the range chart is $D_L\overline{R} = 0(5) = 0$. .



For samples of size 4, $\sigma = \frac{\overline{R}}{2.059}$.

If $R = 5, \sigma = \frac{5}{2.059} = 2.43$.

Table IV.11 Number of Correct Guesses Needed for Significance in the Triangle Test[a]

	Correct guesses for significance	
Panel size	**5% Level**	**1% Level**
6	5	6
7	5	6
8	6	7
9	6	7
10	7	8
11	7	8
12	8	9
13	8	9
14	9	10
15	9	10
16	9	11
17	10	11
18	10	12
19	11	12
20	11	13
21	12	13
22	12	14
23	12	14
24	13	15

[a]Pick-up Table from 3rd ed.

Table IV.12 Number of Positive or Negative Signs Needed for Significance for the Sign Test

	Number of positive or negative signs for significance[a]	
Sample size	**5% Level**	**1% Level**
6	6	—
7	7	—
8	8	8
9	8	9
10	9	10
11	10	11
12	10	11
13	11	12
14	12	13
15	12	13
16	13	14
17	13	15
18	14	15
19	15	16
20	15	17

[a]This is a two-sided test. Choose positive or negative signs, whichever is larger.

Table IV.13 Values Leading to Significance for the Wilcoxon Signed Rank Test (Two-Sided Test)

Sample size, *N*	5% Level[a]	1% Level
6	0	—
7	2	—
8	3	0
9	5	1
10	8	3
11	10	5
12	13	7
13	17	10
14	21	13
15	25	16
16	30	19
17	35	23
18	40	28
19	46	32
20	52	37

[a]If the smaller rank sum is less than or equal to the table value, the comparative groups are different at the indicated level of significance.

Table IV.14 Critical Values for Number of Runs at the 5% Level of Significance

Sample size, *N*	Two-sided test Lower number[a]	Upper number	One-sided test Lower number
10	2	9	3
12	3	10	3
14	3	12	4
16	4	13	5
18	5	14	6
20	6	15	6
22	7	16	7
24	7	18	8
26	8	19	9
28	9	20	10
30	10	21	11
32	11	22	11
34	11	24	12
36	12	25	13
38	13	26	14
40	14	27	15

[a]If the number of runs is less than or equal to the lower number or greater than or equal to the upper value, the sequence is considered nonrandom at the 5% level of significance. The sample size (*N*) is the number of values above and below the median. For odd-size samples where one value is the median, use the next smaller sample size for the critical values.

Table IV.15 Probability of Getting at Least One Run of Given Size for *N* Samples

N	5% Level	1% Level
10	5	—
20	7	8
30	8	9
40	9	10
50	10	11

Table IV.16 Critical Values for Wilcoxon Rank Sum Test[a] ($\alpha = 0.05$)

Size of larger sample	Size of smaller sample (M)						
	$M = 3$	4	5	6	7	8	9
M	5,16	11,25	18,37	26,52	37,68	49,87	63,108
$M + 1$	6,18	12,28	19,41	28,56	39,73	51,93	66,114
$M + 2$	6,21	12,32	20,45	29,61	41,78	54,98	68,121
$M + 3$	7,23	13,35	21,49	31,65	43,83	56,104	71,127
$M + 4$	7,26	14,38	22,53	32,70	45,88	58,110	74,133
$M + 5$	8,28	15,41	24,56	34,74	46,94	61,115	77,139
$M + 6$	8,31	16,44	25,60	36,78	48,99	63,121	79,146
$M + 7$	9,33	17,47	26,64	37,83	50,104	65,127	82,152
$M + 8$	10,35	17,51	27,68	39,87	52,109	68,132	85,158
$M + 9$	10,38	18,54	29,71	41,91	54,114	70,138	88,164
$M + 10$	11,40	19,57	30,75	42,96	56,119	72,144	90,171
$M + 15$	13,53	24,72	36,94	50,118	66,144	84,172	104,202
$M + 20$	16,65	28,88	42,113	58,140	76,169	96,200	118,223
$M + 25$	18,78	32,104	48,132	66,162	86,194	108,228	132,264

[a]From Wilcoxon F, and Wilcox RA. Some Rapid Approximate Statistical Procedures. Pearl River, NY: Lederle Laboratories, 1964. If rank sum of smaller sample is equal to or lower than smaller numbers in table or equal to or larger than larger number, groups are significantly different at 0.05 level.

Table IV.17 Critical Difference for Significance ($\alpha = 0.05$) Comparing All Possible Pairs of Treatments for Nonparametric One-Way ANOVA[a]

N (for each treatment)	Number of treatments				
	3	4	5	6	7
3	15	23	30	37	45
4	24	35	46	57	69
5	33	48	63	79	96
6	43	63	83	104	125
7	54	79	105	131	158
8	66	96	128	160	192
9	79	115	152	190	229
10	92	134	178	223	268
11	106	155	205	257	309
12	121	176	233	292	352
13	136	199	263	329	397
14	152	222	294	368	444
15	169	246	326	408	492
16	186	271	359	449	542
17	203	296	393	492	593
18	221	323	428	536	646
19	240	350	464	581	700
20	259	378	501	627	756
21	278	406	538	674	814
22	298	435	577	723	872
23	319	465	617	773	932
24	340	496	657	824	994
25	361	527	699	875	1056

[a]From Wilcoxon F, Wilcox RA. Some Rapid Approximate Statistical Procedures. Pearl River, NY: Lederle Laboratories, 1964.

Table IV.18 Critical Differences for Significance ($\alpha = 0.05$) Comparing All Possible Pairs of Treatments for Nonparametric Two-Way ANOVA[a]

N (for each treatment)	Number of treatments				
	3	**4**	**5**	**6**	**7**
3	6	8	10	13	15
4	7	10	12	15	18
5	8	11	14	17	20
6	9	12	15	18	22
7	9	13	16	20	24
8	10	14	17	21	25
9	10	14	18	23	27
10	11	15	19	24	28
11	11	16	20	25	30
12	12	16	21	26	31
13	12	17	22	27	32
14	13	18	23	28	34
15	13	18	24	29	35
16	13	19	24	30	36
17	14	19	25	31	37
18	14	20	26	32	38
19	14	20	27	33	39
20	15	21	27	34	40
21	15	21	28	35	41
22	16	22	29	35	42
23	16	22	29	36	43
24	16	23	30	37	44
25	17	23	31	38	45

[a]From Wilcoxon F, Wilcox RA. Some Rapid Approximate Statistical Procedures. Pearl River, NY: Lederle Laboratories, 1964.

Table IV.19 Factors for Two-Sided Tolerance Limits for Normal Distributions[a]

	$\gamma = 0.75$					$\gamma = 0.90$				
	p					***p***				
n	**0.75**	**0.90**	**0.95**	**0.99**	**0.999**	**0.75**	**0.90**	**0.95**	**0.99**	**0.999**
2	4.498	6.301	7.414	9.531	11.920	11.407	15.978	18.800	24.167	30.227
3	2.501	3.538	4.187	5.431	6.844	4.132	5.847	6.919	8.974	11.309
4	2.035	2.892	3.431	4.471	5.657	2.932	4.166	4.943	6.440	8.149
5	1.825	2.599	3.088	4.033	5.117	2.454	3.494	4.152	5.423	6.879
6	1.704	2.429	2.889	3.779	4.802	2.196	3.131	3.723	4.870	6.188
7	1.624	2.318	2.757	3.611	4.593	2.034	2.902	3.452	4.521	5.750
8	1.568	2.238	2.663	3.491	4.444	1.921	2.743	3.264	4.278	5.446
9	1.525	2.178	2.593	3.400	4.330	1.839	2.626	3.125	4.098	5.220
10	1.492	2.131	2.537	3.328	4.241	1.775	2.535	3.018	3.959	5.046
11	1.465	2.093	2.493	3.271	4.169	1.724	2.463	2.933	3.849	4.906
12	1.443	2.062	2.456	3.223	4.110	1.683	2.404	2.863	3.758	4.792
13	1.425	2.036	2.424	3.183	4.059	1.648	2.355	2.805	3.682	4.697
14	1.409	2.013	2.398	3.148	4.016	1.619	2.314	2.756	3.618	4.615
15	1.395	1.994	2.375	3.118	3.979	1.594	2.278	2.713	3.562	4.545
16	1.383	1.977	2.355	3.092	3.946	1.572	2.246	2.676	3.514	4.484
17	1.372	1.962	2.337	3.069	3.917	1.552	2.219	2.643	3.471	4.430
18	1.363	1.948	2.321	3.048	3.891	1.535	2.194	2.614	3.433	4.382
19	1.355	1.936	2.307	3.030	3.867	1.520	2.172	2.588	3.399	4.339
20	1.347	1.925	2.294	3.013	3.846	1.506	2.152	2.564	3.368	4.300
21	1.340	1.915	2.282	2.998	3.827	1.493	2.135	2.543	3.340	4.264
22	1.334	1.906	2.271	2.984	3.809	1.482	2.118	2.524	3.315	4.232
23	1.328	1.898	2.261	2.971	3.793	1.471	2.103	2.506	3.292	4.203
24	1.322	1.891	2.252	2.959	3.778	1.462	2.089	2.489	3.270	4.176
25	1.317	1.883	2.244	2.948	3.764	1.453	2.077	2.474	3.251	4.151
26	1.313	1.877	2.236	2.938	3.751	1.444	2.065	2.460	3.232	4.127
27	1.309	1.871	2.229	2.929	3.740	1.437	2.054	2.447	3.215	4.106
30	1.297	1.855	2.210	2.904	3.708	1.417	2.025	2.413	3.170	4.049
35	1.283	1.834	2.185	2.871	3.667	1.390	1.988	2.368	3.112	3.974
40	1.271	1.818	2.166	2.846	3.635	1.370	1.959	2.334	3.066	3.917
45	1.262	1.805	2.150	2.826	3.609	1.354	1.935	2.306	3.030	3.871
50	1.255	1.794	2.138	2.809	3.588	1.340	1.916	2.284	3.001	3.833
55	1.249	1.785	2.127	2.795	3.571	1.329	1.901	2.265	2.976	3.801
60	1.243	1.778	2.118	2.784	3.556	1.320	1.887	2.248	2.955	3.774
65	1.239	1.771	2.110	2.773	3.543	1.312	1.875	2.235	2.937	3.751
70	1.235	1.765	2.104	2.764	3.531	1.304	1.865	2.222	2.920	3.730
75	1.231	1.760	2.098	2.757	3.521	1.298	1.856	2.211	2.906	3.712
80	1.228	1.756	2.092	2.749	3.512	1.292	1.848	2.202	2.894	3.696
85	1.225	1.752	2.087	2.743	3.504	1.287	1.841	2.193	2.882	3.682
90	1.223	1.748	2.083	2.737	3.497	1.283	1.834	2.185	2.872	3.669
95	1.220	1.745	2.079	2.732	3.490	1.278	1.828	2.178	2.863	3.657
100	1.218	1.742	2.075	2.727	3.484	1.275	1.822	2.172	2.854	3.646
110	1.214	1.736	2.069	2.719	3.473	1.268	1.813	2.160	2.839	3.626
120	1.211	1.732	2.063	2.712	3.464	1.262	1.804	2.150	2.826	3.610
130	1.208	1.728	2.059	2.705	3.456	1.257	1.797	2.141	2.814	3.595
140	1.206	1.724	2.054	2.700	3.449	1.252	1.791	2.134	2.804	3.582
150	1.204	1.721	2.051	2.695	3.443	1.248	1.785	2.127	2.795	3.571
160	1.202	1.718	2.047	2.691	3.437	1.245	1.780	2.121	2.787	3.561
170	1.200	1.716	2.044	2.687	3.432	1.242	1.775	2.116	2.780	3.552
180	1.198	1.713	2.042	2.683	3.427	1.239	1.771	2.111	2.774	3.543
190	1.197	1.711	2.039	2.680	3.423	1.236	1.767	2.106	2.768	3.536
200	1.195	1.709	2.037	2.677	3.419	1.234	1.764	2.102	2.762	3.529
250	1.190	1.702	2.028	2.665	3.404	1.224	1.750	2.085	2.740	3.501
300	1.186	1.696	2.021	2.656	3.393	1.217	1.740	2.073	2.725	3.481
400	1.181	1.688	2.012	2.644	3.378	1.207	1.726	2.057	2.703	3.453
500	1.177	1.683	2.006	2.636	3.368	1.201	1.717	2.046	2.689	3.434
600	1.175	1.680	2.002	2.631	3.360	1.196	1.710	2.038	2.678	3.421
700	1.173	1.677	1.998	2.626	3.355	1.192	1.705	2.032	2.670	3.411
800	1.171	1.675	1.996	2.623	3.350	1.189	1.701	2.027	2.663	3.402
900	1.170	1.673	1.993	2.620	3.347	1.187	1.697	2.023	2.658	3.396
1000	1.169	1.671	1.992	2.617	3.344	1.185	1.695	2.019	2.654	3.390

(Continued)

Table IV.19 *(Continued)*

	$\gamma = 0.95$					$\gamma = 0.99$				
	p					***p***				
n	**0.75**	**0.90**	**0.95**	**0.99**	**0.999**	**0.75**	**0.90**	**0.95**	**0.99**	**0.999**
∞	1.150	1.645	1.960	2.576	3.291	1.150	1.645	1.960	2.576	3.291
2	22.858	32.019	37.647	48.430	60.573	114.363	160.193	188.491	242.300	303.054
3	5.922	8.380	9.916	12.861	16.208	13.378	18.930	22.401	29.055	36.616
4	3.779	5.369	6.370	8.299	10.502	6.614	9.398	11.150	14.527	18.383
5	3.002	4.275	5.079	6.634	8.415	4.643	6.612	7.855	10.260	13.015
6	2.604	3.712	4.414	5.775	7.337	3.743	5.337	6.345	8.301	10.548
7	2.361	3.369	4.007	5.248	6.676	3.233	4.613	5.488	7.187	9.142
8	2.197	3.136	3.732	4.891	6.226	2.905	4.147	4.936	6.468	8.234
9	2.078	2.967	3.532	4.631	5.899	2.677	3.822	4.550	5.966	7.600
10	1.987	2.839	3.379	4.433	5.649	2.508	3.582	4.265	5.594	7.129
11	1.916	2.737	3.259	4.277	5.452	2.378	3.397	4.045	5.308	6.766
12	1.858	2.655	3.162	4.150	5.291	2.274	3.250	3.870	5.079	6.477
13	1.810	2.587	3.081	4.044	5.158	2.190	3.130	3.727	4.893	6.240
14	1.770	2.529	3.012	3.955	5.045	2.120	3.029	3.608	4.737	6.043
15	1.735	2.480	2.954	3.878	4.949	2.060	2.945	3.507	4.605	5.876
16	1.705	2.437	2.903	3.812	4.865	2.009	2.872	3.421	4.492	5.732
17	1.679	2.400	2.858	3.754	4.791	1.965	2.808	3.345	4.393	5.607
18	1.655	2.366	2.819	3.702	4.725	1.926	2.753	3.279	4.307	5.497
19	1.635	2.337	2.784	3.656	4.667	1.891	2.703	3.221	4.230	5.399
20	1.616	2.310	2.752	3.615	4.614	1.860	2.659	3.168	4.161	5.312
21	1.599	2.286	2.723	3.577	4.567	1.833	2.620	3.121	4.100	5.234
22	1.584	2.264	2.697	3.543	4.523	1.808	2.584	3.078	4.044	5.163
23	1.570	2.244	2.673	3.512	4.484	1.785	2.551	3.040	3.993	5.098
24	1.557	2.225	2.651	3.483	4.447	1.764	2.522	3.004	3.947	5.039
25	1.545	2.208	2.631	3.457	4.413	1.745	2.494	2.972	3.904	4.985
26	1.534	2.193	2.612	3.432	4.382	1.727	2.469	2.941	3.865	4.935
27	1.523	2.178	2.595	3.409	4.353	1.711	2.446	2.914	3.828	4.888
30	1.497	2.140	2.549	3.350	4.278	1.668	2.385	2.841	3.733	4.768
35	1.462	2.090	2.490	3.272	4.179	1.613	2.306	2.748	3.611	4.611
40	1.435	2.052	2.445	3.213	4.104	1.571	2.247	2.677	3.518	3.493
45	1.414	2.021	2.408	3.165	4.042	1.539	2.200	2.621	3.444	3.399
50	1.396	1.996	2.379	3.126	3.993	1.512	2.162	2.576	3.385	4.323
55	1.382	1.976	2.354	3.094	3.951	1.490	2.130	2.538	3.335	4.260
60	1.369	1.958	2.333	3.066	3.916	1.471	2.103	2.506	3.293	4.206
65	1.359	1.943	2.315	3.042	3.886	1.455	2.080	2.478	3.257	4.160
70	1.349	1.929	2.299	3.021	3.859	1.440	2.060	2.454	3.225	4.120
75	1.341	1.917	2.285	3.002	3.835	1.428	2.042	2.433	3.197	4.084
80	1.334	1.907	2.272	2.986	3.814	1.417	2.026	2.414	3.173	4.053
85	1.327	1.897	2.261	2.971	3.795	1.407	2.012	2.397	3.150	4.024
90	1.321	1.889	2.251	2.958	3.778	1.398	1.999	2.382	3.130	3.999
95	1.315	1.881	2.241	2.945	3.763	1.390	1.987	2.368	3.112	3.976
100	1.311	1.874	2.233	2.934	3.748	1.383	1.977	2.355	3.096	3.954
110	1.302	1.861	2.218	2.915	3.723	1.369	1.958	2.333	3.066	3.917
120	1.294	1.850	2.205	2.898	3.702	1.358	1.942	2.314	3.041	3.885
130	1.288	1.941	2.194	2.883	3.683	1.349	1.928	2.298	3.019	3.857
140	1.282	1.833	2.184	2.870	3.666	1.340	1.916	2.283	3.000	3.833
150	1.277	1.825	2.175	2.859	3.652	1.332	1.905	2.270	2.983	3.811
160	1.272	1.819	2.167	2.848	3.638	1.326	1.896	2.259	2.968	3.792
170	1.268	1.813	2.160	2.839	3.527	1.320	1.887	2.248	2.955	3.774
180	1.264	1.808	2.154	2.831	3.616	1.314	1.879	2.239	2.942	3.759
190	1.261	1.803	2.148	2.823	3.606	1.309	1.872	2.230	2.931	3.744
200	1.258	1.798	2.143	2.816	3.597	1.304	1.865	2.222	2.921	3.731
250	1.245	1.780	2.121	2.788	3.561	1.286	1.839	2.191	2.880	3.678
300	1.236	1.767	2.106	2.767	3.535	1.273	1.820	2.169	2.850	3.641
400	1.223	1.749	2.084	2.739	3.499	1.255	1.794	2.138	2.809	3.589
500	1.215	1.737	2.070	2.721	3.475	1.243	1.777	2.117	2.783	3.555
600	1.209	1.729	2.060	2.707	3.458	1.234	1.764	2.102	2.763	3.530
700	1.204	1.722	2.052	2.697	3.445	1.227	1.755	2.091	2.748	3.511
800	1.201	1.717	2.046	2.688	3.434	1.222	1.747	2.082	2.736	3.495
900	1.198	1.712	2.040	2.682	3.426	1.218	1.741	2.075	2.726	3.483
1000	1.195	1.709	2.036	2.676	3.418	1.214	1.736	2.068	2.718	3.472
∞	1.150	1.645	1.960	2.576	3.291	1.150	1.645	1.960	2.576	3.291

[a]Factors t' such that the probability is γ that at least a proportion P of the distribution will be included between $\overline{X} \pm t's$ where $\overline{X}$ and s are estimates of the mean and the standard deviation computed from a sample size of n.

Table IV.20 Test for Outliers (Upper Band for Critical Values for Studentized Residual)

($\alpha = .10$)

	q									
n	1	2	3	4	5	6	8	10	15	25
5	1.87									
6	2.00	1.89								
7	2.10	2.02	1.90							
8	2.18	2.12	2.03	1.91						
9	2.24	2.20	2.13	2.05	1.92					
10	2.30	2.26	2.21	2.15	2.06	1.92				
12	2.39	2.37	2.33	2.29	2.24	2.17	1.93			
14	2.47	2.45	2.42	2.39	2.36	2.32	2.19	1.94		
16	2.53	2.51	2.50	2.47	2.45	2.42	2.34	2.20		
18	2.58	2.57	2.56	2.54	2.52	2.50	2.44	2.35		
20	2.63	2.62	2.61	2.59	2.58	2.56	2.52	2.46	2.11	
25	2.72	2.72	2.71	2.70	2.69	2.68	2.66	2.63	2.50	
30	2.80	2.79	2.79	2.78	2.77	2.77	2.75	2.73	2.66	2.13
35	2.86	2.85	2.85	2.85	2.84	2.84	2.82	2.81	2.77	2.55
40	2.91	2.91	2.90	2.90	2.90	2.89	2.88	2.87	2.84	2.72
45	2.95	2.95	2.95	2.95	2.94	2.94	2.93	2.93	2.90	2.82
50	2.99	2.99	2.99	2.99	2.98	2.98	2.97	2.95	2.89	
60	3.06	3.06	3.05	3.05	3.05	3.05	3.05	3.04	3.03	3.00
70	3.11	3.11	3.11	3.11	3.11	3.11	3.10	3.10	3.09	3.07
80	3.16	3.16	3.16	3.15	3.15	3.15	3.15	3.15	3.14	3.12
90	3.20	3.20	3.19	3.19	3.19	3.19	3.19	3.19	3.18	3.17
100	3.23	3.23	3.23	3.23	3.23	3.23	3.23	3.22	3.22	3.21

($\alpha = .05$)

	q									
n	1	2	3	4	5	6	8	10	15	25
5	1.92									
6	2.07	1.93								
7	2.19	2.08	1.94							
8	2.28	2.20	2.10	1.94						
9	2.35	2.29	2.21	2.10	1.95					
10	2.42	2.37	2.31	2.22	2.11	1.95				
12	2.52	2.49	2.45	2.39	2.33	2.24	1.96			
14	2.61	2.58	2.55	2.51	2.47	2.41	2.25	1.96		
16	2.68	2.66	2.63	2.60	2.57	2.53	2.43	2.26		
18	2.73	2.72	2.70	2.68	2.65	2.62	2.55	2.44		
20	2.78	2.77	2.76	2.74	2.72	2.70	2.64	2.57	2.15	
25	2.89	2.88	2.87	2.86	2.84	2.83	2.80	2.76	2.60	
30	2.96	2.96	2.95	2.94	2.93	2.93	2.90	2.88	2.79	2.17
35	3.03	3.02	3.02	3.01	3.00	3.00	2.98	2.97	2.91	2.64
40	3.08	3.08	3.07	3.07	3.06	3.06	3.05	3.03	3.00	2.84
45	3.13	3.12	3.12	3.12	3.11	3.11	3.10	3.09	3.06	2.96

($\alpha = .05$)

	q									
n	1	2	3	4	5	6	8	10	15	25
50	3.17	3.16	3.16	3.16	3.15	3.15	3.14	3.14	3.11	3.04
60	3.23	3.23	3.23	3.23	3.22	3.22	3.22	3.21	3.20	3.15
70	3.29	3.29	3.28	3.28	3.28	3.28	3.27	3.27	3.26	3.23
80	3.33	3.33	3.33	3.33	3.33	3.33	3.32	3.32	3.31	3.29
90	3.37	3.37	3.37	3.37	3.37	3.37	3.36	3.36	3.36	3.34
100	3.41	3.41	3.40	3.40	3.40	3.40	3.40	3.40	3.39	3.38

(Continued)

Table IV.20 *(Continued)*

	($\alpha = .01$)									
	q									
n	1	2	3	4	5	6	8	10	15	25
5	1.98									
6	2.17	1.98								
7	2.32	2.17	1.98							
8	2.44	2.32	2.18	1.98						
9	2.54	2.44	2.33	2.18	1.99					
10	2.62	2.55	2.45	2.33	2.18	1.99				
12	2.76	2.70	2.64	2.56	2.46	2.34	1.99			
14	2.86	2.82	2.78	2.72	2.65	2.57	2.35	1.99		
16	2.95	2.92	2.88	2.84	2.79	2.73	2.58	2.35		
18	3.02	3.00	2.97	2.94	2.90	2.85	2.75	2.59		
20	3.08	3.06	3.04	3.01	2.98	2.95	2.87	2.76	2.20	
25	3.21	3.19	3.18	3.16	3.14	3.12	3.07	3.01	2.78	
30	3.30	3.29	3.28	3.26	3.25	3.24	3.21	3.17	3.04	2.21
35	3.37	3.36	3.35	3.34	3.34	3.33	3.30	3.28	3.19	2.81
40	3.43	3.42	3.42	3.41	3.40	3.40	3.38	3.36	3.30	3.05
45	3.48	3.47	3.47	3.46	3.46	3.45	3.44	3.43	3.38	3.23
50	3.52	3.52	3.51	3.51	3.51	3.50	3.49	3.48	3.45	3.34
60	3.60	3.59	3.59	3.59	3.58	3.58	3.57	3.56	3.54	3.48
70	3.65	3.65	3.65	3.65	3.64	3.64	3.64	3.63	3.61	3.57
80	3.70	3.70	3.70	3.70	3.69	3.69	3.69	3.68	3.67	3.64
90	3.74	3.74	3.74	3.74	3.74	3.74	3.73	3.73	3.72	3.70
100	3.78	3.78	3.78	3.77	3.77	3.77	3.77	3.77	3.76	3.74

n = number of observations

q = number of independent variables (including count for intercept if fitted)

Source: Lund, *Technometrics 17*(4), Nov. 1975.

Appendix V
Outlier Tests and Chemical Assays

V.1 INTRODUCTION

In a recent landmark decision resulting from a trial involving the Federal Government and Barr Laboratories, Judge Wolin made many judgments based on his constant probing and the testimony of expert witnesses [1]. Remarkably, most of what he had to say was clear, correct, and to the point, despite his sparse background in the subject material. Much of the Decision related to testing drug products during their production when failing results (out of specification) were observed. A summary of the Decision is available from the FDA [2]. A previous paper by this author [3] presented some alternatives to retesting when a single out of specification result was observed for which no obvious cause was apparent, a situation that is common in my experience. This paper discusses some issues related to the elimination of an out of specification (OOS) result with no obvious cause, based on an outlier test. The Judge, in his Decision, stated that tests for outliers that can be used to exclude an aberrant observation are not appropriate for chemical tests. His reasoning was that the USP includes tests for outliers, but presents these tests only in the context of biological assays, which tend to be very variable. This, he suggests, is appropriate because of the large variability of these kinds of procedures. Judge Wolin further suggests in his Decision that such outlier analyses should not be used for chemical assays, because if they were appropriate, the USP would have recommended the procedure for chemical assays. Thus, the judgment is that, by default, outlier tests for chemical assays should not be used. All of this raises several questions, including (a) Was it the USP's intention to exclude outlier tests for chemical assays? (b) Was this an oversight or was it intentional? (c) Does the USP not discuss outlier tests for chemical assays because the issue is complex with many possible alternatives?

I do not believe that it was Judge Wolin's intention that his Decision should result in nonscientifically based procedures by pharmaceutical firms. I also believe that he would be disturbed if his Decision and FDA's interpretation of his Decision would lead to increased costs because good judgment was cast aside in lieu of fear of a "483 citation." For example, one firm discarded a batch of product because a single content uniformity value failed, despite the fact that 100 individual repeat assays all yielded results between 85% and 115%. Another firm assayed the blend for a capsule product more than 50 times using single dose unit samples during a validation study (because the recommended 3 dosage units were not feasible), with one value being at 119%. All other values were between 90% and 110%. For fear of a "483," the company was reluctant to release the batch. They would have been equally fearful, had the OOS value been 111%, because they interpreted the Decision to impose limits of 90% to 110% for 3 dosage unit weight assays at the blend stage. The final product passed with all content uniformity values between 90% and 110% and an RSD of 2%. Would this firm have been better off performing an absolute minimum number of assays to validate the batch in order to decrease the probability of a failing assay, or to proceed as they did to ensure a thorough validation with increased risk of failure? Once more, I cannot believe that it was Judge Wolin's intention to impose such irrational hardships on the industry. Thus, part of the incentive for this paper (and one previously published. Ref. [2]) is to propose some rational alternatives in the spirit of the Judge's Decision.

V.2 CAN OUTLIER TESTS BE JUSTIFIED?

In fact, the outlier problem remains perplexing, whether applied to questions of fundamental science or problems of more direct practical application. Stories abound in the history of science about how a single outlier, discarded, was eventually found to have contained important

information. Similarly, anecdotes exist about outliers not discarded obscuring the truth. Thus, scientists understand that there is no one answer to the problem, and that there are risks associated with making decisions about how to handle outlying observations. Although the question of how to deal with apparent outliers resulting from chemical assays cannot be resolved easily, the use of outlier tests is ubiquitous in both practical laboratory SOPs as well as the chemical and statistical literature. Pages could be filled with references on this subject, including many from scientists associated with the National Bureau of Standards, for example, the prominent statisticians, Drs. Youden [4] and Mandell [5]. Dr. Youden [4] commented that the experimenter is better equipped to detect outliers than the statistician when a small number of values (e.g., 3) are observed. In fact, with only 3 observations, a value must appear to be extremely divergent before it could be considered an outlier. Thus, he suggests that the experienced experimenter probably would be less conservative than the statistician in finding an observation suspect (the statistical test may be considered conservative in the decision to reject an outlier). Natrella [6] discusses this problem, noting that "There have been many criteria proposed for guiding the rejection of observations." She also states that "no available criteria are superior to the judgment of an experienced investigator . . . ." She gives several statistical procedures for identifying outliers.

It is obvious that there is both theoretical and practical interest in this problem. Again, scientific judgment appears dominant in approaching such problems. Judgment can be defined to be a result of education, knowledge, experience, and common sense. All of these must come into play, and we can be 100% sure that there will never be unanimous agreement on controversial issues. However, because many statistical and chemical treatises discuss the outlier problem, I do not believe that its use can be dismissed out of hand, only because the USP lacks a specific recommendation. Other often used references and documents (OAOC, etc.), including some that are government sponsored, recommend use of outlier tests, when appropriate, for all kinds of data, in particular chemical assays. Virtually every well meaning, knowledgeable scientist would probably entertain the possibility of excluding an outlying value from a set of experimental data. One could give an example of a single assay showing zero drug content, an extreme case, in which it would be absurd not to follow-up with further testing, even if no cause for the "erroneous" result could be found. Similarly, if 3 assays were performed on a relatively homogeneous blend such as a 20 tablet composite, with results of 99, 101, and 0, the null assay would have to be considered suspect. Of course, most situations that might provoke use of an outlier test are less extreme, and probably would need the application of judgment. Certainly, excessive use of outlier tests would suggest some persistant problem that needs to be resolved, unrelated to the assay. Perhaps, there exists a compromise that could satisfy both the conservative (never apply an outlier test) and more liberal (always apply an outlier test and discard the outlying value if present) critic?

V.3 WHY IS THERE NOT A USP TEST FOR OUTLIERS FOR CHEMICAL ASSAYS?

The answer as to why outlier tests are not specifically recommended for chemical assays in the USP is not entirely clear, but I can conjure up a possible scenario. Because of the variability of biological assays, to obtain a more precise estimate of drug content, replicate assays are frequently employed. This is a good scientific approach. The average of replicate assays always gives a better estimate of the true average drug content than a single assay. For very variable assays, a single result may fail because of the large assay variability, not related to the true drug content. For chemical assays, the assay variability is usually relatively small, and a single assay may give a good estimate of the true drug content of the batch. On the other hand, chemical assays with large variability should use replicate assays, with the average result representing the true drug content. Thus, the USP may not want to commit to any specific assay scheduling.

The USP does not comment on the number of assays to be performed, and, in particular, does not suggest multiple assays on a single "homogeneous" portion of material, such as a composite mixture or solution. The number of assays to be performed would appear to be a matter of judgment, each laboratory using its own criteria. This seems reasonable and appropriate. Clearly, in any event, if a single assay or duplicate assays (with no previous estimate of the standard deviation) are performed, outlier tests cannot be applied. At least three assays are needed for an independent application of an outlier test. Thus, the USP cannot apply

outlier tests to chemical assays unless at least three assays are performed. In my experience, only one or two assays are routinely performed for the chemical analysis of composite material. Therefore, for the USP to have an outlier test for chemical assays, at least three assays must be performed. As previously noted, the USP makes no such recommendation. In fact, if a firm is considering multiple assays on a composite, for example, and no provision is made for an outlier test, a decision to perform a single assay would probably cause the least problems, and would be the most prudent from an economic point of view. The more assays that are performed on good material, the greater the chance that at least one of the assays will fail. Yet, from a scientific viewpoint, performing multiple assays and using the average result as a measure of the batch parameter is clearly superior to a single assay. This important point is discussed in more detail later and is also exemplified by the multiple assays performed in a validation batch noted earlier.

V.4 SOME COMMENTS ON THE NATURE OF OUTLIERS AND OUTLIER TESTS, AND OTHER INCONSISTENCIES IN THE DECISION THAT OUTLIER TESTS BE USED FOR BIOLOGICAL ASSAYS BUT NOT FOR CHEMICAL ASSAYS

When performing multiple assays on a single source of material, such as a relatively homogeneous mix or a solution, there is a reasonable probability that one of the replicates may be deviant due to chance or due to an outright error. Whether or not a cause for the deviant assay is documented, the USP suggests (for biological assays) the value may be excluded if an outlier test confirms that the observation is deviant at the 4% level (the chance that the value will be incorrectly excluded is less than 1 in 25). The USP makes it clear that outlier tests should be used sparingly, when unavoidable. Certainly, the situation that is "unavoidable" is open to interpretation or judgment. It would appear to me that one situation that might fit the USP's definition is where inclusion of the outlier would cause the batch to fail and no cause can be found for the outlying value following a suitable investigation. Since such general statements need some interpretation, one would want to know the relevant batch history as well as other measures of the batch performance as part of the justification for performing an outlier test and discarding the outlying result. According to my experience, exclusion of biological assay results based on the outlier test is rarely questioned. This situation should be considered carefully in light of the potential 100% exclusion of outlier tests for chemical assays under all circumstances.

What is the nature of an outlier test? Very important in any such test is an assumption about the underlying distribution of the population data, the distribution of analytical results that might arise from the analysis of a sample, in our context. If we consider the assay results to have an approximate normal distribution, then the outlier test recommended in the USP is appropriate. We probably would be not too far wrong using this assumption for the analytical results derived from a single homogeneous sample. The outlier test recommended in the USP compares the ranges of values in order to assess if the extreme value is far enough removed to be considered discordant relative to the rest of the data. The assumption is that the data are normally distributed and if the probability that the extreme value comes from the distribution is less than 1 in 25, then the value may be considered discordant. It is extremely important to understand that this test is not dependent on the absolute variability of data, but rather on the distance of the suspected outlier from the rest of the data relative to the dispersion of the remaining data. Thus, this test will reject an outlier with the same probability no matter what the variance of the data. The following example may clarify this concept. In a microbiological assay, the following three values were obtained for potency based on three replicate assays: 52.3, 99.9, 101.9. The USP outlier test would be just satisfied, that is, we could exclude the outlier, 52.3. Note that for 3 assays, the outlier must be very far (and obviously) removed from the other two values in order to be discarded. In a chemical assay, the following three values were observed, 86.14, 97.64, 97.87. Again, the value of 86.14 is found to be an outlier. The higher precision of the chemical assay as suggested by the two values close together allows a less distant outlier to be detected. Note that if two of three assays are identical (which may occur if rounding results in identical assays), the third result will always be an outlier. The important point to remember is that the probability of incorrectly eliminating the outlier is less than 1 in 25 for both of these examples. Thus, the risk of incorrectly eliminating an outlier is not dependent on the underlying variability of the normal distribution associated with the assay data.

As suggested previously, if a testing recommendation is not scientifically sound, less valid testing situations will be used to satisfy the recommendations in lieu of more valid approaches. The exclusion of outlier testing for chemical assays may promote less good testing procedures, in my opinion.

V.5 WHAT IS THE PURPOSE OF PERFORMING REPLICATE ASSAYS AND WHEN IS AVERAGING APPROPRIATE?

Although the Barr Decision suggests that averaging is not correct in some circumstances, averaging is appropriate in the situation where multiple assays are used to obtain a better estimate of the true parameter (which is the case for biological assays as well as chemical assays). The reason for performing multiple assays is not to detect nonuniformity, but rather to obtain a better estimate of a parameter, the true drug content. The more assays performed the better the estimate based on the average. This would apply to any assay, but would be more important for variable assays. For chemical assays that are usually (but not always) more precise than biological assays, a single assay may be sufficient to get a good estimate of the drug content. An important consideration is that the average result is what is needed in this circumstance. Still, as noted above, a single assay among the replicates that is found to be OOS may suggest further testing, depending on circumstances (e.g., as noted in the Decision, assays of 91, 91, and 89). It would appear perfectly reasonable to me that if replicate chemical assays (3 or more) are to be performed on a sample (a priori as specified in an SOP), that the same considerations be given to outliers in this situation as is given to biological assays. (Due to its far-ranging implications, perhaps the USP can look further into this very important question.)

The more difficult question to answer is how to apply outlier tests when retesting or resampling is considered to be appropriate. This has been addressed briefly in a previous publication [3], but I will pursue this further here.

V.6 IN WHAT SITUATIONS MIGHT OUTLIER TESTS BE APPLICABLE?

V.6.1 Homogeneous Sample (Solution or Composite Powder)

When performing replicate assays on the same portion of material, the average result is typically used as representing the batch parameter. However, although not specifically recommended in official documents, if one of the replicate values is outside of official specifications (whether an outlier or not), a prudent manufacturer may decide to perform further analyses [3]. In particular, in my opinion, if replicate assays (at least 3) are performed based on SOPs, an outlier test is appropriate. Another application of outlier analysis may occur when a single assay fails and no cause is found. In this case, I recommend further sampling as discussed in the previous paper [3]. If the further assays indicate that the original result is an outlier, then it may be discarded in the calculation of the average. The calculation of the number of samples to be reassayed is also discussed in Ref. [2]. For example, consider the following hypothetical scenario. The original assay is 75% from a composite that should have a mean of 100%. Three new samples are assayed from the same composite with results of 98%, 99% and 100%. The lower limit for passing is 93%. Would you accept or reject this test? (The value of 75% tests as an outlier). If the original OOS result does not meet the outlier criterion, then scientific judgment is needed. If the average passes including the outlier, a prudent manufacturer will examine other batch records and batch history to aid in a decision. For example, with no evidence of batch failure, a passing average in this example may be considered to represent the batch. The same considerations may apply if the average does not pass when the original result is included. If the original result was 75% and three reassays were 93%, 96% and 105%, the 75% value would not be a significant outlier. Considerable judgment would be required here. Should the batch be rejected based only on this evidence? Is further testing appropriate? According to the Court, a product should not be tested into compliance, certainly a reasonable and prudent decision. On the other hand, the hypothetical situation presented here begs for further testing, in my opinion. I would hesitate to make any specific recommendations for this case, but further information about the product would be needed to come to any decision. Again, to establish inflexible rules for every situation does not seem to be a good substitute for scientific judgment. That is not to say that reasonable guidelines are not needed and are not important. For a further discussion, see Ref. [3].

V.6.2 Outlier Tests for Destructive Testing

A particularly difficult situation for the application of outlier tests is testing where the sample, once analyzed, is no longer available. This situation is most prevalent in the context of Quality Control testing of content uniformity and dissolution results. Similar situations may arise in stability testing. Another controversial area in which this problem has been extensively discussed is in bioequivalence testing, where the outlying subject is either not available or has changed since the original observation. Another situation that may be included here is when a large sample of homogeneous material presented for analysis continues to fail after multiple testing, and the possibility exists (but undocumented) that the sample does not truly represent the batch, perhaps due to mishandling or an error in preparation. In these cases, further testing may be indicated, and this has been discussed in Ref. [3]. Because we cannot retest the original material, we can never be certain whether the original analysis is correct. In particular, if the result is a failure, we will never know the truth unless an obvious cause is discovered. This would be the case in content uniformity (CU) testing where a single value outside the range of 75% to 125% is observed. This single value would almost certainly be tested as an outlier. If not, the batch would be suspect. Before discussing this situation, we might try to gain some insight into the nature of the CU test. The CU test does not say that OOS values do not exist in the batch. For example, if 0.1% (1/1000) of the tablets in a batch were outside 75% to 125%, assuming a normal distribution, about 94% of the tablets would be between 85% and 115% and about 6% between 75% to 85% and 115% to 125%. The chances of finding one of these OOS tablets in a random sample of 10 is about 1 in a 100, a very small probability. Yet, 1 in every 1000 tablets is OOS. The probability that the CU test would pass based on the first 10 tablets is >0.88. The probability that the CU test would pass based on the second tier testing is >0.94. Therefore, the CU test is not very discriminating in finding OOS tablets. We would have to have at least 1% of the tablets OOS (less than 75% or greater than 125%) before the CU test would have a good chance (about 50–50) of failing. Thus, the CU test can be considered as a screening test, but relatively nondiscriminating in finding tablets OOS if there are less than 1% in the batch. If we observe a tablet outside 75% to 125%, which tests as an outlier with no obvious cause, should the batch be rejected? There is no way of knowing with certainty whether the value is real or due to some malfunction during the assay, or if real was only a chance observation of an event that has very small probability. I propose that in such situations, following a failure investigation, if appropriate, that a sufficient number of tablets be assayed to give high assurance that the proportion of OOS tablets in the batch is small. Remembering that we cannot ever know with certainty that such tablets do not exist in the batch and that the CU test does not discriminate against a small percentage of such tablets, this seems a prudent approach. This problem has also been addressed in the previous publication where in most cases (small RSD and average potency near 100%) with a sufficient number of passing reassays, we can have high confidence that more than 99.9% of the tablets are within 85% to 115% [3]. It would seem to me that such a probability statement is stronger and carries more information than the usual USP test with regard to tablet uniformity. As suggested in the decision [1], resampling should be conducted using the original sample if possible. Thus, in the case of CU testing or a composite sample (which continually fails), the new samples should be taken from the larger sample of product submitted for analysis by Quality Control Personnel. For example, if the CU test is conducted on tablets taken from a bottle of 1000 tablets submitted by QC, the resampling should be from the remaining tablets.

The approach to demonstrating the validity of data presented here is only one way of coping with a difficult problem. However, any method that is backed by scientific reasoning and common sense should certainly be an improvement over arbitrary approaches. In a sense, the application of this kind of reasoning to such methods may be compared to the application of probability and statistical reasoning substantiating or defining findings in criminal court decisions.

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Appendix VI
Should a Single Unexplained Failing Assay be Reason to Reject a Batch?

The problem of what to do with data that appear to be erroneous, but for which no cause is apparent, has puzzled scientists for as long as data have been collected and evaluated. These data can be characterized as outliers, not appearing to be of the same kind as other data collected under the same circumstances. One might suppose that situations exist where such outliers can be considered absurd, for example, nobody with any knowledge of the process could conceive that such a value could exist. For example, if an automatic device for weighing individual tablets would record a zero, we would be "certain" that the result was not due to a weightless tablet, but rather due to some malfunction of the process. However, in the great majority of cases, the cause for an outlying result cannot be ascertained. In the case of scientific experiments for research purposes, the outlier appears among other experimental results, and the scientist can freely hypothesize reasons and explanations for its presence. Thus, the scientist can make a case for exclusion or inclusion of the outlier, and discuss reasons, implications, etc., with impunity. The future will demonstrate the correctness of his evaluation and judgment; "Time will tell." In a regulatory environment, time is of the essence. We cannot wait for time to prove a hypothesis about an outlying observation, correct or not. Usually, a decision must be made quickly. Although there is no absolute right or wrong way to proceed, "judgment" seems to be a key word. Under a given set of circumstances, what is to be done with the "outlier" is not easy to answer. These problems were at the heart of a recent litigation involving the Federal Government (FDA) and a generic company (Barr Labs, Inc.) [1] that involved testing of solid dosage forms or products for reconstitution. Much of the government's case against Barr related to the passing of batches in which a single failing or outlying assay was observed. The government suggested that if a single assay was not within specifications, in the face of all other tests performed on the batch, the product should be rejected. This "outlying" result or test failure could occur as a result of in-process testing or final product testing, either situation resulting in the rejection of the batch. This was the point of much of the trial proceedings, with a willing judge looking for the truth. In fact, there is no truth. What is to be done is a matter of judgment and common sense, grounded in experience, knowledge, and scientific know-how. Nevertheless, it is certainly possible that two knowledgeable and intelligent experts might disagree on what to do in any given situation. Good judgment does not necessarily lead to a single universal truth. Thus, the procedures recommended in this paper represent my judgment and experience.

In my opinion, a single outlying or failing result among many test results accumulated during the manufacture of a batch of product does not necessarily mean that the batch is unacceptable. In fact, I would think quite the contrary, that if all measures of batch quality other than the "outlier" suggests that the batch is acceptable, indeed the batch probably represents an acceptable product. In any event, the decision as how to proceed should consider other measurements observed during production as well as the product history. If a product has a history of problems, then failing results must be taken very seriously, and the onus of quality falls heavily on the product. On the other hand, if the product has a history of good quality, the outlier may not be due to the product, but rather due to a human or equipment malfunction. Thus, the data should be taken in context. Data available for the batch under consideration and past batches consist of, for example, raw material and blend assays during production, dissolution, content uniformity, final product assay, weight variation, hardness, thickness, and friability. Nevertheless, judgment is difficult to document, and who is to say what person has the qualities to make the correct decision. We can only hope to make a decision that is sensible under the circumstances, knowing that all circumstances differ.

As stated in the "Opinion" [2], "The goal is to distinguish between an anomaly and a reason to reject the batch." If a single assay fails, and all other evidence indicates "quality," the manufacturer has the responsibility to demonstrate that the failing result does not represent the product. If the data were observed in a scientific experiment, the researcher could hypothesize reasons for accepting the bulk of the evidence, with possible justifications for the aberrant result, as noted previously. No harm is done. In a manufacturing environment where GMPs dictate procedures, explanations, no matter how rational or scientifically rigorous, are useless, if a judgment is made by an FDA inspector that the result impugns the quality of the product. There is no unanimity concerning the procedure of evaluating an outlier. This small paper discusses approaches in a few commonly encountered situations in the presence of a failing result or outlier. The discussion presupposes that a cause for the aberrant data is not apparent. *Clearly, if a cause can be identified, for example, analyst mistake, instrument malfunction, or sample preparation error, then a reassay on the same or a new sample (as appropriate) according to the original procedure, would be a reasonable procedure to follow.*

VI.1 CASE 1

The original material from which the failing result or outlier was observed is still available and is (relatively) homogeneous. For example, this would occur in the case of an assay of a blend composite or the assay of a composite of 20 tablets for the final product assay. We assume relatively good homogeneity. The same situation would apply for the assay of a solution when some sample is still available after the assay.

VI.2 CASE 1A

A single assay is reported and fails, for example, outside the 90% to 110% release limits. No cause can be determined. How many reassays are necessary to discredit (or verify) the original assay and ensure the integrity of the batch? The Court's "Opinion" [2] suggests that 7 of 8 passing results may possibly suffice. The recommendation is subjective, although not altogether unreasonable. The number of samples to be retested may be quantified in an objective way, but the final decision still requires "judgment." Although the following analysis could apply to any of the situations described above, I will use the example of a final composite assay for tablets (a homogeneous mix of 20 tablets) to illustrate one possible approach. Thus, when failing or aberrant data with no obvious cause are observed, a reasonable sample size for reassay could be calculated as follows:

Estimate the true batch average and RSD from other data compiled during the batch testing, in particular content uniformity (CU). (We assume that CU data have passed. If not, a failure investigation is warranted.) Assay a sufficient number of new samples so that the 99% confidence interval for the average result, calculated from the available assays on the composite sample, is within specifications. In order to make the calculation for the number of samples to be reassayed, we need to estimate both assay and tablet variability. We can either assume that assay variability is considerably larger than tablet variability (use the RSD from CU); or estimate assay and tablet content variability separately from other available data (previous lots, assay data, etc.) in order to make a more realistic estimate. Bolton has discussed how this may be done in a previous publication [3]. For simplicity, estimate the average tablet content and RSD from the CU data. Note that the RSD estimated from the CU data will be an overestimate of the RSD for the composite (S^2[CU] = S^2[assay] + S^2[tablet uniformity]; S^2[composite] = S^2[assay] + S^2[tablet uniformity/20]), so that the sample size for the reassay will be overestimated, a maximum estimate. (We assume that assay variance is large compared to tablet variance.) The confidence interval depends on the sample size and d.f., and we can estimate a sample size iteratively. Use Table VI.1 for the estimate of number of samples to be reassayed from the composite (or original sample) as a function of mean potency and RSD. Use a slightly larger sample if in doubt. This table is based on a one-sided confidence interval. Typically, we are concerned about an out-of-specification result that is either too low or too high. Note that the numbers in Table VI.1 are based on the sample having the mean and RSD shown in the table. Therefore, the a priori estimate of the sample mean and RSD should be made with care. If in doubt, choose a sample somewhat larger than given in the table. On the other hand, if estimates

Table VI.1 Estimate of Approximate Number of Samples to Be Reassayed Based on Estimate of Mean and RSD for One-Sided 99% Confidence Limit (See Text)

	Mean potency (%)			
RSD (%)	**94**	**96**	**98**	**100[a]**
1	4	3	3	3
2	5	4	3	3
3	7	5	4	4
4	9	6	5	4
5	12	7	6	5
6	16	9	7	6

[a]For estimates greater than 100%, use the 98% column for 102%, etc.

of RSD are made from CU data, the estimate is apt to be too large, and this would tend to make the choice of sample size conservative.

An example should make this clear: Specifications for an active ingredient are 90% to 110%. A single assay of 89% is observed on a composite sample of 20 tablets. From CU data, the average result is 97% with RSD = 4. From Table VI.1, $N \approx 6$. If RSD is 3 in this example, $N \approx 5$.

The number of reassayed samples is sensible. If the average is close to 100% and the RSD is small, only a few samples need to be reanalyzed. If the RSD is large and the average is close to the limits, a larger sample is necessary. *Note that if the sample size, mean potency, and RSD match the values in Table VI.1, the one-sided 99% CI will be within specifications (90–110)*. Finally, one may want to know if the original "outlier" or failing result should be included in the calculation of the average and standard deviation. I would recommend applying the USP test for outliers (Dixon's test) [4] to make a decision as to whether the original outlying observation should be included (see Note 1 on Court Opinion at the end of this paper.) For example, if the original assay is 85%, but we believe that the average potency should be 98% with RSD of 2%, we would assay (at least) three more samples from the same composite (from Table VI.1). If the observed reassay values are 96%, 98%, and 99%, the original assay of 85% is an outlier (Dixon test), and only the 3 reassay values are used in the calculation. The mean is 97.7% and the RSD is 1.55%. The 99% (one-sided) CI is 97.7–6.23 = 91.47, which is within the 90% to 100% limits, and passes. A sample size of 4 or more would give a "comfort" zone.

Note that the Court recommendation of 7 of 8 passing results could be overly conservative in some cases, but less than adequate in other cases. In fact, with moderate variation, 8 samples would be a good number if the average observed potency is close to the specification limits. If the observed potency is close to 100% with moderate variability, less samples are needed.

Also, one might be concerned that if more than one assay fails, the product may still pass (i.e., the average is within limits and the 99% CI is within limits). This would seem to be a most unlikely occurrence, because the inclusion of a failing result would increase the variance considerably if the rest of the values were well within the specification limits. For example, the six assays, 88% 89% 97% 98% 97% and 101%, have an average of 95% and a s.d. of 5.25. The confidence limit would be below 90%.

VI.3 CASE 1B

Replicate assays are performed and the average of the assays is within limits, but one assay fails. No cause can be found. For example, three assays of a homogeneous blend show results of 88%, 95%, and 98%. The average is within 90% to 100%, but one assay is out of limits. One could accept the batch based on the average result (93.7%), but prudence may dictate further testing. We would like to establish a reasonable retesting procedure. Based on the discussion above, it would seem reasonable to assay new samples according to Table VI.1 based on an estimate of the average and RSD. This estimate should be made based on all information available, for example, CU results, not only the results of the assays in question. One could further determine that the passing assays be part of the retesting if there is evidence that one of the values is in error, for example, based on other batch data. Thus, in this case, if a sample of size 4 is called

for, only two samples could be tested and combined with the remaining data (2 passing values). Thus, judgment is critical. But, the rationale for retesting should be recorded and made clear. The procedure could be part of SOPs for retesting. For example, in this example, CU data may have shown an average of 98% and an RSD of 3%. In the current example, the value of 88% appears to be an outlier and the retesting plan would be based on the CU data. On the other hand, if the CU data showed an average of 94% and an RSD of 4%, one might believe that the 88% value may be a legitimate value to be included in the average. In this case, the RSD of the three original assays may be factored into the decision of how much retesting is to be done. Consider the following example to help clarify this decision-making process.

Two assays are performed on a composite sample (2 portions of the same composite), with assay results of 90% and 98%. Note that, in the absence of an outright analytical error, differences in results of such replicates can be, at first, attributed to assay variability. The variability (RSD) of such duplicates based on retrospective data (accumulated from past lots, e.g., from control charts) is determined to be 2%. This suggests that the difference between the two assays (8%) is excessive and probably due to an analytical error. Also, the CU data show an average of 97% and an RSD of 3.5%. From Table VI.1, a sample of size 5 is recommended. Include the 98% observation, but not the 90% value, as one of the 5 samples. (Of course, there is nothing wrong with taking a conservative approach and reassaying 6 new samples.) Note again that one is penalized (more samples to be assayed) when a product is either very variable, not close to 100% in potency, or both.

VI.4 CASE 2

The material from which the failing result or outlier was observed is no longer available. This could occur, for example, for single tablet assays where the test is destructive, or for assays where stability is an issue, and a repeat assay on the same material may not be indicative of the original assayed material. This situation may also occur if repeated testing of a sample shows failure, but where the failure is not necessarily indicative of the quality of the product. An example of this latter situation is repeated failures on a single composite, where the failures could be possibly attributed to an error in preparation of the composite. The process of testing further samples is termed "resampling" (as opposed to "retesting" in the Opinion).

VI.5 CASE 2A

Specific examples of the situation described in CASE 2 above may be considered for the cases of dissolution and content uniformity. In these cases, the original material is not present, and multiple units have been assayed. Outliers may be observed more frequently in these cases because of the multiplicity of assays. Clearly, the more assays performed, the greater the probability of an analytical "error" causing an outlier, or the higher the probability of including an occasional aberrant tablet among those items assayed. For example, one could reasonably argue that in a large batch of tablets or capsules, there is a high probability that the batch contains one or more unusually low and/or high potency units. The chances that such aberrant units will be contained in the sample tested (from 6 to 30 units, for example) are very small if only a few of these outliers exist in the batch. Thus, if an outlying value is observed without any obvious cause, we have no way of knowing the true situation. A very conservative view would be to throw out the batch, no matter if all other tests are within specifications (the "FDA" position in the Barr Case). From a practical (cost) and scientific point of view, throwing out the batch based on such an event seems severe. If we decide that further testing should be done to assess the true nature of the batch, in terms of doing the right thing, we want to be "sure" that the observed outlier is not representative of the batch. Of course, we can never be 100% sure. The degree of assurance should be high and would be difficult to quantify. However, it seems fair to say that if there were any sense that the failure could represent a public health hazard, the desired degree of assurance should be greater.

At the present time, there is no unanimity on what is to be done. For example, in a content uniformity test, a single failing result of 70% is observed for a tablet assay. In one instance, at least, I know that a firm assayed 100 additional tablets (all of which were between 85% and 115%), and nevertheless, the batch was rejected. [The reason for the excessive testing was to

Table VI.2A Minimum Number of Tablets Needed for Various Observed Values of Mean Potency and RSD for Product to Be Acceptable (99% Tolerance Interval)

	Mean potency					
RSD	**95%**	**96%**	**97%**	**98%**	**99%**	**100%**
1%	6(7)	5(6)	5(6)	5(6)	5(5)	4(5)
2%	13 (25)	11(18)	9(15)	8(12)	8(11)	7(10)
3%	60 (>1000)	35 (250)	22 (90)	18 (50)	15(35)	13 (25)
4%	Fails	700 (Fails)	140 (Fails)	70 (Fails)	45 (800)	30 (190)
5%	Fails	Fails	Fails	Fails	500 (Fails)	140 (Fails)
6%	Fails	Fails	Fails	Fails	Fails	Fails

99% assurance that 99% of tablets within 85% to 115% (99% assurance that 99.9% of tablets within 85% to 115% for potent drugs).

meet GMP requirements, according to one defensive (my opinion) interpretation of a failure investigation.]

The question is how much more testing should be done to give a given degree of assurance. To come upon such a number, we need a measure of the "degree of assurance." One reasonable measure is to have assurance that the great majority of units (tablets) are within 85% to 115%. For example, we may want 99% assurance that 99% of the tablets are within 85% to 115%. From my point of view, such a conclusion would be satisfactory for most products. For very potent products, we may want to have 99% assurance that 99.9% of the tablets are within 85% to 115%. If we assume that the tablet drug content is normally distributed, tolerance intervals can be calculated based on assay results. I would propose that further testing be done in cases of a failing result caused by a single outlier (where no cause can be found), and the mean (% of label) and RSD calculated from the reassays.

In this example (CU), all reassays should be within 85% to 115%, with the exception that not more than 1 (3 in the case of capsules) in every 30 could be within 75% to 125%, as defined for CU limits in the USP [5 If one or more items among the new values assay outside 75% to 125%, a full investigation is warranted and indicated. With an estimate of the mean (%) and RSD from the assayed samples, the tolerance interval can be calculated, that is, we can say with 99% assurance that p percent of the tablets are within some upper and lower limit. Tables VI.2A and VI.2B show some possible scenarios of extended testing in these situations. The number of tablets (capsules) to be reassayed are given for 95% and 99% tolerance probabilities. Note that in all these cases, there is very high assurance that practically 100% of the tablets will be within 75% to 125% of label. This plan certainly seems reasonable. Products with a large RSD (e.g., 5%) must be very close to 100% in order to have any chance of passing. If such products contain potent drugs (a matter of judgment), then a product that shows 5% RSD cannot pass if an outlier is observed (a full failure investigation is indicated.) Thus, the product must exhibit moderate or low variability and be close to 100% in order to give assurance that the product is acceptable. As noted previously, one must understand that the average result and RSD are not

Table VI.2B Minimum Number of Tablets Needed for Various Observed Values of Mean Potency and RSD for Product to Be Acceptable (95% Tolerance Interval)

	Mean potency					
RSD	**95%**	**96%**	**97%**	**98%**	**99%**	**100%**
1%	3 (4)	3(3)	3(3)	2(3)	2(3)	2(3)
2%	8 (15)	7(11)	6(9)	6(8)	5(7)	5(6)
3%	35 (>1000)	19(140)	14(50)	11(30)	9(19)	8(15)
4%	Fails	400 (Fails)	80 (Fails)	35 (>1000)	24 (400)	18(100)
5%	Fails	Fails	Fails	Fails	250 (Fails)	80 (Fails)
6%	Fails	Fails	Fails	Fails	Fails	Fails

95% assurance that 99% of tablets within 85% to 115% (95% assurance that 99.9% of tablets within 85% to 115% for potent drugs).

known until the assays are completed. (The RSD and mean potency are determined from the assay results.) These values should be estimated in advance in order to determine the sample size needed for reassay. These values can be estimated from the batch assays. (Use the passing content uniformity data or past batch data for this estimate.) Clearly, the failing value, the suspected faulty result, should not be included in sample size calculations. If unsure about the number of samples to be reassayed, one should estimate conservatively, that is, a larger number of reassays.

For example, a CU test showed 9 passing results (85–115%) and one value less than 75%. The 9 passing values showed a mean of 97% with an RSD of 3%. According to Table VI.2A, 22 more tablets are assayed. If the average of these 22 tablets is close to 97% with RSD approximately equal to 3%, we would have 99% confidence that 99% of the tablets are between 85% and 115%. If the number of tablets to be reassayed based on Table VI.2A is less than 20, reassay at least 20 according to USP CU test specifications [4] the outlier occurred during the first stage of CU testing. If the outlier (<75% or >125%) occurred during the second stage of testing (a total of 30 tablets have been tested), then the numbers in Table VI.2A can be used directly as is.

An important point to be emphasized once more is that the sample sizes in Tables VI.2A and VI.2B will give the indicated tolerance interval if the observed mean and RSD are as indicated in the table. The values of the mean and RSD are not known until the assays are completed. Thus, the numbers in Tables VI.2A and VI.2B are based on a good guess of the expected mean and RSD. A conservative approach would use larger sample sizes than indicated to protect against a bad estimate or chance outcomes. How many more samples to use is strictly a matter of judgment and cost considerations.

A similar table can be constructed for dissolution. This is generally one-sided, in that low values result in failures. For example if the lower limit is 80% dissolution in 30 minutes, the number of retests should result in 95% assurance that 99% of the tablets have a dissolution above 80% in 30 minutes.

One potential cause for product failure is the observation of a large RSD in the CU test. If a product passes based on the individual observations, but fails the RSD test, the individual observations should be evaluated for possible outliers. If a single outler is observed as a possible cause, reassay using the sample size given in Tables VI.2A and VI.2B. If the removal of a single value still results in a failing RSD, a full batch investigation is warranted. For example, suppose that 10 tablets are assayed and 9 have results between 101% and 103%, one value is at 109%, and one value is 86%. Suppose the calculated RSD is greater than 6% (a failure). A reasonable approach would be to reassay, assuming that the 86% value was an outlier. The remaining 9 values have an average result of 103% and RSD of 2.5%. From Table VI.2A, about 15 to 20 tablets would be reassayed. In this example, if the tablets were evenly spread from 85% to 115%, it is possible that elimination of a single tablet would not bring the RSD within specifications. In this case a full investigation would be required. In my experience, this situation would be very unlikely to occur.

VI.6 CASE 2B

Another somewhat different example would be a situation where a single assay fails (or is borderline) and the original sample is no longer available or has been compromised. Again, no cause for the result is obvious, and we cannot differentiate between a true failing result or an analytical error. We need high assurance that the original value does not represent the batch. We could follow the previous example, and estimate the resampling size from Tables VI.2A and VI.2B. However, in these situations, often the material available may be limited. For example, with stability samples, insufficient material may be available for reassay. Another situation that may be considered similar is the case where a composite sample shows consistent failing results and no cause is obvious. The result may have been caused by faulty preparation of the composite. In both of these cases, new samples need to be prepared to verify the integrity of the batch (or stability). In these situations, repeat assay on a new *single* sample (new composite of 20 tablets or new bottle of liquid product) would not be sufficient to assure product quality. One conceivable approach to this problem, if material is lacking, is to take sufficient samples according to Table VI.1, so the results would give a 99% confidence interval for the true potency. The new sample, in this example, would consist of new composites (each individual sample is

a 20 tablet composite) or new bottles of liquid on stability (if available). Consider the following example: A composite assay shows 80% potency after 4 assays. Evidence from CU and other batch data suggest that there is an analytical or preparation error. Note that the composite is an average of at least 20 random tablets, and this low observed value is almost surely not due to lack of mixing (heterogeneous mix). The average potency appears to be about 99% with an RSD of 2% based on other available data. Table VI.1 indicates that three new samples should be taken. Three new composites of 20 tablets each are prepared and assayed, and a 99% confidence interval calculated (one-sided). If the confidence limit is contained in the release specifications, the product is considered to be acceptable. If this were a liquid product (which continues to fail upon reassay), we would need to sample three new bottles. (If three stability samples are not available, one might consider sampling from the field.)

VI.7 CONCLUSION

In my opinion, a single failing or outlying test result (with no documentable cause) is not sufficient to fail a batch of product if other test results for the batch indicate no problems. In these cases, a sufficient amount of further testing should be performed so that the product quality can be assured with high probability. This paper proposes one way of approaching the question of "what is the sufficient number of samples to reassay?"

Notes on the Court's Opinion

1. The Opinion [6] suggests that the fact that the outlier test in the USP is directed toward biological assays, and no mention is made of chemical assays, means that the test is not applicable to chemical assays. It is unfortunate that this inference is made. Perhaps the USP, inadvertently, is at fault, for lack of further explanation when describing the test. In addition, the Opinion further states the reason for the omission of chemical assays with regard to testing for outliers is due to the "innate variability of microbiological assays," "... subject to the whims of microorganisms." In fact, the legitimacy of tests for outliers is not dependent on inherent variability in the sense that the variability is taken into account in the test. Thus, an assay with large variability, such as a microbiological assay, would have to show considerable divergence due to the suspected outlier for the value to be rejected. Because of lower variability, testing for an outlier in a chemical assay might reject a less distant observation. Also, there are surely some chemical assays that are more variable than some biological assays. Thus, the use of an outlier test should not be judged based on the variability of the observation, but, rather on other criteria, for example, the nature of the distribution of results or, perhaps, on philosophical grounds.
2. On pages 74 to 75 of the Opinion [7], the following statement appears: "Unless a firm with certainty establishes grounds to reject the tablet falling outside the 75 to 125 range, the batch should not be released." There is no way to be 100% certain (certainty) in this situation (or any situation for that matter). If the tablet is no longer available for assay and no cause for the outlying result can be found, one can never resurrect the original scenario with any confidence. I believe that if we replace the words, "with certainty", with "with a high degree of assurance", that the methods proposed in this paper fulfill the latter definition.

REFERENCES

1. United States v. Barr Laboratories, Inc., Consolidated Docket No. 92-1744 (AMW).
2. United States v. Barr Laboratories, Inc., Consolidated Docket No. 92-1744 (AMW), p. 26.
3. Bolton S. Computation of in-house quality control limits for pharmaceutical dosage forms based on product variability. J Pharm Sci 1983; 72: 405.
4. USP XXII, USP Convention, Inc., Rockville, MD 20852, 1990, p. 1503.
5. USP XXII, USP Convention, Inc., Rockville, MD 20852, 1990, p. 1618CU test.
6. United States v. Barr Laboratories, Inc., Consolidated Docket No. 92-1744 (AMW), pp. 17, 44.
7. United States v. Barr Laboratories, Inc., Consolidated Docket No. 92-1744 (AMW), pp. 74, 75.

Appendix VII
When is it Appropriate to Average and its Relationship to the Barr Decision

VII.1 BACKGROUND: ASSAY AND CONTENT UNIFORMITY TESTS

Analytical procedures to determine the drug content of pharmaceutical dosage forms are of two kinds. One is to estimate the true average drug content of the product (e. g., mg/tablet or mg/mL), and the other is to determine the uniformity of the product, that is, to assess the degree to which different dosage units may differ. For true solutions, the question of uniformity is mute, because solutions are homogeneous by definition (In certain cases, it may be desirable to check uniformity for large volumes of solutions to ensure dissolution and adequate mixing prior to transfer). For solid dosage forms, uniformity is determined by assaying different portions of the powdered blend at the initial stages of the process, and individual finished tablets at the final stage. For assessing uniformity, there are no "official" regulations for conformance for blends. The finished product content uniformity test is defined in the USP. Release limits for blend testing for uniformity is at the discretion of the pharmaceutical firm, and should have a scientific as well as practical basis. The subject of blend testing was an important issue in the Barr Trial and Judge Wolin's Decision [1]. In particular, Judge Wolin condemned the averaging of different samples of powdered blend when the purpose of the test was to determine uniformity. This is obvious to the pharmaceutical scientist. Not that it is wrong to average the results (we are always interested in the average), but we do not want to obscure the variability by mixing heterogeneous samples and then reporting only an average, when the purpose of the test is to assess that variability. Therefore, procedures for assessing and reporting variability are clear, although the regulations for blend testing and interpretation of data are not "official" and need scientific judgment. (A further dilemma here is that some pharmaceutical firms do not perform blend testing on some products, at their discretion.)

VII.2 AVERAGING REPLICATES FROM A HOMOGENEOUS SAMPLE

The problem that I want to present here is: When is averaging appropriate and correct, and how do we deal with the individual values that make up the average in these circumstances? This can be simplified by limiting this question to one particular situation:

AVERAGING IS APPROPRIATE AND CORRECT WHEN MULTIPLE ASSAYS ARE PERFORMED ON THE SAME SAMPLE, OR ON REPLICATE SAMPLES FROM THE SAME HOMOGENOUS MIX, FOR PURPOSES OF DETERMINING THE TRUE AVERAGE CONTENT.

I do not believe that any knowledgeable scientist would argue or contradict this. It is a scientific, statistical fact that the average of multiple assays on the same material will give a better estimate of the true content than single assays (the more assays, the better the estimate). Thus, a pharmaceutical firm would better fulfill its obligation of supplying conforming material to the public by performing multiple assays. Nevertheless, the number of assays performed for purposes of estimating the true drug content is not fixed by law, and many companies perform a single assay, whereas other companies may perform three or more assays. In fact, the manner in which the replicates are performed may differ among companies. For example, a replicate assay may be defined as coming from replicate analyses of the same final solution prepared from a single portion of material, such as replicate HPLC injections from the same solution. The variability among the replicate readings in this case represents instrumental variability rather than product variability. If we are dealing with a solution or a homogenized composite of 20

tablets, there are other sources of variability that are not accounted for in such a replicate scheme. In particular, the variability arising from the sample preparation for analysis is neglected in the former scheme because only one sample has been analyzed. Sample preparation variability would include weighing variability as well as variability during the various steps of preparing the product for the analysis. Therefore, the average of replicates using different sample preparations will give a better estimate of the true drug content than the same number of replicate analyses on the same sample. The latter gives a good estimate of a single sample, whereas the former better estimates the batch. Again, this is a scientific, statistical fact. We can define the variability of such an assay measurement as the sum of independent variances

$$\text{Variance (assay)} = \text{variance(I)} + \text{variance(P)} + \text{variance(O)},$$

where I = instrumental, P = preparation and O = other sources of variation.

The variance of the average of 3 replicates where the replicates are multiple injections from the same sample is

$$\frac{\text{variance(I)}}{3} + \text{variance(O)} + \text{variance(P)}.$$

The variance of the average of 3 replicates where the replicates are multiple preparations from the same sample is:

$$\frac{\text{variance(I)} + \text{variance(O)} + \text{variance(P)}}{3}.$$

Therefore, given a choice, to obtain a more precise estimate of the average drug content of a batch, assaying multiple preparations from the same homogeneous sample is a more desirable procedure than assaying multiple injections from a single preparation. This would apply for both solutions and homogeneous powders. Thus, there is little doubt as to what constitutes a better testing procedure for estimating drug content

USE MORE INDEPENDENT SAMPLES!

Again, there are no official regulations on how many samples to use. Assaying a single sample may be acceptable in this respect.

VII.3 HOW DO WE DEAL WITH SINGLE OOS RESULTS WHEN THE AVERAGE CONFORMS?

What, then, is the problem? The problem is that there is confusion as to how to handle the individual observations that make up the average in certain situations. There should be no argument as to when it is appropriate to average. As emphasized throughout this discussion, averaging multiple observations is appropriate when the purpose is to estimate the average drug content. If all of the individual observations fall within release limits, there is no ambiguity. The question is, "What do we do if one of the individual observations falls outside of the release limits?"

Although not explicitly stated, official limits are absolute. A product either does or does not pass. The official limits for drug content, as stated in the USP, for example, are based on the average drug content. Clearly, some individual units may lie outside these limits as defined in the content uniformity test. From a legal point of view, it appears that if the measure of the average content falls within limits, the product is acceptable. Thus, an average result of 90.5 based on a single assay or duplicates of 89.5 and 91.5 is within limits. On the other hand, such a result suggests that the true average may be below 90 with substantial probability. A prudent manufacturer would want more assurance that the product is truly within specifications. In-house limits such as 95 to 105 are constructed to give such assurance. These limits are usually computed so that there is high assurance that the product truly meets official specifications if an analytical result falls within these limits. The in-house specifications are not legal limits, but, rather, are computed, conservative limits to ensure that the legal limits will be met. The

construction of such limits should include all sources of variability including analytical error. Thus, a single assay of 95.5% should be sufficient to release the product if the in-house limits are computed correctly. In this situation, there is no question about the decision, the product passes or does not pass. Suppose, that a company wants to improve this assessment of lot performance by performing triplicate assays in this same situation. Because the single assay is close to the in-house limit, repeat assays are apt to give values below 95. For example, triplicate assays may give values of 94.5, 95.5, and 96.5, with an average of 95.5. In this case, the average result is definitive and the single value below 95 should not invalidate the average. Otherwise, we would be saying that a single assay of 95.5 is a better indicator of batch quality than triplicate assays that average 95.5. Clearly, this is contradictory to scientific and statistical fact. If we act otherwise, we would be defeating the intent and purpose of scientific QC analytical techniques.

How do we account for the fact that an average may fall within limits, but a single assay may fall outside the limits (without obvious cause)? It is a well-known statistical fact that the more observations we make, the greater the likelihood of seeing extreme observations because of inherent variability in the observations. The variability has a probability distribution, say approximately normal. Every observation has some probability of falling outside the release limits due to extreme errors (variability) that can occur during an analysis. These extreme observations are apt to happen from time to time, by chance. If we are unlucky enough to see such an observation, is this irrevocable? Does this mean the batch is not good? The answer requires scientific judgment. In the absence of a definitive mistake, examination of batch records and product history, as well as the nature of the assay and release limits should lead to either acceptance of the batch or further testing (according to SOPs). Further testing should help to assess the true nature of the data, that is, to differentiate a failure from an anomalous result.

Unfortunately, Judge Wolin, in his decision (Barr Decision), excluded outlier tests from chemical assays (this ruling is controversial and will almost certainly be modified in the near future). But, even if a single failing value is not an outlier, is this cause for rejection, when the average is the objective of the test? Certainly, some scientific judgment is needed here. Otherwise, we will be throwing out much good material at the expense of the manufacturer and taxpayer, and we will be condoning nonscientific, suboptimal testing techniques. If, in fact, there is no give or compromise in this dilemma, companies will do an absolute minimal amount of testing to reduce the probability of out-of-specification (OOS) results.

So the question remains as to how to handle this perplexing problem, "What do we do about a single OOS result among replicates that are meant to be averaged?" I do not believe that there can be a single inflexible rule. Scientific judgment and common sense are needed. I will give a couple of examples.

Example 1. The official limits for a product are 90 to 110. In-house limits are set at 95 to 105. The in-house limits are based on the variability of the product, that is, the manufacturer believes that based on the variability inherent in measuring the drug content of the product (perhaps including assay error, stability, uniformity, etc.) that the average content when the product is released based on a 20 tablet composite should be between 95 and 105. Thus, the manufacturer is prepared to release the product if the average composite assay is 95 to 105. Triplicate analyses yield results of 99, 98, and 94.5, an average of 97.17, which passes. However, one assay is below 95 (note the triple jeopardy incurred by the triplicate determinations). Should this product be released? Note that the release limits of 95 to 105 are based on inherent variability of the product, including its measurement. On this basis, the product should pass, because it is the average in which we are interested. If there is any doubt, I would want to look at other product characteristics and batch history. Certainly, if there were no suggestion of a problem based on other relevant data, release of this batch would be indicated. Another scientific contradiction here concerns in-house limits that apparently are not subject to regulations. Firms that use in-house limits for release, certainly a better and more conservative approach to releasing material than using the absolute official limits, may be penalized for using a more scientific approach to drug testing. Also, I believe that there is a qualitative difference for single OOS results when applying "Official" and "in-house" release limits. "Official" limits are irrevocable, set by "law" without a truly scientific basis. An average of 89.9 for a product with official limits of 90 to 110 cannot be released! In-house limits are set by individual companies based on scientific "know-how" and have built-in allowances for variability. Thus, a single replicate falling slightly

below the "Official" limit should probably be treated with greater concern than-the single value outside in-house limits but within official limits as observed in this example.

Example 2. Consider the situation where the Official release limits are 95 to 105 and the three assays are 96.5, 95.5, and 94.5. The average is 95.5 that passes. All other data are conforming. In this case, although it still may be argued convincingly that the product passes, I would suggest additional testing. I believe that this is appropriate even if no cause can be found for the low result. This question was raised in the Barr trial, in which results of 89, 89, 92 were contemplated for a product with release limits of 90 to 110 (paragraph 49, Barr Decision). Further testing was recommended by the witness, and the judge seemed to be satisfied with this approach. The real problem here, is not the problem of averaging, or retesting, but of "retesting into compliance." Clearly, the latter approach is not satisfactory, and should be addressed in SOPs. The SOP should recommend the number of retests to be performed when there is reasonable doubt about the quality of the batch as suggested in this example.

VII.4 DISCUSSION

Because of the lack of specific regulations concerning averaging of data, scientific judgment and common sense should prevail. Certainly, situations exist where averages are the optimal way of treating and reporting data. In particular, replicate measures based on a homogeneous sample are meant to be averaged. Procedures for averaging data and retesting should be contained in the company's SOPs.

The question of what to do if a single OOS result is observed is addressed to some extent in the Barr Decision. A single OOS result that cannot be attributed to the process or to an operator error, as opposed to a laboratory error, is not labeled as a failure. According to Inspector Mulligan of the FDA (Barr Decision, paragraph 21), an OOS result overcome by retesting is not a failure. "The inability to identify an error's cause with confidence affects retesting procedures, see paragraph 38–39. . ." (Barr Decision, paragraph 28). Paragraphs 38 and 39 suggest that retesting is part of the failure investigation. "A retest is similarly acceptable when review of the analyst's work is inconclusive." Thus, retesting is not disallowed when the retests are used to isolate the cause or nature of the outlying result. The amount of retesting should be sufficient to differentiate an anomaly and a reason to reject a batch (paragraph 39). Thus, according to the decision, retesting may be done with discretion (based on SOPs) to help identify a cause for OOS results.

An important consideration is that good testing procedures should not be penalized. As noted in the examples above, a single OOS result contained in an average that passes specifications should not be reason to reject a batch in general without further testing. Otherwise, firms will be forced into performing single assays to reduce the risk of failure. This is based on the fact that the penalty for an OOS result would be the same for both (a) one of several assays OOS or (b) a single assay OOS. Biological assays are often based on the average of triplicates, in which the average result is the basis for release, regardless of the individual values. In principal, chemical assays should be treated in a similar manner, with scientific judgment always in mind.

REFERENCE

1. Barr Decision, Civil Action No. 92–1744, OPINION, United States District Court for the District of New Jersey, Judge Alfred M. Wolin, February, 1993.

Appendix VIII
Excel Workbooks and SAS Programs

Excel Workbooks

Microsoft *Excel* provides a powerful package to solve many statistical problems. The following Workbooks are provided as examples of how this package can be used to solve problems presented in this book. It is hoped that the reader will be able to apply the principles illustrated in these examples to the real-life statistical problems that he or she encounters. It is anticipated that the reader has some familiarity with Excel and the basic mathematical functions available in Excel. The reader should also be familiar with the basic methods to copy and paste values and formulas from one cell or group of cells to another.

Many of the examples use Excel's built-in statistical modules. These are available in the Statistical Analysis ToolPak add-in. If this feature is activated in your installation of Excel, you will see it by choosing Tools in the main menu of Excel. If you find the Data Analysis option, the add-in is activated. If not, choose Tools and then select Add-Ins. From the choice of Add-ins, select both the Analysis ToolPak and the Analysis ToolPak-VBA options. This will install the package.

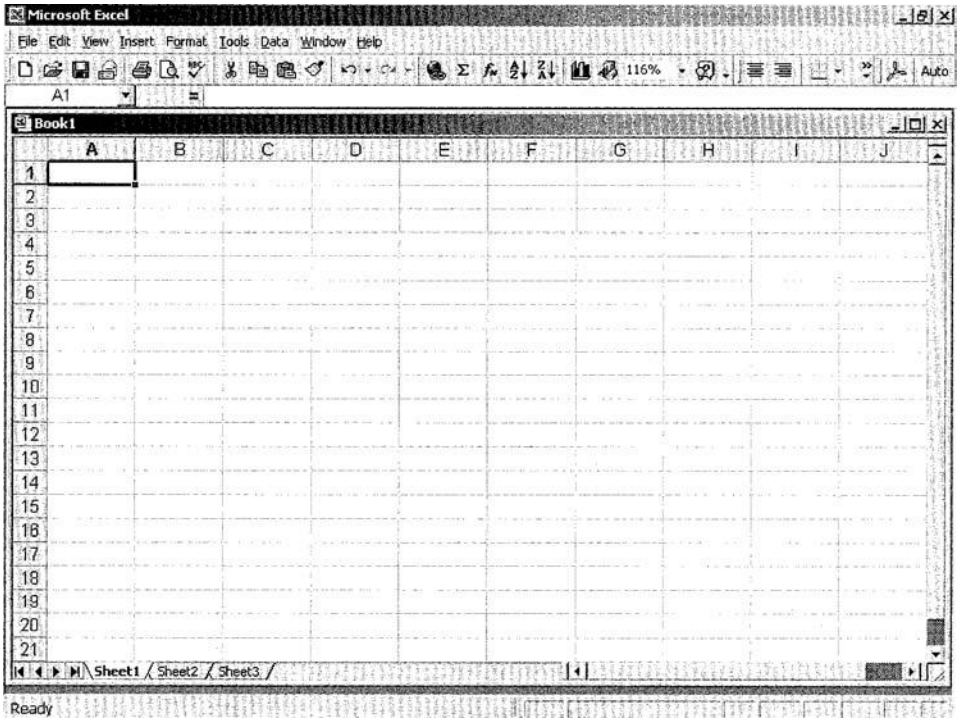
In the following examples, sequences of Excel commands will be presented to accomplish the data analyses. The Main Menu bar, in the following illustration, is just below the Microsoft Excel heading. It has the headings of File, Edit, View, Insert, Format, Tools, Data, Window and Help.
The command sequence:

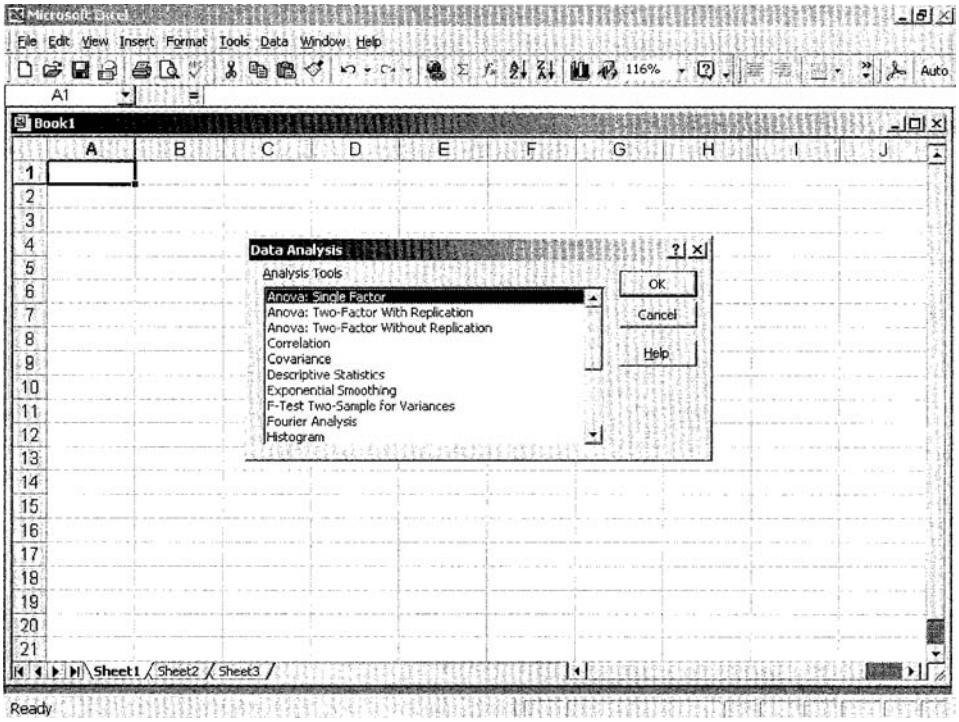
Main Menu Tools → Data Analysis → Descriptive Statistics

Refers to the steps:

1. Choose Tools from the Main Menu
2. Select Data Analysis under the Tools menu
3. Move the highlight down to Descriptive Statistics
4. Click OK

The first example is based on the Serum Cholesterol Changes for 156 Patients shown in Table 1.1. Workbook 1.1 shows how to perform descriptive analyses of the data and how to obtain a cumulative frequency distribution.


Microsoft Excel
File Edit View Insert Format Tools Data Window Help
A1
Book1
Sheet1 Sheet2 Sheet3
Ready


File Edit View Insert Format Tools Data Window Help
A1
Book1
Data Analysis
Analysis Tools
Anova: Single Factor
Anova: Two-Factor With Replication
Anova: Two-Factor Without Replication
Correlation
Covariance
Descriptive Statistics
Exponential Smoothing
F-Test Two-Sample for Variances
Fourier Analysis
Histogram
OK
Cancel
Help
Sheet1 Sheet2 Sheet3
Ready

Workbook 1.1 Descriptive Analyses and Cumulative Frequency Distribution (partial workbook shown)

	A	B	C	D	E	F	G
1	*Change*	*Change*		*Point*	*Change*	*Rank*	*Percent*
2	17			125	55	1	100.00%
3	−12	Mean	−10.6218	91	46	2	99.30%
4	25	Standard Error	2.216327	60	40	3	98.70%
5	−37	Median	−9.5	105	39	4	98.00%
6	−29	Mode	17	109	38	5	97.40%
7	−39	Standard Deviation	27.68191	50	35	6	96.10%
8	−22	Sample Variance	766.2883	88	35	6	96.10%
9	0	Kurtosis	−0.16183	11	34	8	94.80%
10	−22	Skewness	−0.28357	126	34	8	94.80%
11	−63	Range	152	18	33	10	94.10%
12	34	Minimum	−97	97	27	11	93.50%
13	−31	Maximum	55	113	26	12	92.90%
14	−64	Sum	−1657	3	25	13	92.20%
15	−12	Count	156	37	24	14	90.90%
16	−49			92	24	14	90.90%
17	5			98	23	16	90.30%

Commands in Analyses

Cells A1 – A157	Enter "Change", then in A2-A157 the 156 change values from Table 1.1.
Main Menu	Tools → Data Analysis → Descriptive Statistics
Dialog Box	
Input Range:	Highlight or enter A1:A157
Grouped By:	Click on Columns option
Labels in First Row:	Click on this option
Output Range	Click on Column B or enter B1
Summary Statistics	Click on this option
OK	Click to calculate
Main Menu	Tools → Data Analysis → Rank and Percentile
Dialog Box	
Input Range:	Highlight or enter A1:A157
Grouped By:	Click on Columns option
Labels in First Row:	Click on this option
Output Range	Click on Column D or enter D1
OK	Click to Calculate

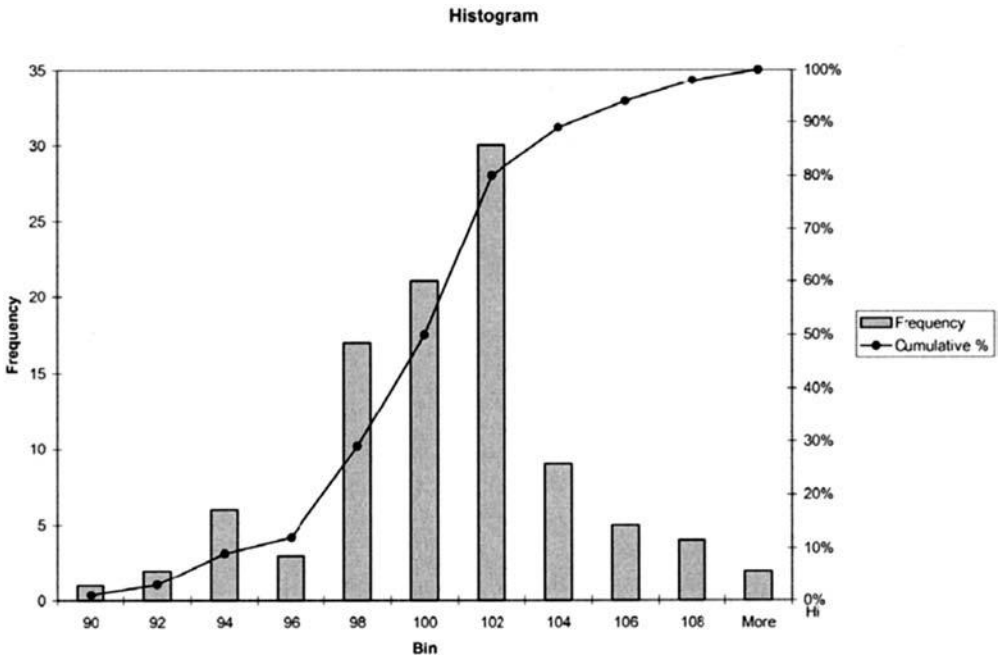
Notes on Analyses Interpretation:
Columns C lists the value of the sample statistic referenced in Column B
The statistic "Mode" (most frequent value) is not a unique value in this data set.

Workbook 1.4 Entry of Tablet Potencies When Frequency Distribution Is Given (partial worksheet shown)

	A	B	C	D	E	F	G	H	I
1	90	92	93	94	95	96	97	98	99
2		92		94		96	97	98	99
3				94			97	98	99
4				94			97	98	99
5				94			97	98	99
6							97	98	99
7							97	98	99
8								98	99
9								98	
10								98	

Column D lists the observation number, in Column A, for the Change value in Column E
Column F lists the rank (highest to lowest) for the Change value shown in Column E
Column G lists the cumulative frequency percentile for the Change value in column E

The next example creates a histogram and a cumulative frequency plot from the tablet potency values presented in Table 1.4.



Each Xi value is entered into a separate worksheet column, the number of replicate entries of a value is given by its frequency, Wi, in Table 1.4. Entering a value once and then copying it through the range of desired cells simplifies the process.

The Xi values in each column are then copied to a new worksheet to create a single column of all 100 tablet potencies, as shown in the following partial worksheet.

	A
1	**Potency**
2	90
3	92
4	92
5	93
6	94
7	94
8	94
9	94
10	94
11	95
12	96
13	96
14	97
15	97
16	97
17	97
18	97
19	97
20	97

Descriptive analyses can now be conducted on the values in Column A of this second worksheet (e.g. creation of histogram and cumulative % plots).

Commands in Analyses

Main Menu Bar	Tools → Data Analysis → Histogram
Dialog Box	
Input Range:	Highlight or enter A1:A101
Labels	Click on this option
Output	Click on New Worksheet Ply
Cumulative Percentage	Click on this option
Chart Output	Click on this option
OK	Click to plot histogram
Click on Histogram	
Main Menu Bar	Chart → Location
Dialog Box	
As New Sheet:	Click on this option and enter "Histogram" in box to right
Click on cumulative percentage line:	Format symbol and colors as desired
Click on y-axis	Format scale, font, number as desired
Click on histogram Bars	Format color, patterns, fill effects as desired

Note: If it were necessary to format the x-axis (Bin) values, this is done by changing the format of the Bin values column in the worksheet containing these values.

Next the tablet assay results shown in Table 5.1 are used to demonstrate construction of a 95% confidence interval for the sample mean under the assumption that the data are normally distributed. The mean, μ, and the standard deviation, σ, for the population are unknown and must be estimated from the data. As such, the t-distribution is used to obtain the confidence interval limits.

Workbook 5.1 Confidence Interval When Mean and Sigma Are Unknown

	A	B	C	D	E	F
1	**Potency**	**n**	**Mean**	**S**	**alpha**	**Confidence**
2	101.8	10	103.0	2.22	0.05	0.95
3	102.6					
4	99.8	**df**	**t-value**	**Cl Lower**	**Cl Upper**	
5	104.9	9	2.26	101.41	104.59	
6	103.8					
7	104.5					
8	100.7					
9	106.3					
10	100.6					
11	105.0					
12						
13						

Commands in Analysis (commands for up to 100 entries in column A):

Cells in Column A	Enter tablet potency results from Table 5.1	
Cell B2	= COUNT(A2:A101)	Total number of potency values
Cell B5	= B2–1	Degrees of freedom (df) = n-1
Cell C2	= AVERAGE(A2:A101)	Arithmetic mean of potency values
Cell D2	= STDEV(A2:A101)	Sample standard deviation for values
Cell E2	Enter alpha level	0.05 for 95% CI, 0.10 for 90% CI, etc.
Cell F2	= 1-E2	Confidence Interval coverage
Cell C5	= TINV(E2,B5)	Critical t-value for alpha & df
Cell D5	= C2-C5*D2/SQRT(B2)	95% Confidence Interval lower limit
Cell E5	= C2 + C5*D2/SQRT(B2)	95% Confidence Interval upper limit

The following uses the percent dissolution values of Table 5.9 to demonstrate how to use Excel's built in statistical tools to conduct an independent sample t-test.

Workbook 5.9 Two Independent Sample t-Test

	A	B	C	D	E
1	**FORM A**	**FORM B**	t-Test: Two-Sample Assuming Equal Variances		
2	68	74			
3	84	71		*FORM A*	*FORM B*
4	81	79	Mean	77.1	71.4
5	85	63	Variance	33.43333333	48.71111111
6	75	80	Observations	10	10
7	69	61	Pooled Variance	41.07222222	
8	80	69	Hypothesized Mean Diff	0	
9	76	72	Df	18	
10	79	80	t Stat	1.988775482	
11	74	65	P(T<=t) one-tail	0.031073458	
12			t Critical one-tail	1.734063062	
13			P(T<=t) two-tail	0.062146917	
14			t Critical two-tail	2.100923666	

Commands in Analyses

Columns A & B	Enter Form A and Form B values from Table 5.9
Main Menu Bar	Tools → Data Analysis → t-Test: Two-Sample Assuming Equal Variances
Dialog Box	
Variable 1 Range:	Highlight or enter A1:A11
Variable 2 Range:	Highlight or enter B1:B11
Hypothesized Mean Diff:	Enter the null hypothesis difference between means, 0
Labels:	Click on this option
Alpha:	Enter desired alpha level for t-Test, 0.05
Output Range	Highlight cell C1 or enter C1.
OK	Click to perform calculations. Results appear in Columns C-E.

The next workbook performs the analysis for a paired sample t-test as shown in Table 5.11. The comparison of the Areas under the blood-level curve calculated for six animals dosed in a bioavailability study with both a new drug formulation (A) and the marketed formulation (B) is easily performed using Excel's built-in statistical program.

Workbook 5.11 Paired Sample *t*-Test

	A	B	C	D	E	F	G
1	**Animal**	**FORM A**	**FORM B**	**Ratio**	**Expected**		
2	1	136	166	0.82	1		
3	2	168	184	0.91	1		
4	3	160	193	0.83	1		
5	4	94	105	0.90	1		
6	5	200	198	1.01	1		
7	6	174	197	0.88	1		
8							
9	t-Test: Paired Two Sample for Means				t-Test: Paired Two Sample for Means		
10							
11		*FORM A*	*FORM B*			*Ratio*	*Expected*
12	Mean	155.33333	173.83333		Mean	0.891654	1
13	Variance	1332.2667	1278.1667		Variance	0.004747	0
14	Observations	6	6		Observations	6	6
15	Pearson Correlation	0.9354224			Pearson Correlation	#DIV/0!	
16	Hypothesized Mean Difference	0			Hypothesized Mean Difference	0	
17	Df	5			df	5	
18	t Stat	−3.484781			t Stat	−3.85212	
19	P(T<=t) one-tail	0.0087842			P(T<=t) one-tail	0.005988	
20	t Critical one-tail	2.0150492			t Critical one-tail	2.015049	
21	P(T<=t) two-tail	0.0175684			P(T<=t) two-tail	0.011975	
22	t Critical two-tail	2.5705776			t Critical two-tail	2.570578	

Commands in Analyses

Columns A, B, C & D	Enter values from Table 5.11.
Column E	Enter value of 1 for each entry in Column D (for analysis of ratios)
Main Menu Bar	Tools Data → Analysis → t-Test: Paired Two-Sample for Means
Dialog Box	
Variable 1 Range:	Highlight or enter B1:B7
Variable 2 Range:	Highlight or enter C1:C7
Hypothesized Diff:	Enter the null hypothesis difference between means, 0
Labels:	Click on this option
Alpha:	Enter desired alpha level for t-test, 0.05
Output Range	Click on cell or enter A9.
OK	Click to perform calculations

Note: To obtain an analysis of the Form A/Form B ratios, perform the same sequence of operations using the Ratio values (D1:D7) as Variable 1 and the Expected values (E1:E7) as Variable 2. Choose output Range as E9.

Section 5.2.6 discusses how to construct a 95% confidence interval on the difference between the proportions of headaches observed in two different groups of patients. The calculation uses a normal approximation and incorporates a continuity correction.

The following Excel workbook shows how to carry out the calculations.

Workbook 5.2.6 Continuity-Corrected 95% Confidence Interval

	A	B	C	D	E	F
1		**Group I**	**Group II**	**alpha**	**Z-value**	**correction**
2	**Headaches**	35	46	0.05	1.96	0.00491
3						
4	**N**	212	196	**difference**	**se**	**Z*se**
5	**P**	0.165	0.235	0.070	0.03958	0.077575
6	**Q**	0.835	0.765			
7				**Cl_low**	**Cl_high**	
8				−0.013	0.152	

Commands in Analysis

Data Entry:	Enter Section 5.2.6 values into cells B2, C2, B4, C4, D2	
Cell B5:	= B2/B4	p = #/n
Cell C5:	= C2/C4	
Cell B6:	= 1-B5	q = 1 − p
Cell C6:	= 1-C5	
Cell D5:	= C5-B5	difference between p values (group I-II)
Cell E2:	= NORMSINV(1-D2/2)	Critical Z- value for 95% confidence interval
Cell E5:	= SQRT(B5*B6/B4 + C5*C6/C4)	$se = (\Sigma(pq/n))^{1/2}$
Cell F2:	= 0.5*(1/B4 + 1/C4)	continuity correction = 0.5 $(1/n_I + 1/n_{II})$
Cell F5:	= E2*E5	
Cell D8:	= D5 – (F5 + F2)	CI low = diff – [se*Z + correction]
Cell E8:	= D5 + (F5 + F2)	CI high = diff + [se* Z + correction]

Excel has utilities for performing linear regression analyses and creating graphs of the results of such analyses. The power of these utilities can be seen in this next example which uses tablet assay results from a stability study (Table 7.5).

In this workbook, linear regression is used to model the stability of tablet potency over time. A 95% confidence interval about the stability line is constructed and the results are graphically illustrated using Excel's Chart Wizard.

Commands in Analyses

Columns A & B	Enter Month and Assay values from Table 7.5	
Main Menu Bar	Tools → Data Analysis → Regression	
Dialog Box		
Input Y Range:	Highlight or enter B1:B19	
Input X Range:	Highlight or enter A1:A19	
Labels:	Click on this option	
Output Range	Click on cell C1 or enter C1.	Results start in Column C.
OK	Click to perform calculations	
Cell D16	= AVERAGE(A2:A19)	Mean value for the X values
Cell D17	= 18*(VARP(A1:A19))	equal to $\Sigma(X_i - \text{mean})^2$

Open a second worksheet in this workbook. This sheet will be used to calculate the predicted values for the stability regression line and the 95% confidence interval band around the line. The measured potency values from Worksheet 1 and the predicted values and their confidence bounds from this new worksheet (Worksheet 2) will be used to create a stability trending graph.

Commands in Analyses

Column A	Enter 0 & 1 into Cells A2 & A3, highlight & drag through Cell A62 to obtain Month numbers 0 through 60.
Cells E2 and F2	Copy Slope and Intercept values from Worksheet 1
Cell E5	Enter 16, the residual df from ANOVA in Worksheet 1 equal to N-2
Cell F5	Enter or copy the SSQ_Diff value from Worksheet 1
Cell F8	Enter or copy the Month Mean value from Worksheet 1
Cell E8	= TINV(0.05,E5), t-value for two-sided, 95% confidence interval
Cell E11	= SQRT(1.825), square root of residual MS from ANOVA in Worksheet 1
Cell B2	= $F$2 + A2*$E$2, intercept + month * slope
Cells B3-B62	Copy formula from B2 into these cells to obtain predicted values
Cell C2	= $B2-$E$8*$E$11*SQRT(1/($E$5 + 2) + POWER(($A2-$F$8),2)/$F$5)
Cells C3-C62	Copy formula from C2 to obtain 95% Conf. Interval lower bound
Cell D2	= $B2 + $E$8*$E$11*SQRT(1/($E$5 + 2) + POWER(($A2-$F$8),2)/$F$5)
Cells D3-D62	Copy formula from D2 into these cells to obtain 95% Conf. Interval upper bound

Create graph

Highlight cells A1:B62, click Chart Wizard icon and choose XY scatter plot.
Click Next and choose the series tab.
Click on ADD.
Click in the Name box and enter *95% CI*.
For X-values, choose A1:A62.
For Y-values choose Cl:C62.
Repeat the process to add the graph of the 95% CI upper limits (D1:D62 values).
Next, repeat the process for the Month (X) and Assay (Y) values from Worksheet 1.
Click on Next and enter the title and axes labels for the graph.
Click on finish.

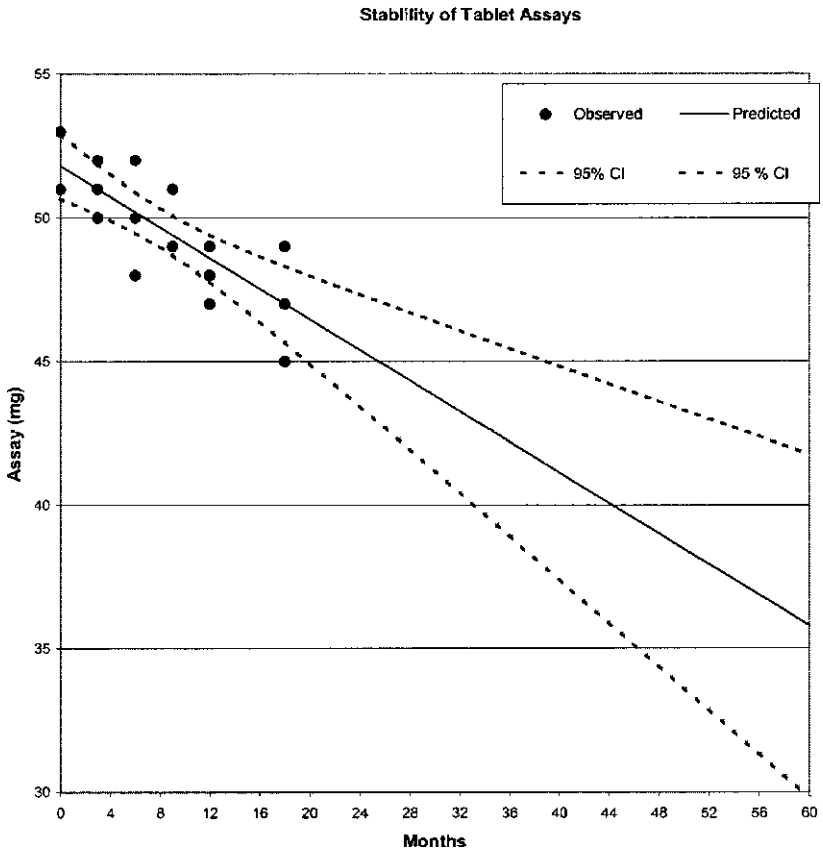
From the Main Toolbar Menu, choose Chart and then under that choose Location
Enter a Name so that the graph is placed as a chart separate from Worksheet 2.
The lines on the graph can now be edited by double clicking on each one.
Edit the predicted line to be solid with no symbols.
Edit the confidence interval curves to be smoothed, no-symbol, dashed.
The y and x axes can be edited (double click on each) to change the range of the Scale.

Workbook 7.5 Linear Regression of Tablet Stability Results (Worksheet 1)

	A	B	C	D	E	F	G	H	I	J
1	**Month**	**Assay**	**SUMMARY OUTPUT**							
2	0	51								
3	0	51	*Regression Statistics*				*Coeff*	*Stand Error*	*t Stat*	*P-value*
4	0	53	Multiple R	0.778		Intercept	51.8	0.535524	96.7277	1.42E-23
5	3	51	R Square	0.605		Month	−0.267	0.053822	−4.9546	0.000143
6	3	50	Adjusted R Sq	0.581						
7	3	52	Standard Err	1.351						
8	6	50	Observations	18						
9	6	52								
10	6	48	ANOVA							
11	9	49		*Df*	*SS*	*MS*	*F*	*Significance F*		
12	9	51	Regression	1	44.8	44.8	24.548	0.0001434		
13	9	51	Residual	16	29.2	1.825				
14	12	49	Total	17	74					
15	12	48								
16	12	47	**Month Mean**	8						
17	18	47	**SSQ_diff**	630						
18	18	45								
19	18	49								

Workbook 7.5 Linear Regression of Tablet Stability Results (Worksheet 2) (Listing of first 14 rows of the 62-row worksheet)

	A	B	C	D	E	F
1	**Month**	**Predicted**	**95% Cl Low**	**95% Cl Hi**	**slope**	**intercept**
2	0	51.8	50.7	52.9	−0.26667	51.8
3	1	51.5	50.5	52.6		
4	2	51.3	50.3	52.2	**Df**	**SSQDx**
5	3	51.0	50.1	51.9	16	630
6	4	50.7	49.9	51.5		
7	5	50.5	49.7	51.2	**t-val**	**Meanx**
8	6	50.2	49.5	50.9	2.12	8
9	7	49.9	49.2	50.6		
10	8	49.7	49.0	50.3	**S_yx**	
11	9	49.4	48.7	50.1	1.351	
12	10	49.1	48.4	49.8		
13	11	48.9	48.1	49.6		
14	12	48.6	47.8	49.4		



The following Workbook uses the spectrophotometric calibration curve results of Table 7.6. While it employs only the basic mathematical functions of Excel, it provides a powerful method for performing weighted linear regression analysis which can be used in situations where a straight-line model is appropriate. In this example, the weight is the inverse of concentration squared ($1/X^2$), but the method can be easily adapted to other appropriate weights (some function that is inversely proportional to the variance in y).

Commands in Analyses

Cells A2:B11	Enter the X and y values from Table 7.6	
Cell C2	= 1/(A2^2) Weight, w, is inverse of concentration squared	
Cells C3:C11	Copy the formula from Cell C2	
Cell D2	= C2*A2*B2	wXy
Cells D3:D11	Copy the formula from Cell D2	
Cell E2	= C2*A2	wX
Cells E3:E11	Copy the formula from Cell E2	
Cell F2	= C2*B2	wy
Cells F3:F11	Copy the formula from Cell F2	
Cell G2	= C2*A2^2	wX^2
Cells G3:G11	Copy the formula from Cell G2	
Cell A13	= SUM(A2:A11)	ΣX
Cells B13:G13	Copy formula from Cell A13	Σy, Σw, ΣwXy, ΣwX, Σwy & ΣwX^2
Cell B15	= (D13-E13*F13/C13)/(G13 = (E13^2)/C13)	slope
Cell B17	= (F13/C13)-B15*(E13/C13)	intercept

Workbook 7.6 Weighted ($1/X^2$) Linear Regression Analysis

	A	B	C	D	E	F	G
1	**Conc (X)**	**OD (y)**	**1/X^2**	**wXy**	**wX**	**wy**	**wX^2**
2	5	0.105	0.04	0.021	0.2	0.0042	1
3	5	0.098	0.04	0.0196	0.2	0.00392	1
4	10	0.201	0.01	0.0201	0.1	0.00201	1
5	10	0.194	0.01	0.0194	0.1	0.00194	1
6	25	0.495	0.0016	0.0198	0.04	0.000792	1
7	25	0.508	0.0016	0.02032	0.04	0.0008128	1
8	50	0.983	0.0004	0.01966	0.02	0.0003932	1
9	50	1.009	0.0004	0.02018	0.02	0.0004036	1
10	100	1.964	0.0001	0.01964	0.01	0.0001964	1
11	100	2.013	0.0001	0.02013	0.01	0.0002013	1
12	**Sum(X)**	**Sum(y)**	**Sum(w)**	**Sum(wXy)**	**Sum(wX)**	**Sum(wy)**	**Sum(Wx^2)**
13	380	7.57	0.1042	0.19983	0.74	0.0148693	10
14							
15	**Slope (b) =**	0.01986					
16							
17	**Intercept (a) =**	0.00166					

The next example shows how to use Excel to perform a series of calculations iteratively across different parameter values of a function to determine which values give the best fit to the observed values. In this example, using the method of least-squares, the best estimates for the parameters (slope and intercept) of the function (regression line) occur at the minimum sum of

squares for the difference between the predicted values of the regression line and the observed values. The regression line is defined by its slope (K) and its intercept (C0) and there are three observed time (hour)-concentration values (mg/L): (1,63), (2,34), and (3,22). These data are the stability results shown in Table 7.8. It is first necessary to determine a plausible range of values for C0 and K. For C0, this could be done graphically by plotting the data and then extrapolating the curve back to 0 time. A wide range of values should be selected around this estimate for the first iteration. In the first worksheet, a range of 50–400 was chosen. An initial range of estimates for K can be obtained in several ways: by using the estimate of C0 and then solving the equation C = C0*Exp(−K*t) for each time (t)-concentration (C) pair in the data set. Alternatively, the natural logarithm of each concentration can be plotted against time. The slope of the line through the plotted points is an estimate of − K. In this example, K was found to be close to 0.5 and a range of 0.1–0.7 was chosen for evaluation. The analysis requires the calculation of the sum of squares (SSQ) of the deviations (DEV = observed-predicted) for each of the three data points based on all combinations of the chosen C0 and K values. The C0 and K values that result in the minimum SSQ represent the least-squares estimates.

Workbook 7.8 Nonlinear Fit of Stability Data by the Method of Least-Squares (first iteration)

	A	B	C	D	E	F	G	H	I	J
1	**C0**	**K**	**63.0**	**34.0**	**22.0**	**Dev_1**	**Dev_2**	**Dev_3**	**SSQ**	
2	400	0.1	361.9	327.5	296.3	−298.9	−293.5	−274.3	250755.3	
3	200	0.1	181.0	163.7	148.2	−118.0	−129.7	−126.2	46667.7	
4	100	0.1	90.5	81.9	74.1	−27.5	−47.9	−52.1	5759.7	
5	50	0.1	45.2	40.9	37.0	17.8	−6.9	−15.0	589.7	
6	400	0.3	296.3	219.5	162.6	−233.3	−185.5	−140.6	108637.2	
7	200	0.3	148.2	109.8	81.3	−85.2	−75.8	−59.3	16510.9	
8	100	0.3	74.1	54.9	40.7	−11.1	−20.9	−18.7	906.9	
9	50	0.3	37.0	27.4	20.3	26.0	6.6	1.7	719.7	
10	400	0.5	242.6	147.2	89.3	−179.6	−113.2	−67.3	49586.7	
11	200	0.5	121.3	73.6	44.6	−58.3	−39.6	−22.6	5477.8	
12	100	0.5	60.7	36.8	22.3	2.3	−2.8	−0.3	13.4	**
13	50	0.5	30.3	18.4	11.2	32.7	15.6	10.8	1428.7	
14	400	0.7	198.6	98.6	49.0	−135.6	−64.6	−27.0	23302.8	
15	200	0.7	99.3	49.3	24.5	−36.3	−15.3	−2.5	1559.8	
16	100	0.7	49.7	24.7	12.2	13.3	9.3	9.8	360.4	
17	50	0.7	24.8	12.3	6.1	38.2	21.7	15.9	2178.7	
18								**MIN**	13.4	

Additional iterations are performed to refine the estimates to the desired level of precision. In this example, precision to one decimal place for C0 and to three decimal places for K was considered appropriate.

Commands in Analyses (Commands are repeated for each iteration)

Columns A and B	Enter all possible combinations of the selected C0 and K values.	
Cell C2	= A2*EXP(-B2*1)	Predicted Concentration at 1 hour
Cell D2	= A2*EXP(-B2*2)	Predicted Concentration at 2 hour
Cell E2	= A2*EXP(-B2*3)	Predicted Concentration at 3 hour
Cell F2	= 63-C2	1 hour deviation (observed-predicted)
Cell G2	= 34-D2	2 hour deviation
Cell H2	= 22-E2	3 hour deviation
Cell I2	= SUMSQ(F2,G2,H2)	Sum of squared deviations (SSQ)

Workbook 7.8 Nonlinear Fit of Stability Data by the Method of Least-Squares (section of the worksheet to refine the estimates)

A	B	C	D	E	F	G	H	I	
C0	**K**	**63.0**	**34.0**	**22.0**	**Dev_1**	**Dev_2**	**Dev_3**	**SSQ**	
130	0.4	87.1	58.4	39.2	−24.1	−24.4	−17.2	1473.1	
115	0.4	77.1	51.7	34.6	−14.1	−17.7	−12.6	670.5	
100	0.4	67.0	44.9	30.1	−4.0	−10.9	−8.1	201.7	
85	0.4	57.0	38.2	25.6	6.0	−4.2	−3.6	66.8	
130	0.5	78.8	47.8	29.0	−15.8	−13.8	−7.0	491.4	
115	0.5	69.8	42.3	25.7	−6.8	−8.3	−3.7	128.0	
100	0.5	60.7	36.8	22.3	2.3	−2.8	−0.3	13.4	
85	0.5	51.6	31.3	19.0	11.4	2.7	3.0	147.6	
130	0.6	71.3	39.2	21.5	−8.3	−5.2	0.5	96.5	
115	0.6	63.1	34.6	19.0	−0.1	−0.6	3.0	9.4	**
100	0.6	54.9	30.1	16.5	8.1	3.9	5.5	110.9	
85	0.6	46.6	25.6	14.1	16.4	8.4	7.9	401.1	
130	0.7	64.6	32.1	15.9	−1.6	1.9	6.1	43.2	
115	0.7	57.1	28.4	14.1	5.9	5.6	7.9	129.2	
100	0.7	49.7	24.7	12.2	13.3	9.3	9.8	360.4	
85	0.7	42.2	21.0	10.4	20.8	13.0	11.6	736.6	
							MIN	9.4	

Workbook 7.8 Nonlinear Fit of Stability Data by the Method of Least-Squares (further refining of the estimates) (C0 range examined was 100–130, K range 0.50–0.70; only section with minimum is shown)

A	B	C	D	E	F	G	H	I	
C0	**K**	**63.0**	**34.0**	**22.0**	**Dev_1**	**Dev_2**	**Dev_3**	**SSQ**	
104	0.53	61.2	36.0	21.2	1.8	−2.0	0.8	7.9	
105	0.53	61.8	36.4	21.4	1.2	−2.4	0.6	7.4	
106	0.53	62.4	36.7	21.6	0.6	−2.7	0.4	7.9	
105	0.54	61.2	35.7	20.8	1.8	−1.7	1.2	7.5	
106	0.54	61.8	36.0	21.0	1.2	−2.0	1.0	6.5	
107	0.54	62.4	36.3	21.2	0.6	−2.3	0.8	6.6	
107	0.55	61.7	35.6	20.5	1.3	−1.6	1.5	6.3	
108	0.55	62.3	36.0	20.7	0.7	−2.0	1.3	5.9	
109	0.55	62.9	36.3	20.9	0.1	−2.3	1.1	6.4	
108	0.56	61.7	35.2	20.1	1.3	−1.2	1.9	6.8	
109	0.56	62.3	35.6	20.3	0.7	−1.6	1.7	5.8	**
110	0.56	62.8	35.9	20.5	0.2	−1.9	1.5	5.8	
111	0.56	63.4	36.2	20.7	−0.4	−2.2	1.3	6.8	
110	0.57	62.2	35.2	19.9	0.8	−1.2	2.1	6.5	
111	0.57	62.8	35.5	20.1	0.2	−1.5	1.9	6.0	
112	0.57	63.3	35.8	20.3	−0.3	−1.8	1.7	6.5	

Workbook 7.8 Nonlinear Fit of Stability Data by the Method of Least-Squares (C0 range evaluated was 108.0–110.0 by 0.2; K was 0.550–0.570 by 0.002)

A	B	C	D	E	F	G	H	I	
C0	**K**	**63.0**	**34.0**	**22.0**	**Dev_1**	**Dev_2**	**Dev_3**	**SSQ**	
108.0	0.552	62.2	35.8	20.6	0.8	−1.8	1.4	5.838	
108.2	0.552	62.3	35.9	20.7	0.7	−1.9	1.3	5.804	
108.4	0.552	62.4	35.9	20.7	0.6	−1.9	1.3	5.807	
108.6	0.552	62.5	36.0	20.7	0.5	−2.0	1.3	5.850	
108.4	0.554	62.3	35.8	20.6	0.7	−1.8	1.4	5.772	
108.6	0.554	62.4	35.9	20.6	0.6	−1.9	1.4	5.756	
108.8	0.554	62.5	35.9	20.6	0.5	−1.9	1.4	5.779	
108.6	0.556	62.3	35.7	20.5	0.7	−1.7	1.5	5.766	
108.8	0.556	62.4	35.8	20.5	0.6	−1.8	1.5	5.732	
109.0	0.556	62.5	35.9	20.6	0.5	−1.9	1.4	5.735	
109.2	0.556	62.6	35.9	20.6	0.4	−1.9	1.4	5.777	
109.0	0.558	62.4	35.7	20.4	0.6	−1.7	1.6	5.733	
109.2	0.558	62.5	35.8	20.5	0.5	−1.8	1.5	5.718	**
109.4	0.558	62.6	35.8	20.5	0.4	−1.8	1.5	5.741	
109.2	0.560	62.4	35.6	20.4	0.6	−1.6	1.6	5.761	
109.4	0.560	62.5	35.7	20.4	0.5	−1.7	1.6	5.727	
109.6	0.560	62.6	35.8	20.4	0.4	−1.8	1.6	5.731	

A	B	C	D	E	F	G	H	I	
C0	**K**	**63.0**	**34.0**	**22.0**	**Dev_1**	**Dev_2**	**Dev_3**	**SSQ**	
109.1	0.557	62.5	35.8	20.5	0.5	−1.8	1.5	5.723	
109.2	0.557	62.6	35.8	20.5	0.4	−1.8	1.5	5.735	
109.3	0.557	62.6	35.9	20.6	0.4	−1.9	1.4	5.755	
109.1	0.558	62.4	35.7	20.5	0.6	−1.7	1.5	5.721	
109.2	0.558	62.5	35.8	20.5	0.5	−1.8	1.5	5.718	**
109.3	0.559	62.5	35.7	20.4	0.5	−1.7	1.6	5.719	
109.1	0.559	62.4	35.7	20.4	0.6	−1.7	1.6	5.744	
109.2	0.559	62.4	35.7	20.4	0.6	−1.7	1.6	5.727	
109.3	0.559	62.5	35.7	20.4	0.5	−1.7	1.6	5.719	

Columns C through I	Copy Row 2 formulas through rows 3–17	
Cell I18	= MIN(I2:I17)	Minimum of SSQ values
Cell J2	= IF(I2 = I$18,"**","")	Flags row if it contains minimum SSQ
Cell J3-J17	Copy formula from Cell J2	Flags row with best C0 and K estimates

Based on these results, it appears that the best estimate of C0 is near 100 and for K near 0.5. The next iterations further refine the estimates.
Final Iteration: C0 range evaluated was 109.0–109.4 by 0.1; K was 0.556–0.560 by 0.001
The least-squares estimates, at the desired levels of precision, are C0 = 109.2 and K = 0.558.

This next example uses Excel's built-in two-factor ANOVA, without replication, to evaluate the tablet dissolution data given in Table 8.9.

Commands in Analyses

Columns A, B, C, D	Enter dissolution values from Table 8.9.
Main Menu	Tools → Data Analysis → Anova: Two-Factor without Replication
Dialog Box	
Input Range:	Highlight or enter A1:D9
Labels:	Click on this option
Alpha:	Enter 0.05
Output Range	Click on or enter A11
OK	Click to perform calculations

Cell F3	= ABS(D23-D25)/SQRT(2*D32/8)	Calculate pair-wise t-test
Cell F4	= ABS(D24-D25)/SQRT(2*D32/8)	
Cell G3	= TDIST(F3,C32,2)	Determine pair-wise p-value
Cell G4	= TDIST(F4,C32,2)	

This next example uses Excel's built-in two-factor ANOVA, with replication, to evaluate the replicate tablet dissolution data given in Table 8.12.

Commands in Analyses

Columns A,B,C,D	Enter dissolution values from Table 8.12.
Main Menu	Tools → Data Analysis → Anova: Two-Factor with Replication
Dialog Box	
Input Range:	Highlight or enter A1:D17
Rows per sample:	Enter 2
Alpha:	Enter 0.05
New Worksheet Ply:	Click on this option
OK	Click to perform calculations

Workbook 8.9 Two-Way Analysis of Variance of Tablet Dissolution Results

	A	B	C	D	E	F	G
1	**LAB**	**Generic A**	**Generic B**	**Standard**			
2	1	89	83	94		**t-value**	**p-value**
3	2	93	75	78	**A vs Std**	0.09	0.927
4	3	87	75	89	**B vs Std**	2.23	0.043
5	4	80	76	85			
6	5	80	77	84			
7	6	87	73	84			
8	7	82	80	75			
9	8	68	77	75			
10							
11	Anova: Two-Factor Without Replication						
12							
13	*SUMMARY*	*Count*	*Sum*	*Average*	*Variance*		
14	1	3	266	88.6666667	30.33333		
15	2	3	246	82	93		
16	3	3	251	83.6666667	57.33333		
17	4	3	241	80.3333333	20.33333		
18	5	3	241	80.3333333	12.33333		
19	6	3	244	81.3333333	54.33333		
20	7	3	237	79	13		
21	8	3	220	73.3333333	22.33333		
22							
23	A		8	666	83.25	58.78571	
24	B		8	616	77	10	
25	STANDARD	8	664	83	45.14286		
26							
27							
28	ANOVA						
29	*Source of Variation*	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
30	Rows	391.8333	7	55.9761905	1.931799	0.139436	2.764196
31	Columns	200.3333	2	100.166667	3.456861	0.060239	3.73889
32	Error	405.6667	14	28.9761905			
33							
34	Total	997.8333	23				

Workbook 8.12 Two-Way ANOVA of Replicated Dissolution Results (worksheet 1)

	A	B	C	D
1	**Lab**	**Generic A**	**Generic B**	**Standard**
2	1	87	81	93
3		91	85	95
4	2	90	74	74
5		96	76	82
6	3	84	72	84
7		90	78	94
8	4	75	73	81
9		85	79	89
10	5	77	76	80
11		83	78	88
12	6	85	70	80
13		89	76	88
14	7	79	74	71
15		85	86	79
16	8	65	73	70
17		71	81	80

Workbook 8.12 Two-Way ANOVA of Replicated Dissolution Results (continued)

	A	B	C	D	E	F	G
58							
59	ANOVA						
60	*Source of Variation*	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
61	Sample	783.6667	7	111.9524	4.569485	0.00231	2.422631
62	Columns	400.6667	2	200.3333	8.176871	0.001959	3.402832
63	Interaction	811.3333	14	57.95238	2.365403	0.030779	2.129795
64	Within	588	24	24.5			
65							
66	Total	2583.667	47				
67							
68	Drugs	400.6667	2	200.3333	3.456861	0.060239	3.73889

(New Worksheet Ply)

	A	B	C	D	E
1	Anova: Two-Factor With Replication				
2					
3	SUMMARY	Generic A	Generic B	Standard	Total
4	*1*				
5	Count	2	2	2	6
6	Sum	178	166	188	532
7	Average	89	83	94	88.66667
8	Variance	8	8	2	27.86667
9–45	***(Rows not shown)***	***xxxxxxxx***	***xxxxxxxx***	***xxxxxxxx***	***xxxxxxxx)***
46	*8*				
47	Count	2	2	2	6
48	Sum	136	154	150	440
49	Average	68	77	75	73.33333
50	Variance	18	32	50	37.86667
51					
52	*Total*				
53	Count	16	16	16	
54	Sum	1332	1232	1328	
55	Average	83.25	77	83	
56	Variance	65.26667	20.66667	59.6	

Commands in Analyses

Cell A68	Enter "Drugs"	Drugs effect is that for columns in the ANOVA table
Cell B68	= B62	Drugs SS
Cell C68	= C62	Drugs degrees of freedom
Cell D68	= D62	Drugs MS
Cell E68	= D62/D63	F-ratio = Drugs MS/Interaction MS
Cell F68	= FINV(E68,2,14)	p-value for Drugs F-ratio with 2 & 14 degrees of freedom
Cell G68	= FDIST(0.95,2,14)	Critical F-distribution value with 2 & 14 degrees of freedom

Notes on Interpretation

The analysis for Drugs in row 68 is based on the assumption that Drugs is a fixed effect and Laboratories (Rows) is a random effect. The analysis in row 62 for the Column (Drugs) effect assumes that both Drugs and Laboratories are fixed effects. If the laboratories are a random sample of all the available laboratories and the results are to be generalized to all laboratories, then use the row 68 results. If the eight laboratories are the only ones of interest, then the results in row 62 should be used.

The next workbook shows how to perform an Analysis of Covariance using the data from Table 8.18. In this example, two different manufacturing methods (I and II) were used to produce four lots of products whose potency and raw material potency are shown.

Workbook 8.18 Analysis of Covariance to Compare Two Methods (worksheet 1)

	A	B	C	D	E	F
1	**Method**	**MI**	**MII**	**Meth2**	**Material**	**Product**
2	I	98.4	0	0	98.4	98.0
3	I	98.6	0	0	98.6	97.8
4	I	98.6	0	0	98.6	98.5
5	I	99.2	0	0	99.2	97.4
6	II	0	98.7	1	98.7	97.6
7	II	0	99	1	99.0	95.4
8	II	0	99.3	1	99.3	96.1
9	II	0	98.4	1	98.4	96.1
10						
11				**Mean**	98.775	
12	**F-parallel**	**p-value**		**Adj Mean**	**I**	97.8639
13	0.010	0.925			**II**	96.3611
14					**Diff (II-I)**	1.50278
15					**p-value**	0.036637
16	**Slope**	**Intercpt I**	**Intercept II**			
17	−0.81481	178.3472	176.8444			

Commands in Analyses

Columns A, E and F	Enter Method, Material and Product values from Table 8.18.
Column B	Copy Method I values into rows 2–5, enter 0 elsewhere.
Column C	Copy Method II values into rows 6–9, enter 0 elsewhere.
Column D	Enter 0 for Method I row and 1 for Method II row.
Cell E11	= AVERAGE(E2:E9) Mean for Material values.
Main Menu	Tools → Data Analysis → Regression (ANOVA for separate lines)
Dialog Box	
Input Y Range:	Highlight or enter F1:F9
Input X Range:	Highlight or enter B1:D9
Labels:	Click on this option
New Worksheet Ply:	Click on this box
OK	Click to perform calculations
Main Menu	Tools → Data Analysis → Regression (ANOVA for parallel lines)
Dialog Box	
Input Y Range:	Highlight or enter F1:F9
Input X Range:	Highlight or enter D1:E9
Labels:	Click on this option
New Worksheet Ply:	Click on this box
OK	Click to perform calculations
Cell A17	Copy slope (Material coefficient) from parallel lines Worksheet
Cell B17	Copy Intercept coefficient from same Worksheet
Cell C17	= B17 + coefficient for Meth2 from parallel lines Worksheet
Cell F12	= B17 + E11*A17
Cell F13	= C17 + E11*A17
Cell F14	= F12-F13 Difference between adjusted Method means
Cell F15	p-value for difference from Meth2 in parallel lines Worksheet
Cell A13	= (SS resid. parallel lines – SS resid. separate lines)/(SS resid separate/4)
Cell B13	= FDIST(A13,1,4)

Workbook 8.18 Analysis of Covariance to Compare Two Methods (section of worksheet ply for separate lines)

	A	B	C	D	E
10	ANOVA				
11		*df*	*SS*	*MS*	*F*
12	Regression	3	5.82575	1.941916667	2.916885718
13	Residual	4	**2.663**	0.66575	
14	Total	7	8.48875		
15					
16		*Coefficients*	*Standard Error*	*t Stat*	*P-value*
17	Intercept	188.4	134.2219351	1.403645386	0.233093906
18	MI	−0.916666667	1.359891744	−0.674073264	0.537213
19	MII	−0.733333333	1.216324153	−0.602909456	0.579083754
20	Meth2	−19.61	180.1993982	−0.108823893	0.918582825

Notes on Analyses (separate lines)

Cell C13 contains the residual SS for separate lines (2.663) to be used in the test for parallelism (Cell A13 in Worksheet 1). The Intercept (188.4 in B17) is the intercept for the Method I line. The slope for the Method I line is the coefficient for MI (– 0.917 in B18). The intercept for Method II is the addition of the coefficient for Meth2 (B20) to the Method I intercept (B17), which is 188.4–19.6 = 168.8. The slope for the Method II line is the coefficient for MII (-0.733 in B19).

(section of worksheet ply for parallel lines)

	A	B	C	D	E
10	ANOVA				
11		*df*	*SS*	*MS*	*F*
12	Regression	2	5.819028	2.909514	5.449095
13	Residual	5	**2.669722**	0.533944	
14	Total	7	8.48875		
15					
16		*Coefficients*	*Standard Error*	*t Stat*	*P-value*
17	Intercept	178.3472	80.13591	2.225559	0.076591
18	Meth2	**−1.50278**	0.530852	−2.83088	**0.036637**
19	Material	−0.81481	0.811906	−1.00358	0.361646

Notes on Analyses (parallel lines)

Cell C13 contains the residual SS for parallel lines (2.67) to be used in the test for parallelism (Cell A13 in Worksheet 1). The coefficient for the Intercept (178.3 in B17) is the intercept for the Method I line. The coefficient for the intercept of Meth2 is the difference between the intercepts for Methods I and II (value −1.50 in B18) which, because the two lines are parallel, is also the difference between the two methods. We estimate that Method II is 1.50 units lower than Method I with the p-value for this difference (0.0366 in E18) being statistically significant at the 0.05 level. The common slope for the parallel lines for the two methods is given by the coefficient for Material (−0.815 in B19).

The next example is taken from Table 9.2. Here we analyze the results from a 2^3 factorial experiment to determine the effect of three components upon the thickness of a tablet.

Workbook 9.2 Evaluation of Results from a 2^3 Factorial Experiment (worksheet 1)

	A	B	C	D	E	F	G	H
1	**Stearate (A)**	**Drug (B)**	**Starch (C)**	**AB**	**AC**	**BC**	**ABC**	**Response**
2	0	0	0	0	0	0	0	475
3	1	0	0	0	0	0	0	487
4	0	1	0	0	0	0	0	421
5	1	1	0	2	0	0	0	426
6	0	0	1	0	0	0	0	525
7	1	0	1	0	2	0	0	546
8	0	1	1	0	0	2	0	472
9	1	1	1	2	2	2	4	522

Commands in Analyses

Column H	Enter response values from Table 9.2.	
Columns A, B, C	Enter a 0 where Table 9.2 has a " − " and a 1 where there is a "+"	
Cell D2	= 2*A2*B2	Design entry for Stearate-Drug interaction
Cells D3-D9	Copy formula from D2	
Cell E2	= 2*A2*C2	Design entry for Stearate-Starch interaction
Cells E3-E9	Copy formula from E2	
Cell F2	= 2*B2*C2	Design entry for Drug-Starch interaction
Cells F3-F9	Copy formula from F2	
Cell G2	= 4*A2*B2*C2	Design entry for 3-way interaction
Cells G3-G9	Copy formula from G2	
Main Menu	Tools → Data Analysis → Regression (Estimate Main Effects)	
Dialog Box		
Input Y Range:	Highlight or enter H1:H9	

Workbook 9.2 Evaluation of Results from a 2^3 Factorial Experiment (main effects worksheet)

	A	B	C	D	E	F
10	ANOVA					
11		*Df*	*SS*	*MS*	*F*	*Significance F*
12	Regression	3	13768	4589.333	23.91835	0.005135
13	Residual	4	767.5	191.875		
14	Total	7	14535.5			
15						
16		*Coefficients*	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*
17	Intercept	465.25	9.794769	47.49984	1.18E-06	438.0553
18	Stearate (A)	**22**	9.794769	2.246097	0.088025	−5.19469
19	Drug (B)	**−48**	9.794769	−4.90057	0.008041	−75.1947
20	Starch (C)	**64**	9.794769	6.5341	0.002834	36.80531
21		**MS**				
22	**A**	**968**				
23	**B**	**4608**				
24	**C**	**8192**				

Input X Range: Highlight or enter A1:C9
Labels: Click on this option
New Worksheet
Ply: Click on this box
OK Click to perform calculations
Rename New Worksheet "Main Effects"
Main Menu Tools → Data Analysis → Regression (Estimate 2-Factor Interactions)
Dialog Box
Input Y Range: Highlight or enter H1:H9
Input X Range: Highlight or enter A1:F9
Labels: Click on this option
New Worksheet
Ply: Click on this box
OK Click to perform calculations
Rename New Worksheet "Interaction"
Repeat Regression Analysis with Input "X" Range as A1:G9 to obtain estimate for A*B*C interaction

Commands in Analyses (Main Effects Worksheet)
Cell B22 = D18*D18*D13
Cell B23 = D19*D19*D13
Cell B24 = D20*D20*D13

(2-factor interactions worksheet)

	A	B	C	D	E	F
10	ANOVA					
11		*df*	*SS*	*MS*	*F*	*Significance F*
12	Regression	6	605.5	100.9167	0.622942	0.7478876
13	Residual	1	162	**162**		
14	Total	7	767.5			
15						
16		*Coefficients*	*Standard Error*	*t Stat*	*P-value*	*Lower 95%*
17	Intercept	14.25	11.90588	1.196887	0.443097	−137.02791
18	Stearate (A)	−19	15.58846	−1.21885	0.437411	−217.06928
19	Drug (B)	−15	15.58846	−0.96225	0.512246	−213.06928
20	Starch (C)	−23	15.58846	−1.47545	0.379198	−221.06928
21	AB	**5.5**	9	0.611111	0.650783	−108.85535
22	AC	**13.5**	9	1.5	0.374334	−100.85535
23	BC	**9.5**	9	1.055556	0.482798	−104.85535
24		**MS**				
25	**AB**	**60.5**				
26	**AC**	**364.5**				
27	**BC**	**180.5**				

Commands in Analyses (2 factor interactions worksheet)

Cell B25	= D21*D21*D13
Cell B26	= D22*D22*D13
Cell B27	= D23*D23*D13

(worksheet 1 continued)

	A	B	C	D	E	F	G
11	**Effect**	**Estimate**	**Df**	**SS**	**MS**	**F**	**p-value**
12	**A**	22	1	968	968	7.2	0.0748
13	**B**	−48	1	4608	4608	34.3	0.0099
14	**C**	64	1	8192	8192	61.0	0.0044
15	**AB**	5.5	1	60.5	60.5		
16	**AC**	13.5	1	364.5	364.5	2.7	0.1981
17	**BC**	9.5	1	180.5	180.5		
18	**ABC**	9	1	162	162		
19	**Error**		3	403	134.3333		

Commands in Analyses (ANOVA similar to Table 9.5)

Column A	Enter Effect Names	
Column B	Values are coefficients from Main Effects & Interactions Worksheets Coefficient for ABC is from regression including all effects (Wrksht not shown).	
Column C	Enter 1 for all effects except Error. Enter 3 for Error.	
Cells E12-E17	Enter values from Main Effects & 2-Factor Interaction Worksheets	
Cell E18	Enter value for Residual MS from Cell D13 of 2-Factor Interaction Worksheet	
Cell D12-D18	Enter same values that are in Cells E12-E18	
Cell D19	= SUM(D15,D17,D18) Error term is chosen to be sum of AB, BC & ABC terms	
Cell E19	= D19/C19	MS = SS/df
Cell F12	= E12/E$19	F = Effect MS/Error MS
Cells F13, F14, F16	Copy formula from F12	
Cell G12	= FDIST(F12, 1,3)	p-value for Effect from F-distribution
Cell G13,G14,G16	Copy formula from G12	

Section 11.5 presents how to perform repeated measures Analysis of Variance. The methods used in the analysis are illustrated using the results of a comparison of two antihypertensive drugs. One group of patients received the standard drug and a second group the new drug. Diastolic blood pressure was recorded for each patient prior to treatment (baseline) and then at 2, 4, 6, and 8 weeks after treatment. The results, presented in Table 11.22, are analyzed in the following workbook.

Commands in Analyses

Cells A3-F10	Enter patient numbers and diastolic blood pressures from Table 11.22	
Cells A15-A22	Copy patient numbers from Cells A3:A10	
Cell B15	= C3-$B3	Calculates change from baseline
Cells B16-B22	Copy formula from Cell B15	
Cells C15-E22	Copy formula from B15 through B22	
Cell B25	= Sum(B15:B22)	Sum of changes at Week 2
Cells C25-E25	Copy formula from Cell B25	
Cell F25	= Sum(B25:E25)	Sum of changes for all weeks

Worksheet 11.22 Comparison of Two Antihypertensive Drugs (worksheet 1)

	A	B	C	D	E	F
1		**Standard Drug**				
2	**Patient**	**Baseline**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**
3	1	102	106	97	86	93
4	2	105	103	102	99	101
5	5	99	95	96	88	88
6	9	105	102	102	98	98
7	13	108	108	101	91	102
8	15	104	101	97	99	97
9	17	106	103	100	97	101
10	18	100	97	96	99	93
14	**Patient**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	
15	1	4	−5	−16	−9	
16	2	−2	−3	−6	−4	
17	5	−4	−3	−11	−11	
18	9	−3	−3	−7	−7	
19	13	0	−7	−17	−6	
20	15	−3	−7	−5	−7	
21	17	−3	−6	−9	−5	
22	18	−3	−4	−1	−7	
23						
24						Standard
25	Sum	−14	−38	−72	−56	−180
26						

Section for New Drug (not shown):

Cells H2:M2	Enter or Copy the headings in cells A2-F2	
Cell K1	Enter heading "New" for New Drug	
Cells H3-M11	Enter New Drug patient numbers and diastolic readings	
Cell 115	= J3-$13	Calculate changes from baseline
Cells 116–123	Copy formula from Cell 115	
Cells J15-L23	Copy formulas from 115 through 123	
Cell 125	= Sum(I15:123)	New drug sum of changes Week 2
Cells J25-L25	Copy formula from Cell 115	
Cell M25	= Sum(I25:L25)	New drug sum of changes all weeks

(section of analyses shown in Tables 11.24 and 11.25)

	A	B	C	D	E	F	G
27	ANOVA	**Standard**			ANOVA	**New**	
28	*Source*	*SS*	*df*		*Source*	*SS*	*df*
29	Rows	57.5	7		Rows	114.2222	8
30	Columns	232.5	3		Columns	486.9722	3
31	Error	255.5	21		Error	407.7778	24
32							
33	Total	545.5	31		Total	1008.972	35
34							
35	**CT**	**Source**	**df**	**SS**	**MS**	**F**	**p-value**
36	3750.368	Patients	15	171.72	11.45		
37		Weeks	3	669.69	223.23		
38		Drugs	1	196.16	196.16	17.13	0.0009
39		WK × Drug	3	49.78	16.59	1.13	0.3487
40		Error	45	663.28	14.74		
41		Total	67	1750.63			

Commands in Analyses

Main Menu — Tools → Data Analysis → Anova: Two-Factor Without Replication
Dialog Box
  Input Range: — Highlight or enter B15:E22
  Alpha Level — Enter or accept default value of 0.05
  New Worksheet Ply: — Click on this box
  OK — Click to perform calculations
  (**Copy ANOVA values from new worksheet to main Worksheet 1**)
Cells B27-G33 — Copy from cells A19-C25 of new worksheet to get Source, SS & df
Main Menu — Tools → Data Analysis → Anova: Two-Factor Without Replication
Dialog Box
  Input Range: — Highlight or enter I15:L23 (New Drug data not shown)
  Alpha Level — Enter or accept default value of 0.05
  New Worksheet Ply: — Click on this box
  OK — Click to perform calculations
  (**Copy ANOVA values from new worksheet to main worksheet 1**)
Cells E27-G33 — Copy from Cells A19-C25 of new worksheet to get Source, SS & df
Cells A35-G35 — Enter Headings CT, Source, df, SS, MS, F and p-value
Cells B36-B41 — Enter Source names
Cell A36 — = POWER(F25 + M25,2)/68 Correction Term
Cell C36 — 15 (Combined row df for Standard and New Drugs)
Cell C37 — 3 (number of weeks – 1)
Cell C38 — 1 (number of drugs – 1)
Cell C39 — = 3*1 (Product of Week df and Drugs df)
Cell C41 — = 4*17–1 (#Weeks *#Patients – 1)
Cell C40 — = 67 – 15 – 3 – 1 – 3 (error df = Total-Patients-Drugs-WeeksxDrugs)
Cell D36 — = B29 + F29 (Combined Row SS for Standard and New Drugs)
Cell D37 — = (SUMSQ((B25 + I25),(C25 + J25),(D25 + K25),(E25 + L25))/17)-A36
Cell D38 — = F25*F25/32 + M25*M25/36 – A36
Cell D39 — = B30 + F30-D37
Cell D40 — = B31 + F31 (Combined Error SS for Standard and New Drugs)
Cell D41 — = SUM(D36:D40) (Total SS = Sum of all other SS)

Cell E36	= D36/C36 (MS = SS/df)
Cell E37-E40	Copy formula from Cell E36
Cell F38	= E38/E36 (F = MSeffect/MSerror Drugs uses MS Patients as error term)
Cell F39	= E39/E40 (F value for Weeks x Drugs using ANOVA error term)
Cell G38	= FDIST(F38,1,15) (p-value for F with 1 df & 15 df)
Cell G39	= FDIST(F39,3,45)

Table 12.2 shows the average weights of 50 tablets from 30 batches of a tablet product.

In the next example, Excel is used to calculate the three-batch moving average for the weights. These results are then used to construct a control plot of the moving averages along with their upper and lower control limits.

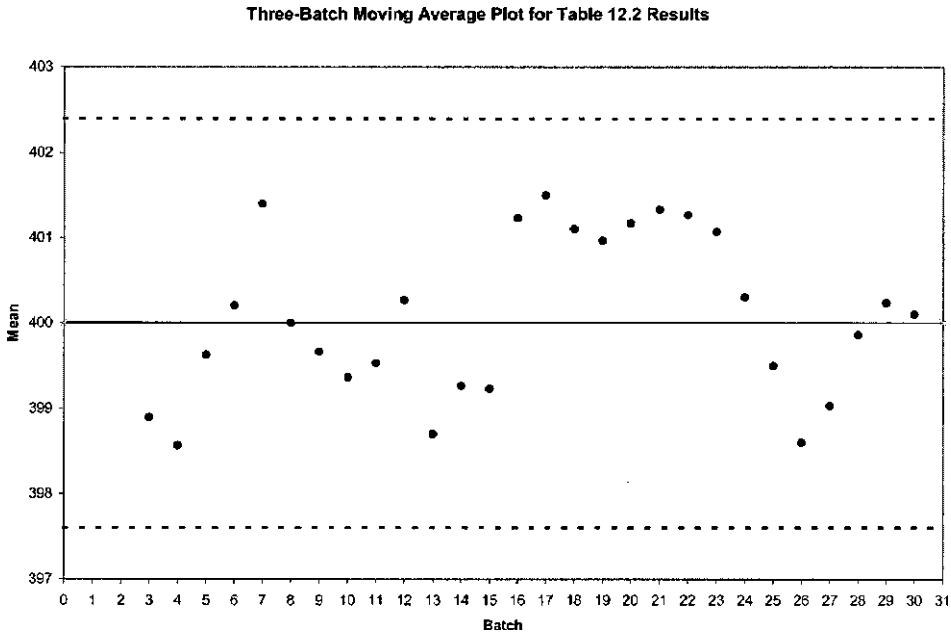
Workbook 12.2 Average Weight of 50 Tablets from 30 Batches of a Product

	A	B	C	D	E	F	G
1	**Batch**	**Average**	**Move Ave**	**Range**	**Mean**	**Low**	**High**
2	0				400.0	397.603	402.397
3	1	398.4	N/A				
4	2	399.5	N/A				
5	3	398.8	398.9	1.1			
6	4	397.4	398.6	2.1			
7	5	402.7	399.6	5.3			
Rows 8–26 not shown							
27	25	398.4	399.5	3.1			
28	26	398.8	398.6	0.4			
29	27	399.9	399.0	1.5			
30	28	400.9	399.9	2.1			
31	29	399.9	400.2	1.0			
32	30	399.5	400.1	1.4			
33	31				400.0	397.603	402.397
34	Mean	400.0		2.35			

Commands in Analyses

Data Entry:	Enter Batch numbers and averages from Table 12.2 into columns A and B, adding a Batch 0 and 31 for graphing purposes.	
Cell C5	= Average(B3:B5)	Average of first 3 batches
Cell C6-C32	Copy formula from Cell C5	
Cell D5	= MAX(B3:B5)-MIN(B3: B5)	Range (Max-Min) of first 3 batches
Cell D6-D32	Copy formula from Cell D5	
Cell B34	= Average(B3:B32)	Average of the 30 batches
Cell D34	Copy formula from Cell B34	Average of moving ranges
Cell E33	= B34	
Cell F33	= $E$33 – 1.02*$D$34	Lower Limit using factor (1.02) from Table IV.10
Cell G33	= $E$33 + 1.02*$D$34	Upper Limit using factor (1.02) from Table IV.10
Cell E2	= E33	
Cell F2	= F33	
Cell G2	= G33	

Click on Chart Wizard and choose to create a XY scatter plot.
Click Next and then click on Series Tab, then on Add.
Click on worksheet icon for X-values.
Choose cells A2 through A33, click icon to accept this range.
For Y-values, click worksheet icon, choose cells C2 through C33.
Click Add for Series 2. X-values are A2 through A33. Y-values F2 through F33.
Click Add for Series 3. X-values are A2 through A33. Y-values are G2 through G33.
Click Add for Series 3. X-values are A2 through A33. Y-values are E2 through E33.
Click Next and add chart title, X and Y axes labels.
Click Legend tab and remove check mark on Show Legend (by clicking it).
Click tab for Gridlines and make sure all choices are blank.
Click Next and choose the name Plot for the New Worksheet for the chart.
Click on Plot Area and choose None for fill effects.
On Main Menu click Tools, Options & Chart.
Choose to plot empty cells as Interpolated.
Click on Lower & Upper limit points and set symbol to None and line to a dashed, black, custom line.
Click on Mean point and set symbol to None and line to a solid, black, custom line.
Click on an X-axis number and then on the Scale tab.
Set Minimum = 0, Maximum = 31, Major Unit = 1.



In the next example, the assay results for a sample of theee tablets from four different batches of a product, as shown in Table 12.9, are used to demonstrate how to calculate the variance components. The experiment was a nested design in which the total variance can be divided into its components of between batches, between tablets within batch, and between assays within tablets.

Workbook 12.9 Determination of Variance Components in a Nested Design

	A	B	C	D	E	F	G
1	Batch	Tablet	Assay1	Assay 2	Assay 3	SSQ	df
2	A	1	50.6	50.5	50.8	0.046667	2
3		2	49.1	48.9	48.5	0.186667	2
4		3	51.1	51.1	51.4	0.06	2
5	B	1	50.1	49.0	49.4	0.62	2
6		2	51.0	50.9	51.6	0.286667	2
7		3	50.2	50.0	49.8	0.08	2
8	C	1	51.4	51.7	51.8	0.086667	2
9		2	52.1	52.0	51.4	0.286667	2
10		3	51.1	51.9	51.6	0.326667	2
11	D	1	49.0	49.0	48.5	0.166667	2
12		2	47.2	47.6	47.6	0.106667	2
13		3	48.9	48.5	49.2	0.246667	2
14					**Total =**	**2.5**	**24**
15					**MS =**	**0.104167**	
16							
17	**A**	**B**	**C**	**D**			
18	50.63	49.50	51.63	48.83			
19	48.83	51.17	51.83	47.47			
20	51.20	50.00	51.53	48.87			

Commands in Analyses

Column A,B,C,D,E	Enter values from Table 12.9 into rows 1 through 13	
Cell G2	Enter 2	Assay degrees of freedom for Tablet
Cells G3-G13	Copy G2 value	
Cell F2	= G2*VARA(C2:E2)	Assay SS for Tablet
Cells F3:F13	Copy formula from F2	
Cell F14	= Sum(F2:F13)	Pooled within-tablet assay SS
Cells G14	Copy formula from F14	Pooled degrees of freedom for assay
Cell F15	= F14/G14	MS = SS/df
Cell A18	= Average (C2:E2)	Tablet 1, Batch A average
Cells A19:A20)	Copy formula from A18	Tablets 2 & 3 averages, Batch A
Cell B18	= Average(C5:E5)	Tablet 1, Batch B average
Cells B19:B20)	Copy formula from B18	

Cell C18	= Average(C8:E8)	Tablet 1, Batch C average
Cells C19:C20)	Copy formula from C18	
Cell D18	= Average(C11:E11)	Tablet 1, Batch D average
Cells D19:D20)	Copy formula from D18	

Workbook 12.9 Determination of Variance Components in a Nested Design (continuation of worksheet)

	A	B	C	D	E	F	G
32	ANOVA						
33	*Source of Variation*	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
34	Between Groups	16.22917	3	5.409722	7.410578	0.01071	4.06618
35	Within Groups	5.84	8	0.73			
36							
37	Total	22.06917	11				
38						**Correct**	**Correct**
39	**S^2w**	**0.104167**				**SS**	**MS**
40	**S^2t**	**0.695278**			**Between**	48.6875	16.22917
41	**S^2b**	**1.559907**			**Within**	17.52	2.190

Commands in Analyses

Main Menu	Tools → Data Analysis →Anova: Single Factor	
Dialog Box		
Input Range:	Highlight or enter A17:D20	
Labels:	Click on this option	
Output Range:	Highlight or enter A32	
OK	Click to perform calculations	
Cell F40	= 3*B34	SS individual = 3 ∗ SS of means
Cell F41	Copy formula from F40	
Cell G40	= F40/C34	MS Between Batches
Cell G41	Copy formula from G40	MS Between Tablets (within batch)
Cell B39	= F15	Between-Assay (within tablet) Variance
Cell B40	= (1/3)*(G41-B39)	Between-Tablet (within batch) Variance
Cell B41	= (1/9)*(G40-G41)	Between-Batch Variance

In the next example, the Day 1 calibration curve results (Peak Area vs. Concentration) from Table 13.8 are used to demonstrate how to obtain the weighted linear regression analysis shown in Table 13.10.

Workbook 13.10 Weighted Linear Regression Analysis

	A	B	C	D	E	F	G	H
1	**X**	**Y**	**wt**	**wt*X**	**wt*X*X**	**wt*Y**	**wt*X*Y**	**wt(Y-Ym)**2**
2	0.05	0.003	400	20	1	1.2	0.06	0.000936
3	0.05	0.004	400	20	1	1.6	0.08	0.000112
4	0.20	0.016	25	5	1	0.4	0.08	0.003289
5	0.20	0.018	25	5	1	0.45	0.09	0.004536
6	1.00	0.088	1	1	1	0.088	0.088	0.006967
7	1.00	0.094	1	1	1	0.094	0.094	0.008005
8	10.00	0.920	0.01	0.1	1	0.0092	0.092	0.008381
9	10.00	0.901	0.01	0.1	1	0.00901	0.0901	0.008037
10	20.00	1.859	0.0025	0.05	1	0.0046475	0.09295	0.008598
11	20.00	1.827	0.0025	0.05	1	0.0045675	0.09135	0.008303
12								
13		**Sum**	852.025	52.3	10	3.859425	0.8584	0.057164
14					**Ym =**	0.0045297		
15	**Slope**	0.09154						
16	**Intercept**	−0.00109						
17								

Commands in Analyses

Columns A and B	Enter Day 1 values from Table 13.8 (X = Conc, Y = Area)	
Cell C2	= 1/(A2^2)	Weight is 1/(X*X)
Cells C3-C11	Copy formula from C2	
Cell D2	= C2*A2	Weight*X = 1/X
Cells D3:D11	Copy formula from D2	
Cell E2	= D2*A2	Weight*X*X = 1
Cells E3:E11	Copy formula from E2	
Cell F2	= C2*B2	Weight*Y = Y/X
Cells F3:F11	Copy formula from F2	
Cell G2	= D2*B2	Weight*X*Y
Cells G3:G11	Copy formula from G2	
Cell C13	= SUM(C2:C11)	Σwt
Cell D13	= SUM(D2:D11)	Σ(wt*X)
Cell E13	= SUM(E2:E11)	$\Sigma(wt*X^2)$
Cell F13	= SUM(F2:F11)	Σ(wt*Y)
Cell G13	= SUM(G2:G11)	Σ(wt*X*Y)
Cell F14	= (SUM(F2:F12))/C13	Weighted mean for Y (Ym)
Cell H2	= C2*(B2-$F$14)^2	$wt*(Y-Ym)^2$
Cells H3:H11	Copy formula from H2	
Cell H13	= SUM(H2:H11)	$\Sigma(wt*(Y-Ym)^2)$
Cell B15	= (G13-((D13*F13)/C13))/(E13-((D13*D13)/C13))	
Cell B16	= (F13-(B15*D13))/C13	

(continuation of worksheet)

	A	B	C	D	E	F	G
18	**X**	**Y**	**Yp**	**wt(Y-Yp)**2**	**Yav**	**wt(Yav-Yp)**2**	**wt(Y-Yav)**2**
19	0.05	0.003	0.003	0.000095	0.003500	0.0000001	0.000100
20	0.05	0.004	0.003	0.000105	0.003500	0.0000001	0.000100
21	0.20	0.016	0.017	0.000037	0.017000	0.0000012	0.000025
22	0.20	0.018	0.017	0.000015	0.017000	0.0000012	0.000025
23	1.00	0.088	0.090	0.000006	0.091000	0.0000003	0.000009
24	1.00	0.094	0.090	0.000013	0.091000	0.0000003	0.000009
25	10.00	0.920	0.914	0.000000	0.910500	0.0000001	0.000001
26	10.00	0.901	0.914	0.000002	0.910500	0.0000001	0.000001
27	20.00	1.859	1.830	0.000002	1.843000	0.0000004	0.000001
28	20.00	1.827	1.830	0.000000	1.843000	0.0000004	0.000001
29							
30			**SUM**	0.0002754		0.0000043	0.0002711
31							

Commands in Analyses

Columns A and B	Copy values from rows 2–11.		
Cell C19	= $B$16 + $A19*$B$15	Predicted Y value (Yp)	
Cell C20-C28	Copy formula from C19		
Cell D19	= (1/(A19*A19))*(B19-C19)^2	wt*(Y-Yp)^2	
Cells D20:D28	Copy formula from D19		
Cells E19 and E20	= (B$19 + B$20)/2	Average Y value:	X = 0.05 (Yav)
Cells E21 and E22	= (B$21 + B$22)/2		X = 0.20
Cells E23 and E24	= (B$23 + B$24)/2		X = 1.00
Cells E25 and E26	= (B$25 + B$26)/2		X = 10.0
Cells E27 and E28	= (B$27 + B$28)/2		X = 20.0
Cell F19	= (1/(A19*A19))*(E19-C19)^2	wt*(Yav-Yp)^2	
Cells F20-F28	Copy Formula from F19		
Cell G19	= (1/(A19*A19))*(B19-E19)^2	wt*(Y-Yav)^2	
Cells G20-G28	Copy Formula from G19		
Cell D30	= SUM(D19:D28)	$SMwt*(Y-Yp)^2	
Cell F30	= SUM(F19:F28)	$SMwt*(Yav-Yp)^2	
Cell G30	= SUM(G19:G28)	$SMwt*(Y-Yav)^2	

Workbook 13.10 Creation of ANOVA Table 13.10

	A	B	C	D	E	F	G
31							
32		**Source**	**df**	**SS**	**MS**	**F**	
33		**Slope**	1	0.056889	0.0568891	1652.7	
34		**Error**	8	0.000275	0.0000344		
35		**Dev Reg**	3	0.000004	0.0000014	0.03	
36		**Within**	5	0.000271	0.0000542		
37		**Total**	9	0.057164			
38							

Commands in Analyses

Cell C37	= 10–1	Number of (x,y) pairs – 1
Cell C33	Enter 1	Slope has a single degree of freedom
Cell C34	= C37-C33	Total df – Slope df
Cell C36	Enter 5	5 concentrations that have duplicate values
Cell C35	= C34-C36	Error df – Within df
Cell D37	= H13	$\Sigma(wt^*(Y-Ym)^2)$
Cell D34	= D30	$\Sigma(wt^*(Y-Yp)^2)$
Cell D33	= D37-D34	Total SS – Error SS
Cell D35	= F30	$\Sigma(wt^*(Yav-Yp)^2)$
Cell D36	= G30	$\Sigma(wt^*(Y-Yav)^2)$
Cell E33	= D33/C33	SS/df
Cells E34-E36	Copy formula from E33	
Cell F33	= E33/E34	
Cell F35	= E35/E36	

The next set of programs are from Chapter 15, Nonparametric Methods. These programs use only the basic mathematical and sorting functions of Excel.

The first of these examples uses the paired time to peak concentration results from a comparative bioavailability study in 12 subjects. The analysis of the data, shown in Table 15.3, is based on the differences between the results for two oral formulations of a drug, A and B. The program implements the Wilcoxon Signed Rank Test shown in Table 15.4.

Commands in Analyses

Columns A, B and C	Enter values from Table 15.3.	
Cell D2	= C2-B2	Calculates B-A difference
Cells D3-D13	Copy D2	
Cell E2	= ABS(D2)	Absolute value of difference
Cells E3-E13	Copy E2	
Cell F2	= E2/D2	+ 1 if difference >0; – 1 if difference <0
Cells F3-F12	Copy F2	

Workbook 15.4 Wilcoxon Signed Rank Test Analysis of Table 15.3 Data

	A	B	C	D	E	F
1	**Subject**	**A**	**B**	**B-A**	**Abs(B-A)**	**Sign(B-A)**
2	1	2.5	3.5	1	1	1
3	2	3	4	1	1	1
4	3	1.25	2.5	1.25	1.25	1
5	4	1.75	2	0.25	0.25	1
6	5	3.5	3.5	0	0	#DIV/0!
7	6	2.5	4	1.5	1.5	1
8	7	1.75	1.5	−0.25	0.25	−1
9	8	2.25	2.5	0.25	0.25	1
10	9	3.5	3	−0.5	0.5	−1
11	10	2.5	3	0.5	0.5	1
12	11	2	3.5	1.5	1.5	1
13	12	3.5	4	0.5	0.5	1

(worksheet contined)

	G	H	I	J	K	L	M
1	**Index**	**SortVal**	**SortSign**	**Rank**	**SignRank**	**Positive**	**Negative**
2	1	0.25	1	2	2	2	
3	2	0.25	−1	2	−2		2
4	3	0.25	1	2	2	2	
5	4	0.5	−1	5	−5		5
6	5	0.5	1	5	5	5	
7	6	0.5	1	5	5	5	
8	7	1	1	7.5	7.5	7.5	
9	8	1	1	7.5	7.5	7.5	
10	9	1.25	1	9	9	9	
11	10	1.5	1	10.5	10.5	10.5	
12	11	1.5	1	10.5	10.5	10.5	
13		**N=**	11		**Sum**	59	7
14					**Z=**	2.312	
15					**p-value**	0.021	

Commands in Analyses

Column G	Enter the count of the non-zero differences.	
Cells H2-H12	Copy nonzero values from Cells E2-E13 using Paste Special, Values option.	
Cells 12-I12	Copy corresponding values from cells F2-F13 (Paste Special, Values).	
Cells H2-I12	Highlight this Range of cells and under Data choose to sort this selection by column H.	
Cell J2-J12	Enter number in column G unless the number in column H is tied with another in column H. Use the average G number for the ties. For example, Cells J2, J3 and J4 get the number 2 because their H value, 0.25, is a three-way tie for index numbers 1, 2 and 3.	
Cell K2	= I2*J2	Signed Rank
Cells K3-K12	Copy formula from K2	
Cell L2	= IF(K2 > 0,J2," ")	Enters rank if sign is positive
Cells L3-L12	Copy formula from L2	
Cell M2	= IF(K2 < 0,J2," ")	Enters rank if sign is negative
Cells M3-M12	Copy formula from M2	
Cell I13	= COUNT(12:I12)	Determines N, the number of signed ranks
Cell L13	= SUM(L2:L12)	Sum of ranks with positive signs
Cell M13	= SUM(M2:M12)	Sum of ranks with negative signs
Cell L14	= ABS(L13-I13*(I13 + 1)/4)/SQRT(I13*(I13 + 0.5)*(I13 + 1)/12)	
Cell L15	= 2*(1-NORMSDIST(L14))	

Using the Peak Concentration (Cmax) results from a two-way, crossover Bioequivalence study, a method for calculating a nonparametric confidence interval on the mean treatment ratio is shown in the following example.

Commands in Analyses

Columns A, B, and C	Enter values from Table 15.6 into rows 2–13.	
Cell D2	= C2/B2 Calculates B/A Ratio	
Cells D3-D13	Copy formula from D2	
Cell D16	= 1/12	Power for Geometric Mean
Cell D15	= Product(D2:D13)	Product of Ratios
Cell D17	= Power(D15,D16)	Product to 1/12th power is Geom. Mean Ratio
Cells E1-L1	Enter Column Labels.	
Cells J2, J3	Enter 95% and 90%.	Level of Confidence Interval for row
Column E	Start in row 2 (Subject) and enter number 1 twelve times, 2 eleven times, 3 ten times, 4 nine times, etc., until 12 is entered into row 79. These numbers represent the first Subject for each pair.	
Column F	Starting in row 2, enter Subject numbers 1–12, next numbers 2–12, next 3–12, next 4–12, etc., until 12 is entered into row 79. These represent the second Subject for each pair.	

Workbook 15.6 Nonparametric Confidence Interval for C_{max}

	A	B	C	D
1	**Subject**	**A**	**B**	**B/A**
2	1	135	102	0.755556
3	2	179	147	0.821229
4	3	101	385	3.811881
5	4	109	106	0.972477
6	5	138	189	1.369565
7	6	135	105	0.777778
8	7	158	130	0.822785
9	8	156	125	0.801282
10	9	174	144	0.827586
11	10	147	133	0.904762
12	11	145	114	0.786207
13	12	147	167	1.136054
14				
15			**Product =**	1.080296
16			**1/12=**	0.083333
17		**Geometric**	**Mean =**	1.006457

Cell G2	= POWER($D$2*D2,0.5)	Geometric mean of Subject 1 ratio paired with itself
Cells G3-G13	Copy G2 formula	Geometric mean ratio of Subject 1 with all others
Cell G14	= POWER($D$3*D3,0.5)	Geometric mean of Subject 2 ratio paired with itself
Cells G15-G24	Copy G14 formula	Geometric mean of Subject 2 with Subjects 3–12
Cell G25	= POWER($D$4*D4,0.5)	Geometric mean of Subject3 ratio paired with itself
Cells G26-G34	Copy G25 formula	Geometric mean of Subject 3 with Subjects 4–12
Cells G35-G79	Continue as above for remaining paired subject ratios.	
Cells H2-H3	Enter index numbers 1 & 2 The number for the geometric mean (after sorting)	
Cells H4-H79	Highlight Cells H2-H3 and drag copy to obtain index numbers 3–78	
Column I	Highlight Cells G2-G79 Choose Copy under Edit on Main Menu toolbar. Place cursor in Cell I2 and then choose Paste Special under Edit on Main Menu	

(worksheet contined)

	E	F	G	H	I	J	K	L
1	**1st Subj**	**2nd Subj**	**Geomean**	**Index**	**Sorted**	**Confidence**	**Low**	**High**
2	1	1	0.755556	1	0.755556	95%	0.800	1.247
3	1	2	0.787708	2	0.766586	90%	0.804	1.065
4	1	3	1.697082	3	0.770729			
5	1	4	0.857182	4	0.777778			
6	1	5	1.017243	5	0.778083			
7	1	6	0.766586	6	0.781981			
8	1	7	0.788454	7	0.786207			
9	1	8	0.778083	8	0.787708			
10	1	9	0.790751	9	0.788454			
11	1	10	0.8268	10	0.789442			
12	1	11	0.770729	11	0.790751			
13	1	12	0.926473	12	0.793709			
14	2	2	0.821229	13	0.799208			
15	2	3	1.769301	14	0.799965			
	Rows 16–74 not shown							
75	10	11	0.843404	74	1.857107			
76	10	12	1.013834	75	1.925349			
77	11	11	0.786207	76	2.080986			
78	11	12	0.945079	77	2.284868			
79	12	12	1.136054	78	3.811881			

In Paste Special dialog box, choose to paste Values and then click OK
Next Highlight all entries in Column I
Choose Sort under Data on Main Menu.
Choose to stay with the current selection when prompted about expanding.
Choose Sort, Ascending for the column labeled "Sorted."
Click OK.

Use Table 15.5 to obtain the ranking numbers for the upper and lower confidence interval limits

Cell K2	= I15	Lower 95% CI limit is 14th ranked geometric mean ratio
Cell L2	= I66	Upper 95% CI limit is 65th ranked geometric mean ratio
Cell K3	= I19	Lower 90% CI limit is 18th ranked geometric mean ratio
Cell L3	= I62	Upper 90% CI limit is 61 st ranked geometric mean ratio

Workbook 15.8 Wilcoxon Rank Sum Test for Differences Between Two Independent Groups

	A	B	C	D	E	F	G	H
1	**Apparatus**	**Dissolved**	**Index**	**App**	**Sorted**	**Rank**	**O Rank**	**M Rank**
2	O	53	1	O	50	1	1	
3	O	61	2	O	52	2	2	
4	O	57	3	O	53	3	3	
5	O	50	4	O	54	4	4	
6	O	63	5	M	55	5.5		5.5
7	O	62	6	M	55	5.5		5.5
8	O	54	7	M	56	7		7
9	O	52	8	O	57	9	9	
10	O	59	9	O	57	9	9	
11	O	57	10	M	57	9		9
12	O	64	11	M	58	11		11
13	M	58	12	O	59	12.5	12.5	
14	M	55	13	M	59	12.5		12.5
15	M	67	14	O	61	14	14	
16	M	62	15	O	62	15.5	15.5	
17	M	55	16	M	62	15.5		15.5
18	M	64	17	O	63	17	17	
19	M	66	18	O	64	18.5	18.5	
20	M	59	19	M	64	18.5		18.5
21	M	68	20	M	66	20		20
22	M	57	21	M	67	21		21
23	M	69	22	M	68	22		22
24	M	56	23	M	69	23		23
25						**N =**	11	12
26						**Sum =**	105.5	170.5
27						**Z =**	1.631	
28						**p-value =**	0.103	

The next example demonstrates how to perform the Wilcoxon Rank Sum Test for comparing the differences between two independent groups. In this example, Excel is used to perform the necessary calculations on the tablet dissolution results given in Table 15.8. The results from a modified dissolution apparatus are compared with those obtained from the original apparatus to see if they are statistically different from each other.

Commands in Analysis

Columns A & B	Enter apparatus and dissolution results from Table 15.8.
Column C	Enter the index numbers 1 through 23.
Column D & E	Copy values from Column A & B. Highlight D2 through E24. From Main Menu Toolbar, choose Data and then Sort. Sort by column "Sorter", in ascending order, indicating there is a Header Row.
Cell F2	= C2 Rank for E2, a unique number in col.
Cell Fx	Copy F2 formula for each row, x, for each Ex that is unique.
Cells F6 & F7	= AVERAGE(C6:C7) Rank for tied E values (2).
Cell Fx & Fy	Copy F6 formula to consecutive Ex & Ey ties of size 2.
Cells F9,F10,F11	= AVERAGE(C9:C11) Rank for tied E values (3).

Commands in Analyses (continued

Cell G2	= IF(D2 = "O", F2, "")	Enters rank for original apparatus O.
Cells G3:G24	Copy G2 formula	
Cell H2	= IF(D2 = "M", F2, "")	Enters rank for modified apparatus.
Cells H3:H24	Copy H2 formula	
Cell G25	= COUNT(G2:G24)	# of original apparatus values.
Cell H25	= COUNT(H2:H24)	# of modified apparatus values.
Cell G26	= SUM(G2:G24)	Original apparatus Rank Sum.
Cell H26	= SUM(H2:H24)	Modified apparatus Rank Sum.
Cell G27	= (ABS(G26-(G25*(G25 + H25 + 1))/2))/(SQRT(G25*H25*(G25 + H25 + 1)/12))	
Cell G28	= 2*(1-NORMSDIST(G27))	2-sided p-value for G27 Z-val

Next we analyze the time-to-sleep values (Table 15.10) from one group of rats given a low dose (L) of an experimental drug, a second group a high dose (H), and a third a dose of a control, sedative (C).

Commands in Analyses

Columns A & B	Enter compound id & time-to-sleep values from Table 15.10	
Column C	Enter the index numbers 1 through 29	
Cells D2-D30	Copy values from A2-A30	
Cells E2-E30	Copy values from B2-B30. Highlight D1 through E30. From Main Menu Toolbar, choose Data and then Sort. Sort by column "Sorter", in ascending order, indicating there is a Header Row.	
Cells F2-F30	= Cn n = 1–30;	If En is a unique value (e. g. F13 = C13)
	= AVERAGE(Cx:Cy),	for the Ex to Ey equal values (ties) e.g. F2-F7 = AVERAGE(C2: C7).
Cells G2-G30	In first cell for a group of tied ranks in F, put # of tied values.	
Cell E32	= COUNT(E2:E30) number of values.	
Cell Hn	= Gn*(Gn*Gn-1)/($E$32*($E$32*$E$32–1)) for each n, where there is an entry in cell Gn. This is the correction factor for the group Gn of ties.	

Workbook 15.10 Kruskal Wallis Test (One-Way Anova) for Differences Between Independent Groups (>2)

	A	B	C	D	E	F	G	H	I	J	K
1	**ID**	**Time**	**Indx**	**Compnd**	**Sorted**	**Rank**	**Tie Size**	**Tie Corr**	**Control**	**Low**	**High**
2	C	8	1	C	1	3.5	6	0.009	3.5		
3	C	1	2	C	1	3.5			3.5		
4	C	9	3	L	1	3.5				3.5	
5	C	9	4	H	1	3.5					3.5
6	C	6	5	H	1	3.5					3.5
7	C	3	6	H	1	3.5					3.5
8	C	15	7	H	2	7.5	2	0.000			7.5
9	C	1	8	H	2	7.5					7.5
10	C	7	9	C	3	10	3	0.001	10		
11	L	10	10	H	3	10					10
12	L	5	11	H	3	10					10
13	L	8	12	H	4	12					12
14	L	6	13	L	5	13				13	
15	L	7	14	C	6	15	3	0.001	15		
16	L	7	15	L	6	15				15	
17	L	15	16	H	6	15					15
18	L	1	17	C	7	18.5	4	0.002	18.5		
19	L	15	18	L	7	18.5				18.5	
20	L	7	19	L	7	18.5				18.5	
21	H	3	20	L	7	18.5				18.5	
22	H	4	21	C	8	22	3	0.001	22		
23	H	8	22	L	8	22				22	
24	H	1	23	H	8	22					22
25	H	1	24	C	9	24.5	2	0.000	24.5		
26	H	3	25	C	9	24.5			24.5		
27	H	1	26	L	10	26				26	
28	H	6	27	C	15	28	3	0.001	28		
29	H	2	28	L	15	28				28	
30	H	2	29	L	15	28				28	
31											
32				**Count**	29		**Sum**	0.016	149.5	191.0	94.5
33							**Correctn**	0.984			
34								**n**	9	10	10
35								**R*R/n**	2483.4	3648.1	893.0
36											
37								**Chi-Sq**	6.89		
38								**p-value**	0.032		
39								**Chi-Sq(c)**	7.00		
40								**p-value**	0.030		

Cells I2–I30	= IF(Dn = "C",Fn," ")	n = 1 to 30; Rank for Control rows.
Cells J2-J30	= IF(Dn = "L",Fn," ")	n = 1 to 30; Rank for Low Dose rows.
Cell K2-K30	= IF(Dn = "H",Fn," ")	n = 1 to 30; Rank for High Dose rows.
Cell H32	= SUM(H2:H30)	Sum of correction factor for ties.
Cell H33	= 1-H32	Correction for ties.
Cell I32	= SUM(I2:I30)	Rank Sum for Control.
Cell J32	= SUM(J2:J30)	Rank Sum for Low Dose.
Cell K32	= SUM(K2:K30)	Rank Sum for High Dose.
Cell I34	= COUNT(I2:I30)	Number of Control Values.
Cell J34	= COUNT(J2:J30)	Number of Low Dose Values.
Cell K34	= COUNT(K2:K30)	Number of High Dose Values.
Cell I35	= I32*I32/I34	(Control Rank Sum Squared)/n.
Cell J35	= J32*J32/J34	(Low Dose Rank Sum Squared)/n.
Cell K35	= K32*K32/K34	(High Dose Rank Sum Squared)/n.
Cell I37	= (12/(E32*(E32 + 1))*(SUM(I35:K35))-3*(E32 + 1))	Chi-Square Statistic
Cell I38	= 2*(1-NORMSDIST(I37))	P-value for I37 Chi-Square
Cell I39	= I37/H33	Statistic corrected for ties.
Cell I40	= 2*(1-NORMSDIST(I39))	P-value for I39 statistic

In the next Workbook, the tablet hardness results in Table 15.11 from five tablet formulations (1–5) produced on four different tablet presses (A-D) are examined by nonparametric, two-way ANOVA to validate that all presses have statistically equivalent performance.

Commands in Analyses

Columns A & B	Enter tablet press and hardness values from Table 15.11 in order shown	
Cell B23	Enter 5, the number of tablet formulations	
Cell B24	Enter 4, the number of tablet presses	
Column C	Enter 5 groups of the index numbers 1–4 (one for each tablet formulation)	
Column D	Enter the tablet formulation number for each value in column C	
Cell E2	= 10*B2*D2 value is proportional to hardness	
Cells E3-E21	Copy formula from Cell E2	
Column F	Copy Column A values	
Column G	Copy Column E, using the Paste Special, values, option under Edit Highlight Columns F and G, rows 1 through 21. From Main Menu Toolbar, choose Data and then Sort. Sort by column "SortMod", in ascending order, indicating there is a Header Row.	
Cells H2-H21	= IF(Fn = "A",Cn," ")	n = 1 to 21; Enters ranks for Press A values.

Workbook 15.11 Friedman and Modified Friedman Tests (Two-Way Anova)

	A	B	C	D	E	F	G	H	I	J	K
1	**Press**	**Value**	**Index**	**Tab**	**ModVal**	**Press**	**SortMod**	**A Rank**	**B Rank**	**C Rank**	**D Rank**
2	A	7.5	**1**	1	75	B	69		1		
3	B	6.9	**2**	1	69	D	70				2
4	C	7.3	**3**	1	73	C	73			3	
5	D	7.0	**4**	1	70	A	75	4			
6	A	8.2	**1**	2	164	D	158				1
7	B	8.0	**2**	2	160	B	160		2		
8	C	8.5	**3**	2	170	A	164	3			
9	D	7.9	**4**	2	158	C	170			4	
10	A	7.3	**1**	3	219	A	219	1			
11	B	7.9	**2**	3	237	D	228				2
12	C	8.0	**3**	3	240	B	237		3		
13	D	7.6	**4**	3	228	C	240			4	
14	A	6.6	**1**	4	264	D	256				1
15	B	6.5	**2**	4	260	B	260		2		
16	C	7.1	**3**	4	284	A	264	3			
17	D	6.4	**4**	4	256	C	284			4	
18	A	7.5	**1**	5	375	D	335				1
19	B	6.8	**2**	5	340	B	340		2		
20	C	7.6	**3**	5	380	A	375	3			
21	D	6.7	**4**	5	335	C	380			4	
22											
23	**r =**	5					**Sum =**	14	10	19	7
24	**c =**	4					**SumR*R**	706			
25							**Chi-Sqr**	9.72			
26							**p-value**	0.0211			
27							**A2**	150			
28							**B2**	141.2		**CritDiff**	5.90
29							**T2**	7.364			
30							**p-value**	0.0047			

Cells I2-I21	= IF(Fn = "B",Cn," ")	n = 1 to 21; Enters ranks for Press B values.
Cells J2-J21	= IF(Fn = "C",Fn," ")	n = 1 to 21; Enters ranks for Press C values.
Cells K2-K21	= IF(Fn = "D",Fn," ")	n = 1 to 21; Enters ranks for Press D values.
Cell H23	= SUM(H2:H21)	Rank Sum for Press A.
Cell I23	= SUM(12:I21)	Rank Sum for Press B.
Cell J23	= SUM(J2:J21)	Rank Sum for Press C.
Cell K23	= SUM(K2:K21)	Rank Sum for Press D.
Cell H24	= SUMSQ(H23:K23)	Sum of Squared Rank Sums
Cell H25	= ((12*H24)/(B23*B24*(B24 + 1)))-3*B23*(B24 + 1)	Friedman X^2
Cell H26	= CHIDIST(H25,B24–1)	p-value for Friedman's test
Cell H27	= SUMSQ(H2:K21)	A2 = Sum of squares for the 29 individual ranks
Cell H28	= H24/B23	B2 = Average Squared Rank Sum
Cell H29	= ((B23 – 1)*(H28-(B23*B24*(B24 + 1)*(B24 + 1))/4)/(H27-H28)	Modified X^2
Cell H30	= FDIST(H29, B24–1,(B23–1)*(B24–1))	p-value for modified Friedman test
Cell K28	= TINV(0.05,(B23–1)*(B24–1))*SQRT((2*B23* (H27-H28))/((B23–1)*(B24–1)))	
	Minimum difference between any two Rank Sums that is significant ($p < 0.05$)	

The tablet harness values are used again to demonstrate how to perform the Quade Test for randomized block designs as shown in Table 15.12.

Workbook 15.12 Quade Test on Table 15.11 Tablet Hardness Values

Commands in Analyses

Columns A, B, & C	Enter press, formulation and hardness values from Table 15.11 in rows 2–21	
Cell A24	Enter 4, the number of tablet presses (columns)	
Cell A27	Enter 5, the number of tablet formulations (rows)	
Cell D2	= MAX(B2:B5)-MIN(B2:B5)	Determines range of tablet 1 hardness
Cells D6, D10, D14, D18	= MAX(Bx:By)-MIN(Bx:By)	for D6 x, y = 6, 9 for D10 x, y = 10, 13 for D14 x, y = 14, 17 for D18 x, y = 18, 21
Cells B23-B27	Enter tablet formulation numbers 1–5	
Cells C23-C27	Copy ranges for each formulation from cells D2, D6, D10, D14 & D18	
Cells D23-D27	Rank the ranges using the average rank for ties (e. g., tied ranks 3 and 4 = 3.5)	
Cells E2-E21	Enter 5 groups of index numbers 1–4 (one group per tablet formulation)	
Cell F2	= 10*B2*D2 modifies hardness value to obtain correct sorting within press	

Workbook 15.12 Quade Test on Table 15.11 Tablet Hardness Values

	A	B	C	D	E	F	G	H	I	J	K	L	M
1	**Press**	**Value**	**Tab**	**Q**	**Index**	**Mod**	**Press**	**q**	**SortMod**	**A**	**B**	**C**	**D**
2	A	7.5	1	0.6	**1**	75	B	1.5	69		−2.25		
3	B	6.9	1		**2**	69	D	1.5	70				−0.75
4	C	7.3	1		**3**	73	C	1.5	73			0.75	
5	D	7.0	1		**4**	70	A	1.5	75	2.25			
6	A	8.2	2	0.6	**1**	164	D	1.5	158				−2.25
7	B	8.0	2		**2**	160	B	1.5	160		−0.75		
8	C	8.5	2		**3**	170	A	1.5	164	0.75			
9	D	7.9	2		**4**	158	C	1.5	170			2.25	
10	A	7.3	3	0.7	**1**	219	A	3.5	219	−5.25			
11	B	7.9	3		**2**	237	D	3.5	228				−1.75
12	C	8.0	3		**3**	240	B	3.5	237		1.75		
13	D	7.6	3		**4**	228	C	3.5	240			5.25	
14	A	6.6	4	0.7	**1**	264	D	3.5	256				−5.25
15	B	6.5	4		**2**	260	B	3.5	260		−1.75		
16	C	7.1	4		**3**	284	A	3.5	264	1.75			
17	D	6.4	4		**4**	256	C	3.5	284			5.25	
18	A	7.5	5	0.9	**1**	375	D	5	335				−7.50
19	B	6.8	5		**2**	340	B	5	340		−2.50		
20	C	7.6	5		**3**	380	A	5	375	2.50			
21	D	6.7	5		**4**	335	C	5	380			7.50	
22		**TAB**	**Rng**	**Rnk**									
23	**k=c**	1	0.6	1.5					**Sum =**	2.00	−5.50	21.00	−17.50
24	**4**	2	0.6	1.5									
25		3	0.7	3.5					**A**	270		**CritDiff**	
26	**r**	4	0.7	3.5					**B**	156.3		21.2	
27	5	5	0.9	5					**T**	5.499			
28									**p-value**	0.0131			
29													

Cells F3-F21 Copy F2 formula
Cells G2-G21 Copy cells A2-A21 press values
Cells H2-H21 Copy the D23-D27 tablet ranks for formulations in column C
Cells 12–I21 Copy F2-F21 values using the Paste Special option under Edit.
Highlight rows 2–21 of Columns G, H and I.
From Main Menu Toolbar, choose Data and then Sort.
Sort G2:I21 selection by column ``SortMod'', in ascending order.

Cells J2-J21	= IF($Gn = "A",$Hn*($En-($A$24 + 1)/2),"")	n = 2 to 21; Sij for Press A.
Cells K2-K21	= IF($Gn = "B",$Hn*($En-($A$24 + 1)/2)," ")	n = 2 to 21; Sij for Press B.
Cells L2-L21	= IF($Gn = "C",$Hn*($En-($A$24 + 1)/2)," ")	n = 2 to 21; Sij for Press C.
Cells M2-M21	= IF($Gn = "D",$Hn*($En-($A$24 + 1)/2),"")	n = 2 to 21; Sij for Press D.
Cell J23	= SUM(J2:J21)	Rank Sum for Press A.
Cell K23	= SUM(K2:K21)	Rank Sum for Press B.
Cell L23	= SUM(L2:L21)	Rank Sum for Press C.
Cell M23	= SUM(M2:M21)	Rank Sum for Press D.
Cell J25	= SUMSQ(J2:M21)	$A = \Sigma Sij^2$
Cell J26	= (SUMSQ(J23:M23))/A27	$B = \Sigma(\Sigma Sij)^2/r)$
Cell J27	= ((A27–1)*J26)/(J25-J26)	Quade test statistic T = (r-1)B/(A-B)
Cell J28	= FDIST(J27,A24–1,(A27–1) *(A24–1))	p-value from $F_{3,12}$ distribution
Cell I26	= TINV(0.05,(A27–1)*(A24–1))*SQRT((2*A27*(J25-J26))/((A27–1)*(A24–1)))	
	Difference between any two Rank Sums which is significant at p = 0.05.	

In the next Workbook, a product made from four lots of raw material each with a different potency (X) is assayed for its potency (Y) after being manufactured using two different methods (I and II). The results, shown in Table 15.13, are used to demonstrate the Quade Nonparametic Covariance Analysis.

Commands in Analysis

Columns A, C & D	Enter method, Assay (Y) and Material (X) values into rows 2–9	
Column B	Enter observation numbers 1–8 into rows 2–9	
Cells A12-A19	Enter Index numbers 1–8 which will be used as a guide when ranking values	
Cells B12-B19	Copy B2-B9 Observation numbers	
Cells C12-C19	Copy D2-D9 X values	
Cells F12-F19	Copy B2-B9 Observation numbers	
Cells G12-G19	Copy C2-C9 Y values	
Cell B21	= (A19 + 1)/2	Mean rank, 4.5, for 8 observations
Cells B12-C19	Highlight this section and sort in ascending order (indicate a header row)	
Cells F12-G19	Highlight this section and sort in ascending order (indicate a header row)	
Cells D12-D19	Rank sorted cells C12-C19, using the average for tied ranks	
Cells H12-H19	Rank sorted cells G12-G19 using the average for tied ranks	
Cell E12	= D12-$B$21	Center X rank by subtracting the mean rank
Cells E13-E19	Copy formula from Cell E12	Center remaining X ranks
Cells I12-I19	Copy formula from Cell E12	Center Y ranks by subtracting the mean rank
Cells E2:E9	Enter centered Y rank, matching sorted Obs number with Obs number in Col B	
Cells F2:F9	Enter centered X rank, matching sorted Obs number with Obs number in Col B	

Workbook 15.13 Quade Nonparametric Covariance Analysis (ANCOVA)
(main worksheet ply)

	A	B	C	D	E	F	G	H	I
1	**Method**	**Obs**	**Y**	**X**	**Adj Ry**	**Adj Rx**			
2	I	1	98.0	98.4	2.5	−3			
3	I	2	97.8	98.6	1.5	−1			
4	I	3	98.5	98.6	3.5	−1			
5	I	4	97.4	99.2	−0.5	2.5			
6	II	5	97.6	98.7	0.5	0.5			
7	II	6	95.4	99.0	−3.5	1.5			
8	II	7	96.1	99.3	−2	3.5			
9	II	8	96.1	98.4	−2	−3			
10									
11	**Index**	**Sort Obs**	**Sort X**	**Rank X**	**Adj Rx**	**Sort Obs**	**Sort Y**	**Rank Y**	**Adj Ry**
12	**1**	1	98.4	1.5	−3	6	95.4	1	−3.5
13	**2**	8	98.4	1.5	−3	7	96.1	2.5	−2
14	**3**	2	98.6	3.5	−1	8	96.1	2.5	−2
15	**4**	3	98.6	3.5	−1	4	97.4	4	−0.5
16	**5**	5	98.7	5	0.5	5	97.6	5	0.5
17	**6**	6	99.0	6	1.5	2	97.8	6	1.5
18	**7**	4	99.2	7	2.5	1	98.0	7	2.5
19	**8**	7	99.3	8	3.5	3	98.5	8	3.5
23									
20		**(N+1)/2**							
21		4.5							

Commands in Analysis (continued)

Main Menu	Tools → Data Analysis → Regression
Dialog Box	
Input Y Range:	Highlight or enter E1:E9
Input X Range:	Highlight or enter F1:F9
Labels:	Click on this option
New Worksheet Ply:	Enter "Regression"
Residuals	Click on this option
OK	Click to perform calculations

(regression worksheet ply)

	A	B	C
20			
21			
22	RESIDUAL OUTPUT		
23			
24	*Observation*	*Predicted Rank Y*	*Residuals*
25	1	1.445122	1.054878
26	2	0.481707	1.018293
27	3	0.481707	3.018293
28	4	−1.20427	0.704268
29	5	−0.24085	0.740854
30	6	−0.72256	−2.77744
31	7	−1.68598	−0.31402
32	8	1.445122	−3.44512
33			

Commands in Analyses (continued)
Main Worksheet Ply:

Cells G2:G9	Copy Predicted values from Cells B25-B32 of Regression Worksheet Ply
Cells H2:H9	Copy Residual values from Cells C25-C32 of Regression Worksheet Ply

(main worksheet ply)

	G	H	I	J
1	**Predicted**	**Residual**	**Method I**	**Method II**
2	1.4451	1.0549	1.0549	0.7409
3	0.4817	1.0183	1.0183	−2.7774
4	0.4817	3.0183	3.0183	−0.3140
5	−1.2043	0.7043	0.7043	−3.4451
6	−0.2409	0.7409		
7	−0.7226	−2.7774		
8	−1.6860	−0.3140		
9	1.4451	−3.4451		
10				

Commands in Analyses (continued)

Cells I2–I5	Copy Residual values for Method I from Cells H2-H5
Cells J2-J5	Copy Residual values for Method II from Cells H6-H9
Main Menu	Tools → Data Analysis → Anova: Single Factor
Dialog Box	
Input Range:	Highlight or enter $I$1:$J$5
Labels:	Click on this option
New Worksheet Ply:	Enter word "ANOVA"
OK	Click to perform calculations

(ANOVA worksheet ply)

	A	B	C	D	E	F	G
1	Anova: Single Factor						
2							
3	SUMMARY						
4	*Groups*	*Count*	*Sum*	*Average*	*Variance*		
5	Method I	4	5.795732	1.448933	1.119382		
6	Method II	4	−5.79573	−1.44893	3.944294		
7							
8							
9	ANOVA						
10	*Source of Variation*	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
11	Between Groups	16.79525301	1	16.79525	6.633621	0.042018	5.987374
12	Within Groups	15.19102748	6	2.531838			
13							
14	Total	31.98628049	7				
15							

Note: The ANOVA Worksheet contains the results of the Analysis of Covariance.

The next Workbook shows how to perform an evaluation for comparability of baseline disease severity (mild, moderate, or very severe) for patients randomized to one of two treatment groups (A or B) in a clinical trial. The data are taken from Table 15.16 and the analysis follows that shown in Table 15.17.

Workbook 15.16 Chi-Square Evaluation of a 2×3 Contingency Table

Commands in Analysis

Cells C4-E5	Enter the patient counts from Table 15.16
Cell A8	Enter the number of rows in Table
Cell A11	Enter the number of columns in Table
Cell C6	= SUM(C4:C5)
Cells D6-E6	Copy formula from Cell C6
Cell F4	= SUM(C4:E4)
Cells F5-F6	Copy formula from Cell F4
Cell C12	= (C$6*$F4)/$F$6
Cells C13 & D12-E13	Copy formula from Cell C12
Cells C14-E14	Copy formula from Cells C6-E6
Cells F12-F14	Copy formula from Cells F4-F6
Cell C20	= (C4-C12)*(C4-C12)/C12
Cells C21 & D20-E21	Copy formula from Cell C19
Cell D22	= SUM(C20:E21)
Cell D23	= CHIDIST(D22,(A8–1)*(A10–1))

(patients categorized by disease severity and treatment)

	A	B	C	D	E	F
1				**Observed**		
2						
3		**Severity:**	Very	Moderate	Mild	Total
4	**Treatment:**	A	13	24	18	55
5		B	19	20	12	51
6		Total	32	44	30	106
7	**Rows:**					
8	2					
9	**Cols:**			**Expected**		
10	3					
11		**Severity:**	Very	Moderate	Mild	Total
12	**Treatment:**	A	16.60	22.83	15.57	55
13		B	15.40	21.17	14.43	51
14		Total	32	44	30	106
15						
16						
17				**$(0\text{-}E)^2/E$**		
18						
19		**Severity:**	Very	Moderate	Mild	
20	**Treatment:**	A	0.782	0.060	0.381	
21		B	0.844	0.065	0.410	
22			**X^2 =**	2.541		
23			**P =**	0.281		

The final Excel Workbook uses the results shown in Table 15.21 on the Incidence of Carcinoma in Drug- and Placebo-Treated Animals to demonstrate the method of calculating exact confidence intervals for a 2 × 2 contingency table.

Workbook 15.21 Fisher's Exact Test for Carcinoma Results in Drug- and Placebo-Treated Animals

	A	B	C	D	E	F	G
1						**A values**	**p-values**
2			**Carcinomas**			0	0.03043
3			**Present**	**Absent**		1	
4		**Placebo**	0	12	12	2	
5		**Drug**	5	9	14	3	
6			5	21	26	4	
7			p-value	0.03043		5	0.01204
8							
9			**Carcinomas**			**Fisher's**	**p-value**
10			**Present**	**Absent**			**0.04247**
11		**Placebo**	5	7	12		
12		**Drug**	0	14	14		
13			5	21	26		
14			p-value	0.01204			
15							

Commands in Analyses

Cells C6,D6,E4,E5	Enter marginal totals from Table 15.21	(A + B), (C + D), (A + C), (B + D)
Cell E6	= SUM(E4:E5)	N = A + B + C + D
Cell C4	Enter Placebo-Present count	A
Cell C5	= C6-C4	B = (A + B)-A
Cell D4	= E4-C4	C = (A + C)-A
Cell D5	= E6-D4-C5-C4	D = Total-B-C-A
Cell D7	= (FACT(C6)*FACT(D6)*FACT(E4)*FACT(E5))/ (FACT(E6)*FACT(C4)*FACT(C5)*FACT(D4)* FACT(D5))	
	Note: The function FACT(x) returns the factorial of the number x or the number in that cell if x is a cell reference (e. g. x = C6).	
Column F	Enter all possible values for A (Placebo-Present count)	
	This is obtained by going from a count of 0 and increasing to a count of A + B (cell C5) or A + C (cell D4), whichever is smaller.	
Cells B9-E14	Highlight and Copy Cells B2:E7 creates a working table	

Set the value for A (Cell C11) to 0 in the working table. If the *p*-value in Cell D14 ≤ T Cell D7 then copy that value (use Paste Special, value) to column G beside the appropriate A value in column F. Continue through all the possible values for A shown in column F.

Cell G10	= SUM(G2:G8)	*p*-value for Fisher's Exact Test

SAS Programs

The following programs written for the SAS System perform the same analyses as those presented in the Excel Workbooks section of this appendix. As such, no commentary is provided for these programs other than that needed to interpret the results of the SAS output. It is assumed that the reader has a basic understanding of the SAS System and knows how to operate SAS in his/her computer environment. The SAS programs utilize only the basic mathematical and statistical functions and standard procedures available in SAS/Base and SAS/STAT. The programs have been kept as simple as possible in hopes that the reader will easily be able to follow each program's logic. All data are contained within the program itself (Cards Statement). The reader should be able to easily modify the program code to input data from an external file.

```
/*   SAS Program to Analyze Table 1.1 */

Options ls=90 ps=60 nodate pagno=1;
Title1 'Serum Cholesterol Changes (mg %) After Administration of a
Cholesterol Lowering Drug';

Data A;
input change;     /* read in serum cholesterol changes */
cards;          /* (only a portion of the 156 data points are shown) */
17
-12
25
-37
-29
-39
-22
0
-22
*
*
*
14
17
-13
-22
-3
-17
1
;

Proc Univariate plot; /* Procedure to obtain descriptive analyses */
var change;           /* identifies variable to be analyzed */

run;
quit;
```

SAS OUTPUT FOR ANALYSES OF TABLE 1.1:

Serum Cholesterol Changes (mg %) After Administration of a Cholesterol Lowering Drug 1

Univariate Procedure

Variable=CHANGE

Moments

				Quantiles(Def=5)			
N	156	Sum Wgts	156	100% Max	55	99%	46
Mean	-10.6218	Sum	-1657	75% Q3	10	95%	34
Std Dev	27.68191	Variance	766.2883	50% Med	-9.5	90%	23
Skewness	-0.28357	Kurtosis	-0.16183	25% Q1	-28.5	10%	-49
USS	136375	CSS	118774.7	0% Min	-97	5%	-60
CV	-260.614	Std Mean	2.216327			1%	-71
T:Mean=0	-4.79252	Pr>|T|	0.0001	Range	152		
Num ^= 0	152	Num > 0	58	Q3-Q1	38.5		
M(Sign)	-18	Pr>=|M|	0.0044	Mode	-27		
Sgn Rank	-2296	Pr>=|S|	0.0001				

Extremes

Lowest	Obs	Highest	Obs
-97(	107)	38(	109)
-71(	142)	39(	105)
-69(	127)	40(	60)
-66(	48)	46(	91)
-64(	13)	55(	125)

Stem	Leaf	#	Boxplot
5	5	1	
4	06	2	
3	3445589	7	
2	0011344567	10	
1	00112234444666777799	20	+-----+
0	000011122455556668999	22	| |
-0	9988876665433321	16	| |
-1	99988777655433222111100	23	*--+--*
-2	98777765543222210	17	+-----+
-3	999877444221110	15	
-4	99977441	8	
-5	8844300	7	
-6	964320	6	
-7	1	1	
-8			
-9	7	1	0

----+----+----+----+---

Multiply Stem.Leaf by 10**+1

```
/* Sas Program to Analyze Table 1.4  */

Options ls=90 ps=60 nodate pagno=1;
Title1 'Tablet Potencies';
Data A;
input @@ wi potency;
cards;     /* data entered as frequency & value */
1 90  0 91  2 92  1 93  5 94  1 95  2 96  7 97  10 98  8 99  13 100  17 101  13 102
9 103  0 104  0 105  5 106  4 107  0 108 0 109 2 110
;
Data B;                  /* sets up file of 27 desired percentiles */
cnt=1; p=1; output;
do p=2 to 16 by 2;
 cnt=cnt+1;  output;
end;
do p=20 to 95 by 5;
 cnt=cnt+1; output;
end;
do p=97 to 100 by 3;
 cnt=cnt+1; output;
end;

Proc sort;
by cnt;

Proc univariate plot pctldef=1 data=a;
freq wi;                                  /* desired percentiles */
output out=c pctlpre=P pctlpts=1 2 4 6 8 10 12 14 16 20 25 30 35 40
                              45 50 55 60 65 70 75 80 85 90 95 97 100;
Data d;
set c;                   /* Captures Potencies at desired percentiles */
keep cnt value;
array v[27] P1 -- P100;
do cnt=1 to 27;
 value=v[cnt]+0.5; /* calculates upper end of class intervals for the */
 output;           /* potency values at desired percentiles */
end;              /* file contains 27 records of class intervals */

Proc sort;
by cnt;

Data e;          /* Merges the 27 desired percentile values with their */
merge b d;       /* corresponding upper limit of the class intervals */
by cnt;
keep value p;
label p = Cumulative Percent;
label value = Potency;

Proc print label data=e;
id value;
var p;

Proc Plot nolegend data=e;
Plot p*value='*'/ vaxis = by 10;

run;
quit;
```

SAS OUTPUT FOR ANALYSES OF TABLE 1.4:

Tablet Potencies 1

Univariate Procedure

Variable=POTENCY

Moments

N	100	Sum Wgts	100		
Mean	100.23	Sum	10023		
Std Dev	3.686873	Variance	13.59303		
Skewness	-0.01867	Kurtosis	0.719475		
USS	1005951	CSS	1345.71		
CV	3.678412	Std Mean	0.368687		
T:Mean=0	271.8564	Pr>|T|	0.0001		
Num ^= 0	100	Num > 0	100		
M(Sign)	50	Pr>=|M|	0.0001		
Sgn Rank	2525	Pr>=|S|	0.0001		

Quantiles(Def=1)

100% Max	110	99%	110
75% Q3	102	95%	107
50% Med	100	90%	106
25% Q1	98	10%	95
0% Min	90	5%	94
		1%	90
Range	20		
Q3-Q1	4		
Mode	101		

Extremes

Lowest	Obs	Highest	Obs
90(	1)	102(	13)
92(	3)	103(	14)
93(	4)	106(	17)
94(	5)	107(	18)
95(	6)	110(	21)

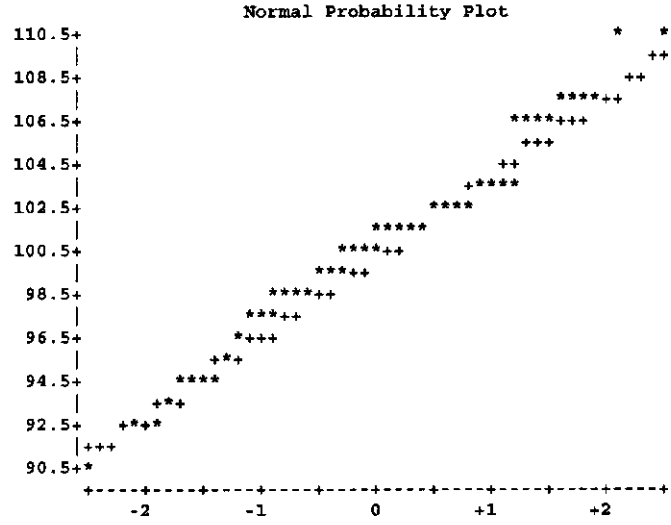
Stem	Leaf	#	Boxplot
110	00	2	0
109			
108			
107	0000	4	|
106	00000	5	|
105			|
104			|
103	000000000	9	|
102	0000000000000	13	+-----+
101	00000000000000000	17	| |
100	0000000000000	13	*--+--*
99	00000000	8	| |
98	0000000000	10	+-----+
97	0000000	7	|
96	00	2	|
95	0	1	|
94	00000	5	|
93	0	1	|
92	00	2	|
91			
90	0	1	0

----+----+----+----+

Tablet Potencies

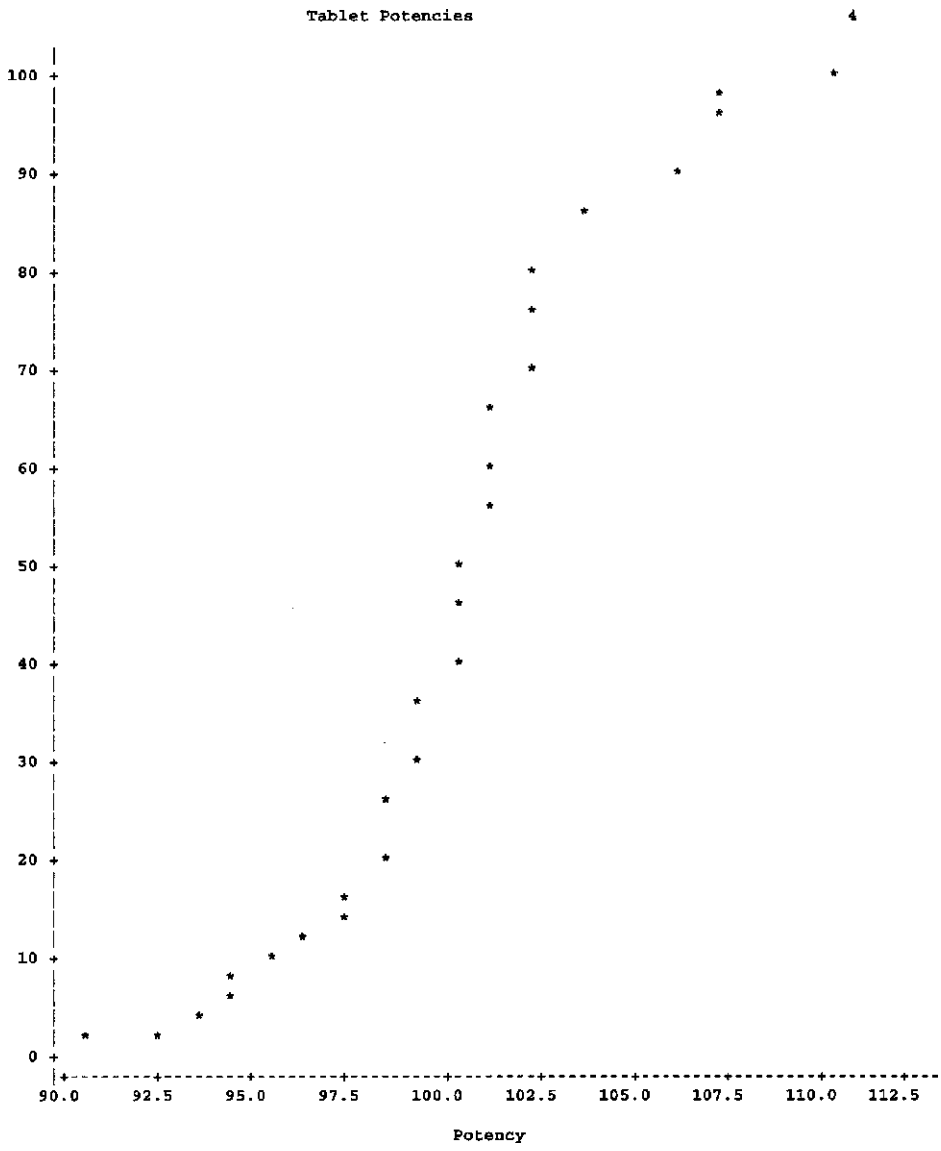
Univariate Procedure

Variable=POTENCY



Tablet Potencies

Potency	Cumulative Percent
90.5	1
92.5	2
93.5	4
94.5	6
94.5	8
95.5	10
96.5	12
97.5	14
97.5	16
98.5	20
98.5	25
99.5	30
99.5	35
100.5	40
100.5	45
100.5	50
101.5	55
101.5	60
101.5	65
102.5	70
102.5	75
102.5	80
103.5	85
106.5	90
107.5	95
107.5	97
110.5	100


Tablet Potencies
100
90
80
70
60
50
40
30
20
10
0
90.0
92.5
95.0
97.5
100.0
102.5
105.0
107.5
110.0
112.5
Potency

```
/* Sas Program to Analyze Table 5.1  */

Options ls=90 ps=60 nodate pagno=1;
Title1 'Tablet Potencies';
Title3 'Calculation of 95% Confidence Interval on the Mean';

Data A;
input @@ potency;
cards;      /* data */
101.8 102.6 99.8 104.9 103.8 104.5 100.7 106.3 100.6 105.0
;

Proc Means noprint;      /* Calculates mean, N and standard deviation */
Var potency;
Output out=mn N=N Mean=Mean Std=Std;          /* makes results available in
data set mn */

Data A;
set mn;                                  /* uses results from Proc Means */
df=N-1;                                  /* degrees of freedom */
alpha = 0.05;                            /* interval will have 1-alpha = 95%
coverage */
tval = tinv (1-alpha/2,df);
Ci_low = mean - tval*std/sqrt(N);
Ci_hi = mean + tval*std/sqrt(N);
label tval=critical t-value;
label std=standard deviation;
label Ci_low= Lower Confidence Limit;
label Ci_hi= Upper Confidence Limit;


Proc print label data = a;
Id mean;
var std N df alpha tval std Ci_low Ci_hi;
format tval std F4.2 Ci_low Ci_hi F7.2;

run;
quit;
```

SAS OUTPUT FOR ANALYSES OF TABLE 5.1:

Tablet Potencies 1

Calculation of 95% Confidence Interval on the Mean

MEAN	standard deviation	N	DF	ALPHA	critical t-value	standard deviation	Lower Confidence Limit	Upper Confidence Limit
103	2.22	10	9	0.05	2.26	2.22	101.41	104.59

```
/* Sas Program to Analyze Table 5.9  */

Options ls=90 ps=60 nodate pagno=1;

Title1 'Tablet Percent Dissolution After 15 Minutes';
Title3 'Two-Sided, Independent Group t-Test';

Data A;
input Form_A Form_B;

cards;     /* data */
68      74
84      71
81      79
85      63
75      80
69      61
80      69
76      72
79      80
74      65
;

Proc Print;
id Form_A;
Var Form_B;

Data B;       /* Formats values for t-test */
set A;
keep form percent;
Form='A'; percent=Form_A; output;
Form='B'; percent=Form_B; output;

Proc TTest;
Class Form;
Var percent;

run;
quit;
```

SAS OUTPUT FOR ANALYSES OF TABLE 5.9:

Tablet Percent Dissolution After 15 Minutes 1

Two-Sided, Independent Group t-Test

FORM_A	FORM_B
68	74
84	71
81	79
85	63
75	80
69	61
80	69
76	72
79	80
74	65

Tablet Percent Dissolution After 15 Minutes 2

Two-Sided, Independent Group t-Test

TTEST PROCEDURE

Variable: PERCENT

FORM	N	Mean	Std Dev	Std Error	Minimum	Maximum
A	10	77.10000000	5.78215646	1.82847842	68.00000000	85.00000000
B	10	71.40000000	6.97933458	2.20705938	61.00000000	80.00000000

Variances	T	DF	Prob>|T|
Unequal	1.9888	17.4	0.0627
Equal	1.9888	18.0	0.0621

For H0: Variances are equal, F' = 1.46 DF = (9,9) Prob>F' = 0.5840

```
/* Sas Program to Analyze Table 5.11  */

Options ls=90 ps=60 nodate pagno=1;

Title1 'Analysis of Variance for Area Under the Curve from a Bioavailability
Study';

Data A;
input Animal Form_A Form_B;
ratio=Form_A/Form_B;

cards;     /* data */
1      136      166
2      168      184
3      160      193
4      94      105
5      200      198
6      174      197
;

Proc Print;
id Animal ;
Var Form_A Form_B Ratio;

Data B;       /* Formats values for test */
set A;
keep animal form type area;

Type='Diffrnce'; Form='A';          area=Form_A;   output;
Type='Diffrnce'; Form='B';          area=Form_B;   output;
Type='Ratio';    Form='A/B';        area=ratio;    output;
Type='Ratio';    Form='Expected';   area=1;        output;

Proc Sort;
By Type

Proc Anova Data=B;
Class Animal Form;
Model Area=Animal Form;
Means Form;
By Type;

run;
quit;
```

SAS OUTPUT FOR ANALYSES OF TABLE 5.11:

Analysis of Variance for Area Under the Curve from a Bioavailability Study 1

ANIMAL	FORM_A	FORM_B	RATIO
1	136	166	0.81928
2	168	184	0.91304
3	160	193	0.82902
4	94	105	0.89524
5	200	198	1.01010
6	174	197	0.88325

Analysis of Variance for Area Under the Curve from a Bioavailability Study 2

TYPE=Diffrnce

Analysis of Variance Procedure
Class Level Information

Class	Levels	Values
ANIMAL	6	1 2 3 4 5 6
FORM	2	A B

Number of observations in data set = 12

Analysis of Variance for Area Under the Curve from a Bioavailability Study 3

TYPE=Diffrnce

Analysis of Variance Procedure

Dependent Variable: AREA

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	6	13656.16666667	2276.02777778	26.92	0.0012
Error	5	422.75000000	84.55000000		
Corrected Total	11	14078.91666667			

R-Square	C.V.	Root MSE	AREA Mean
0.969973	5.586901	9.19510739	164.58333333

Source	DF	Anova SS	Mean Square	F Value	Pr > F
ANIMAL	5	12629.41666667	2525.88333333	29.87	0.0010
FORM	1	1026.75000000	1026.75000000	12.14	0.0176

Analysis of Variance for Area Under the Curve from a Bioavailability Study 4

TYPE=Diffrnce

Analysis of Variance Procedure

Level of FORM	N	AREA Mean	AREA SD
A	6	155.333333	36.5002283
B	6	173.833333	35.7514568

Analysis of Variance for Area Under the Curve from a Bioavailability Study 5

TYPE=Ratio

Analysis of Variance Procedure
Class Level Information

Class	Levels	Values
ANIMAL	6	1 2 3 4 5 6
FORM	2	A E

Number of observations in by group = 12

Analysis of Variance for Area Under the Curve from a Bioavailability Study 6

TYPE=Ratio

Analysis of Variance Procedure

Dependent Variable: AREA

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	6	0.04708292	0.00784715	3.31	0.1052
Error	5	0.01186634	0.00237327		
Corrected Total	11	0.05894926			

R-Square	C.V.	Root MSE	AREA Mean
0.798702	5.150647	0.04871621	0.94582700

Source	DF	Anova SS	Mean Square	F Value	Pr > F
ANIMAL	5	0.01186634	0.00237327	1.00	0.5000
FORM	1	0.03521657	0.03521657	14.84	0.0120

Analysis of Variance for Area Under the Curve from a Bioavailability Study 7

```
                                TYPE=Ratio

                        Analysis of Variance Procedure

Level of                ------------AREA------------
FORM            N               Mean                SD

A               6       0.89165399          0.06889512
E               6       1.00000000          0.00000000
```

```
/* Sas Program to Analyze Table 7.5  */

Options ls=90 ps=60 nodate pagno=1;
Title1 'Tablet Stability Based on Assay';

Data A;
input @@ Month Assay;
cards;      /* data */
0 51   0 51   0 53    3 51   3 50    3 52    6 50     6 52    6 48
9 49   9 51   9 51   12 49  12 48   12 47   18 47   18 45   18 49
;

Proc Sort Data=A;
By Month;

Proc Print;
id Month;
var Assay;

Proc Means N Mean Var noprint; /* Calculates mean of Months in assay data */
var month;
output out=mndat N=Nx Mean=MNx Var=Varx ;

Proc Reg outest=est Data=A;                  /*Regression Analysis*/
Model Assay = Month/clm;

Data B;         /* Months 1-60 with mean for months in assay data */
set mndat;
Keep Month N MNx SSQx;
SSQx=17*Varx;      /*sum of squares of deviations from mean for months */
N=Nx;
do Month=1 to 60;
output;
end;

Proc Sort Data=B;
```

```
By Month;

Data C;                 /* Months 1-60 with slope & intercept values */
set est;
slope=Month;
do i=1 to 60;
Month=i;
output;
end;

Proc sort;
by Month;

Data D;
merge B C;
by Month;
T=TINV(0.975,N-2);          /* t-value for 95% confidence inteval */
Predict=Intercep + Slope*Month;
CI95_Lo=predict-t*_RMSE_*sqrt((1/N) + ((month-MNx)**2/SSQx));
CI95_Hi=predict+t*_RMSE_*sqrt((1/N) + ((month-MNx)**2/SSQx));

Proc Print;
id Month;
var Predict CI95_Lo CI95_Hi;

Data E;
set D A;
Proc Plot data=E;
Plot Assay*Month='*' Predict*Month='.' CI95_Hi*Month='-'
   CI95_Lo*Month='-' / overlay vaxis=30 32 34 36 38 40 42 44 46 48 50 52 54;

run;
quit;
```

SAS OUTPUT FOR ANALYSES OF TABLE 7.5 (Partial Printout):

First page of output is a listing of the Month and Assay values in Table 7.5

Tablet Stability Based on Assay 2

Model: MODEL1
Dependent Variable: ASSAY

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Prob>F
Model	1	44.80000	44.80000	24.548	0.0001
Error	16	29.20000	1.82500		
C Total	17	74.00000			

Root MSE	1.35093	R-square	0.6054
Dep Mean	49.66667	Adj R-sq	0.5807
C.V.	2.71998		

Parameter Estimates

Variable	DF	Parameter Estimate	Standard Error	T for H0: Parameter=0	Prob > |T|
INTERCEP	1	51.800000	0.53552378	96.728	0.0001
MONTH	1	-0.266667	0.05382216	-4.955	0.0001

Obs	Dep Var ASSAY	Predict Value	Std Err Predict	Lower95% Mean	Upper95% Mean	Residual
1	51.0000	51.8000	0.536	50.6647	52.9353	-0.8000
2	51.0000	51.8000	0.536	50.6647	52.9353	-0.8000
3	53.0000	51.8000	0.536	50.6647	52.9353	1.2000
4	51.0000	51.0000	0.417	50.1162	51.8838	2.83E-15
5	50.0000	51.0000	0.417	50.1162	51.8838	-1.0000
6	52.0000	51.0000	0.417	50.1162	51.8838	1.0000
7	50.0000	50.2000	0.336	49.4875	50.9125	-0.2000
8	52.0000	50.2000	0.336	49.4875	50.9125	1.8000
9	48.0000	50.2000	0.336	49.4875	50.9125	-2.2000
10	49.0000	49.4000	0.323	48.7154	50.0846	-0.4000
11	51.0000	49.4000	0.323	48.7154	50.0846	1.6000
12	51.0000	49.4000	0.323	48.7154	50.0846	1.6000
13	49.0000	48.6000	0.384	47.7852	49.4148	0.4000
14	48.0000	48.6000	0.384	47.7852	49.4148	-0.6000
15	47.0000	48.6000	0.384	47.7852	49.4148	-1.6000
16	47.0000	47.0000	0.625	45.6743	48.3257	2.78E-15
17	45.0000	47.0000	0.625	45.6743	48.3257	-2.0000
18	49.0000	47.0000	0.625	45.6743	48.3257	2.0000

Sum of Residuals	0
Sum of Squared Residuals	29.2000
Predicted Resid SS (Press)	38.0436

Tablet Stability Based on Assay 3

MONTH	PREDICT	CI95_LO	CI95_HI
1	51.5333	50.4876	52.5791
2	51.2667	50.3053	52.2281
3	51.0000	50.1162	51.8838
4	50.7333	49.9185	51.5482
5	50.4667	49.7098	51.2235
6	50.2000	49.4875	50.9125
7	49.9333	49.2487	50.6179
8	49.6667	48.9917	50.3417
9	49.4000	48.7154	50.0846
10	49.1333	48.4208	49.8459
11	48.8667	48.1098	49.6235
12	48.6000	47.7852	49.4148
13	48.3333	47.4495	49.2171
14	48.0667	47.1053	49.0281
15	47.8000	46.7543	48.8457
16	47.5333	46.3981	48.6686
17	47.2667	46.0378	48.4955
18	47.0000	45.6743	48.3257
19	46.7333	45.3083	48.1584
20	46.4667	44.9401	47.9932
21	46.2000	44.5704	47.8296
22	45.9333	44.1992	47.6675
23	45.6667	43.8269	47.5064
24	45.4000	43.4536	47.3464
25	45.1333	43.0796	47.1871
26	44.8667	42.7048	47.0285
27	44.6000	42.3295	46.8705
28	44.3333	41.9536	46.7130
29	44.0667	41.5773	46.5560
30	43.8000	41.2007	46.3993
31	43.5333	40.8237	46.2430
32	43.2667	40.4463	46.0870
33	43.0000	40.0688	45.9312
34	42.7333	39.6910	45.7757
35	42.4667	39.3129	45.6204
36	42.2000	38.9347	45.4653
37	41.9333	38.5563	45.3103
38	41.6667	38.1778	45.1555
39	41.4000	37.7991	45.0009
40	41.1333	37.4203	44.8463
41	40.8667	37.0414	44.6919
42	40.6000	36.6624	44.5376
43	40.3333	36.2833	44.3834
44	40.0667	35.9040	44.2293
45	39.8000	35.5248	44.0752
46	39.5333	35.1454	43.9213
47	39.2667	34.7659	43.7674
48	39.0000	34.3864	43.6136
49	38.7333	34.0069	43.4598
50	38.4667	33.6272	43.3061
51	38.2000	33.2476	43.1524
52	37.9333	32.8678	42.9988
53	37.6667	32.4881	42.8453
.	.	.	.
.	.	.	.
60	35.8000	29.8286	41.7714

Last page of output is a low-resolution graph of Assay values, Predicted values and the upper and lower confidence intervals vs. Month.

```
/* Sas Program to Analyze Table 7.6  */

Options ls=90 ps=60 nodate pagno=1;
Title1 'Weighted (1/X**2) Linear Regression of Spectrophotometric Data';

Data A;
input @@ ConcX ODy;
w=(1/ConcX)**2;

cards;      /* data */
5 0.105 5 0.098 10 0.201 10 0.194 25 0.495 25 0.508 50 0.983 50
1.009 100 1.964 100 2.013;

Proc Print;
id ConcX;
var ODy w;

Proc Reg Data=A;                    /*Regression Analysis*/
Model ODy = ConcX;
weight w;

run;
quit;
```

SAS OUTPUT FOR ANALYSES OF TABLE 7.6:

Weighted (1/X**2) Linear Regression of Spectrophotometric Data 1

CONCX	ODY	W
5	0.105	0.0400
5	0.098	0.0400
10	0.201	0.0100
10	0.194	0.0100
25	0.495	0.0016
25	0.508	0.0016
50	0.983	0.0004
50	1.009	0.0004
100	1.964	0.0001
100	2.013	0.0001

```
          Weighted (1/X**2) Linear Regression of Spectrophotometric Data          2

Model: MODEL1
Dependent Variable: ODY

                              Analysis of Variance

                                   Sum of          Mean
Source                    DF      Squares        Square      F Value       Prob>F

Model                      1      0.00187       0.00187     8188.538       0.0001
Error                      8 1.8284045E-6 2.2855057E-7
C Total                    9      0.00187

    Root MSE          0.00048     R-square        0.9990
    Dep Mean          0.14270     Adj R-sq        0.9989
    C.V.              0.33502

                           Parameter Estimates

                      Parameter       Standard    T for H0:
Variable  DF           Estimate          Error   Parameter=0    Prob > |T|

INTERCEP   1          0.001656     0.00215007         0.770        0.4633
CONCX      1          0.019860     0.00021948        90.491        0.0001
```

```
/* Sas Program to Analyze Table 7.8  */

Options ls=90 ps=60 nodate pagno=1;
Title1 'Nonlinear Regresssion of Stability Data';

Data A;
Input Time Conc;
Cards;            /* Data */
1 63
2 34
3 22
;

Proc NLIN Data=A;
parameters C0=100 60 K=0.1 1;    /* Possible starting values for C0 and K */
model Conc=C0*exp(-K*Time);

Run;
Quit;
```

SAS OUTPUT OF ANALYSES OF TABLE 7.8:

Nonlinear Regresssion of Stability Data 1

Non-Linear Least Squares Grid Search Dependent Variable CONC

C0	K	Sum of Squares
60.000000	0.100000	808.552311
100.000000	0.100000	5759.703593
60.000000	1.000000	2706.292436
100.000000	1.000000	1395.672757

Non-Linear Least Squares Iterative Phase Dependent Variable CONC Method: Gauss-Newton

Iter	C0	K	Sum of Squares
0	60.000000	0.100000	808.552311
1	87.927439	0.441778	49.229548
2	106.998026	0.555363	7.246645
3	109.207951	0.558231	5.717857
4	109.221748	0.558272	5.717825
5	109.221925	0.558273	5.717825

NOTE: Convergence criterion met.

Non-Linear Least Squares Summary Statistics Dependent Variable CONC

Source	DF	Sum of Squares	Mean Square
Regression	2	5603.2821747	2801.6410874
Residual	1	5.7178253	5.7178253
Uncorrected Total	3	5609.0000000	
(Corrected Total)	2	888.6666667	

Parameter	Estimate	Asymptotic Std. Error	Asymptotic 95 % Confidence Interval Lower	Upper
C0	109.2219253	8.5009601325	1.2087258208	217.23512471
K	0.5582728	0.0515179098	-0.0963137380	1.21285939

Asymptotic Correlation Matrix

Corr	C0	K
C0	1	0.9118934069
K	0.9118934069	1

```
/* Sas Program to Analyze Table 8.9  */

Options ls=90 ps=60 nodate pagno=1;
Title1 'Two-Way ANOVA of Tablet Dissolution Results';

Data A;
Input Lab GenericA GenericB Standard;
Keep Lab Tablet Percent;          /* creates 3 records for each lab */

Tablet='Std'; Percent=Standard;
Output;                           /* record with Standard results */

Tablet='A'; Percent=GenericA;
Output;                           /* record with GenericA results */

Tablet='B'; Percent=GenericB;
Output;                           /* record with GenericB results */

Cards;                            /* Data */
1       89       83       94
2       93       75       78
3       87       75       89
4       80       76       85
5       80       77       84
6       87       73       84
7       82       80       75
8       68       77       75
;

Proc Print;           /* Data reformatted for ANOVA */
Id Lab;
Var Tablet Percent;

Proc ANOVA;
Class Lab Tablet;          /* Lab & Tablet are categorical variables */
Model Percent = Lab Tablet;
Means Tablet/ Tukey T;    /* Tukey & t-test comparisons of Tablet means*/

Run;
Quit;
```

SAS OUTPUT FOR ANALYSES OF TABLE 8.9:

Two-Way ANOVA of Tablet Dissolution Results 1

LAB	TABLET	PERCENT
1	GenA	89
1	GenB	83
1	Std	94
2	GenA	93
2	GenB	75
2	Std	78
3	GenA	87
3	GenB	75
3	Std	89
4	GenA	80
4	GenB	76
4	Std	85
5	GenA	80
5	GenB	77
5	Std	84
6	GenA	87
6	GenB	73
6	Std	84
7	GenA	82
7	GenB	80
7	Std	75
8	GenA	68
8	GenB	77
8	Std	75

Two-Way ANOVA of Tablet Dissolution Results 2

Analysis of Variance Procedure
Class Level Information

Class	Levels	Values
LAB	8	1 2 3 4 5 6 7 8
TABLET	3	GenA GenB Std

Number of observations in data set = 24

Two-Way ANOVA of Tablet Dissolution Results 3

Analysis of Variance Procedure

Dependent Variable: PERCENT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	9	592.16666667	65.79629630	2.27	0.0818
Error	14	405.66666667	28.97619048		
Corrected Total	23	997.83333333			

R-Square	C.V.	Root MSE	PERCENT Mean
0.593452	6.638792	5.38295369	81.08333333

Source	DF	Anova SS	Mean Square	F Value	Pr > F
LAB	7	391.83333333	55.97619048	1.93	0.1394
TABLET	2	200.33333333	100.16666667	3.46	0.0602

Two-Way ANOVA of Tablet Dissolution Results 4

Analysis of Variance Procedure

T tests (LSD) for variable: PERCENT

NOTE: This test controls the type I comparisonwise error rate not the experimentwise error rate.

Alpha= 0.05 df= 14 MSE= 28.97619
Critical Value of T= 2.14
Least Significant Difference= 5.7726

Means with the same letter are not significantly different.

T Grouping	Mean	N	TABLET
A	83.250	8	GenA
A			
A	83.000	8	Std
B	77.000	8	GenB

Two-Way ANOVA of Tablet Dissolution Results 5

Analysis of Variance Procedure

Tukey's Studentized Range (HSD) Test for variable: PERCENT

NOTE: This test controls the type I experimentwise error rate, but generally has a higher type II error rate than REGWQ.

Alpha= 0.05 df= 14 MSE= 28.97619
Critical Value of Studentized Range= 3.701
Minimum Significant Difference= 7.0444

Means with the same letter are not significantly different.

Tukey Grouping	Mean	N	TABLET
A	83.250	8	GenA
A			
A	83.000	8	Std
A			
A	77.000	8	GenB

```
/* Sas Program to Analyze Table 8.12  */

Options ls=85 ps=60 nodate pagno=1;
Title1 'Two-Way ANOVA of Replicated Dissolution Results';

Data A;
Input @@ Lab GenericA GenericB Standard;
Keep Lab Drug Percent;      /* creates 3 records for each record in data */
Drug='GenA';
Percent=GenericA;
Output;                     /* record with Generic A results */
Drug='GenB';
Percent=GenericB;
 Output;                    /* record with Generic B results */
Drug='Std ';
Percent=Standard;
Output;                     /* record with Standard results */

Cards;                      /* Data */
1      87      81      93   1      91      85      95
2      90      74      74   2      96      76      82
3      84      72      84   3      90      78      94
4      75      73      81   4      85      79      89
5      77      76      80   5      83      78      88
6      85      70      80   6      89      76      88
7      79      74      71   7      85      86      79
8      65      73      70   8      71      81      80
;

Proc Sort;
By lab Drug;

Proc Print;           /* Data reformatted for ANOVA */
Id Lab;
Var Drug Percent;

Proc ANOVA;
Class Lab Drug;
Model Percent = Lab Drug Lab*Drug;   /* Lab*Drug is interaction term */
Test H=Drug E=Lab*Drug;              /* Constructs F-test for Drug */

Run;
Quit;
```

SAS OUTPUT FOR ANALYSES OF TABLE 8.12:

(Page 1 Printout of Data not Shown)

Two-Way ANOVA of Replicated Dissolution Results 2

Analysis of Variance Procedure

Class Level Information

Class	Levels	Values
LAB	8	1 2 3 4 5 6 7 8
DRUG	3	GenA GenB Std

Number of observations in data set = 48

Two-Way ANOVA of Replicated Dissolution Results 3

Analysis of Variance Procedure

Dependent Variable: PERCENT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	23	1995.66666667	86.76811594	3.54	0.0016
Error	24	588.00000000	24.50000000		
Corrected Total	47	2583.66666667			

R-Square	C.V.	Root MSE	PERCENT Mean
0.772416	6.104519	4.94974747	81.08333333

Source	DF	Anova SS	Mean Square	F Value	Pr > F
LAB	7	783.66666667	111.95238095	4.57	0.0023
DRUG	2	400.66666667	200.33333333	8.18	0.0020
LAB*DRUG	14	811.33333333	57.95238095	2.37	0.0308

Tests of Hypotheses using the Anova MS for LAB*DRUG as an error term

Source	DF	Anova SS	Mean Square	F Value	Pr > F
DRUG	2	400.66666667	200.33333333	3.46	0.0602

```
/* Sas Program to Analyze Table 8.18  */


Options ls=85 ps=60 nodate pagno=1;
Title1 'Analysis of Covariance to Compare Two Methods';

Data A;
Input @@ Method Material Product;
Cards;            /* Data */
1 98.4 98.0  1 98.6 97.8  1 98.6 98.5  1 99.2 97.4
2 98.7 97.6  2 99.0 95.4  2 99.3 96.1  2 98.4 96.1
;

Proc Print;
ID Method;
Var Material Product;

Proc GLM data=A;
Title3 'Separate Lines';
Class Method;
Model Product = Material Method Material*Method;
Estimate 'Intercept I'  Intercept 1 Method 1 0 Material*Method 0 0;
Estimate 'Intercept II' Intercept 1 Method 0 1 Material*Method 0 0;
Estimate 'Slope I' Intercept 0 Method 0 0 Material 1 Material*Method 1 0;
Estimate 'Slope II' Intercept 0 Method 0 0 Material 1 Material*Method 0 1;

Proc GLM data=A;
Title3 'Parallel Lines';
Class Method;
Model Product = Material Method;
Estimate 'Intercept I'  Intercept 1 Method 1 0;
Estimate 'Intercept II' Intercept 1 Method 0 1;
Estimate 'Common Slope' Intercept 0 Method 0 0 Material 1;
Lsmeans Method/stderr pdiff;

Run;
Quit;
```

SAS OUTPUT FOR ANALYSES OF TABLE 8.18:

Analysis of Covariance to Compare Two Methods 1

METHOD	MATERIAL	PRODUCT
1	98.4	98.0
1	98.6	97.8
1	98.6	98.5
1	99.2	97.4
2	98.7	97.6
2	99.0	95.4
2	99.3	96.1
2	98.4	96.1

Analysis of Covariance to Compare Two Methods 2

Separate Lines

General Linear Models Procedure
Class Level Information

Class	Levels	Values
METHOD	2	1 2

Number of observations in data set = 8

Analysis of Covariance to Compare Two Methods 3

Separate Lines

General Linear Models Procedure

Dependent Variable: PRODUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	3	5.82575000	1.94191667	2.92	0.1639
Error	4	2.66300000	0.66575000		
Corrected Total	7	8.48875000			

R-Square	C.V.	Root MSE	PRODUCT Mean
0.686291	0.840196	0.81593505	97.11250000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
MATERIAL	1	1.54006579	1.54006579	2.31	0.2029
METHOD	1	4.27896199	4.27896199	6.43	0.0643
MATERIAL*METHOD	1	0.00672222	0.00672222	0.01	0.9248

Source	DF	Type III SS	Mean Square	F Value	Pr > F
MATERIAL	1	0.54450000	0.54450000	0.82	0.4169
METHOD	1	0.00788424	0.00788424	0.01	0.9186
MATERIAL*METHOD	1	0.00672222	0.00672222	0.01	0.9248

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
Intercept I	188.400000	1.40	0.2331	134.221935
Intercept II	168.790000	1.40	0.2330	120.234335
Slope I	-0.916667	-0.67	0.5372	1.359892
Slope II	-0.733333	-0.60	0.5791	1.216324

Analysis of Covariance to Compare Two Methods 4

Parallel Lines

General Linear Models Procedure
Class Level Information

Class	Levels	Values
METHOD	2	1 2

Number of observations in data set = 8

Analysis of Covariance to Compare Two Methods 5

Parallel Lines

General Linear Models Procedure

Dependent Variable: PRODUCT

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	2	5.81902778	2.90951389	5.45	0.0555
Error	5	2.66972222	0.53394444		
Corrected Total	7	8.48875000			

R-Square	C.V.	Root MSE	PRODUCT Mean
0.685499	0.752442	0.73071502	97.11250000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
MATERIAL	1	1.54006579	1.54006579	2.88	0.1502
METHOD	1	4.27896199	4.27896199	8.01	0.0366

Source	DF	Type III SS	Mean Square	F Value	Pr > F
MATERIAL	1	0.53777778	0.53777778	1.01	0.3616
METHOD	1	4.27896199	4.27896199	8.01	0.0366

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
Intercept I	178.347222	2.23	0.0766	80.1359137
Intercept II	176.844444	2.20	0.0788	80.2576983
Common Slope	-0.814815	-1.00	0.3616	0.8119056

Analysis of Covariance to Compare Two Methods 6

Parallel Lines

General Linear Models Procedure
Least Squares Means

METHOD	PRODUCT LSMEAN	Std Err LSMEAN	Pr > |T| H0:LSMEAN=0	Pr > |T| H0: LSMEAN1=LSMEAN2
1	97.8638889	0.3703972	0.0001	0.0366
2	96.3611111	0.3703972	0.0001	

```
/* Sas Program to Analyze Table 9.2  */

Options ls=90 ps=60 nodate pagno=1;
Title1 'Factorial Experiment on Tablet Thickness';
Title3 'Factors:  A = Stearate    B = Drug      C = Starch';

Data A;
input A B C RESPONSE;
Cards;
0.5 60  30 475
1.5 60  30 487
0.5 120 30 421
1.5 120 30 426
0.5 60  50 525
1.5 60  50 546
0.5 120 50 472
1.5 120 50 522 ;

Proc GLM;
Class A B C;
model RESPONSE = A B C A*B A*C B*C A*B*C;
Estimate 'A effect' A -1 1;
Estimate 'B effect' B -1 1;
Estimate 'C effect' C -1 1;
Estimate 'AB effect' A*B 1 -1 -1 1 /divisor=2;
Estimate 'AC effect' A*C 1 -1 -1 1 /divisor=2;
Estimate 'BC effect' B*C 1 -1 -1 1 /divisor=2;
Estimate 'ABC effect' A*B*C -1 1 1 -1 1 -1 -1 1 /divisor=4;

Proc GLM;                  /* Error = AB + BC + ABC */
Class A B C;
model RESPONSE = A B C A*C;
Estimate 'A effect' A -1 1;
Estimate 'B effect' B -1 1;
Estimate 'C effect' C -1 1;
Estimate 'AC effect' A*C 1 -1 -1 1 /divisor=2;
run;
quit;
```

SAS OUTPUT FOR ANALYSIS OF TABLE 9.2

```
                    Factorial Experiment on Tablet Thickness                    1

                  Factors:  A = Stearate    B = Drug      C = Starch

                          General Linear Models Procedure
                             Class Level Information

                            Class    Levels    Values

                            A             2    0.5 1.5
                            B             2    60 120
                            C             2    30 50

                        Number of observations in data set = 8
```

Factorial Experiment on Tablet Thickness 2

Factors: A = Stearate B = Drug C = Starch

General Linear Models Procedure

Dependent Variable: RESPONSE

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	14535.50000000	2076.50000000	.	.
Error	0	.	.		
Corrected Total	7	14535.50000000			

R-Square	C.V.	Root MSE	RESPONSE Mean
1.000000	0	0	484.25000000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
A	1	968.00000000	968.00000000	.	.
B	1	4608.00000000	4608.00000000	.	.
C	1	8192.00000000	8192.00000000	.	.
A*B	1	60.50000000	60.50000000	.	.
A*C	1	364.50000000	364.50000000	.	.
B*C	1	180.50000000	180.50000000	.	.
A*B*C	1	162.00000000	162.00000000	.	.

Source	DF	Type III SS	Mean Square	F Value	Pr > F
A	1	968.00000000	968.00000000	.	.
B	1	4608.00000000	4608.00000000	.	.
C	1	8192.00000000	8192.00000000	.	.
A*B	1	60.50000000	60.50000000	.	.
A*C	1	364.50000000	364.50000000	.	.
B*C	1	180.50000000	180.50000000	.	.
A*B*C	1	162.00000000	162.00000000	.	.

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
A effect	22.0000000	99999.99	0.0	0
B effect	-48.0000000	99999.99	0.0	0
C effect	64.0000000	99999.99	0.0	0
AB effect	5.5000000	99999.99	0.0	0
AC effect	13.5000000	99999.99	0.0	0
BC effect	9.5000000	99999.99	0.0	0
ABC effect	9.0000000	99999.99	0.0	0

Factorial Experiment on Tablet Thickness 3

Factors: A = Stearate B = Drug C = Starch

General Linear Models Procedure
Class Level Information

Class	Levels	Values
A	2	0.5 1.5
B	2	60 120
C	2	30 50

Number of observations in data set = 8

Factorial Experiment on Tablet Thickness 4

Factors: A = Stearate B = Drug C = Starch

General Linear Models Procedure

Dependent Variable: RESPONSE

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	4	14132.50000000	3533.12500000	26.30	0.0113
Error	3	403.00000000	134.33333333		
Corrected Total	7	14535.50000000			

R-Square	C.V.	Root MSE	RESPONSE Mean
0.972275	2.393438	11.59022577	484.25000000

Source	DF	Type I SS	Mean Square	F Value	Pr > F
A	1	968.00000000	968.00000000	7.21	0.0748
B	1	4608.00000000	4608.00000000	34.30	0.0099
C	1	8192.00000000	8192.00000000	60.98	0.0044
A*C	1	364.50000000	364.50000000	2.71	0.1981

Source	DF	Type III SS	Mean Square	F Value	Pr > F
A	1	968.00000000	968.00000000	7.21	0.0748
B	1	4608.00000000	4608.00000000	34.30	0.0099
C	1	8192.00000000	8192.00000000	60.98	0.0044
A*C	1	364.50000000	364.50000000	2.71	0.1981

Parameter	Estimate	T for H0: Parameter=0	Pr > |T|	Std Error of Estimate
A effect	22.0000000	2.68	0.0748	8.19552724
B effect	-48.0000000	-5.86	0.0099	8.19552724
C effect	64.0000000	7.81	0.0044	8.19552724
AC effect	13.5000000	1.65	0.1981	8.19552724

```
/* Sas Program: Repeated Measures (Split-Plot) ANOVA - Table 11.22*/

   Options ls=95 ps=58 nodate pagno=1;
   Titlel 'Split-Plot ANOVA of Table 11.22 Data';

   Data A;
   Input Drug $ Patient Baseline WK2 WK4 WK6 WK8;
   Array R[4] WK2 WK4 WK6 WK8;
   Do i=1 to 4;
   R[i]=R[i]-Baseline;
   End;
   Cards;
   Standard 1      102      106      97      86      93
   Standard 2      105      103      102     99      101
   Standard 5      99       95       96      88      88
   Standard 9      105      102      102     98      98
   Standard 13     108      108      101     91      102
   Standard 15     104      101      97      99      97
   Standard 17     106      103      100     97      101
   Standard 18     100      97       96      99      93
   New      3      98       96       97      82      91
   New      4      106      100      98      96      93
   New      6      102      99       95      93      93
   New      8      102      94       97      98      85
   New      10     98       93       84      87      83
   New      11     108      110      95      92      88
   New      12     103      96       99      88      86
   New      14     101      96       96      93      89
   New      16     107      107      96      93      97  ;

   Proc Print;
   Title3 'Change From Baseline';
   Id Drug Patient;
   Var WK2 WK4 WK6 WK8;

   Data B;          /* Format to : Drug Patient Week Change */
   Set A;
   T1=2; T2=4; T3=6; T4=8;
   Array W[4] T1-T4;
   Array C[4] WK2 WK4 WK6 WK8;
   Do I=1 to 4;
   Week=W[I];   Change=C[I];
   Output;
   End;

   Proc GLM Data=B;
   Class Week Drug Patient ;
   Model change = Week Drug Patient(Drug) Week*Drug/SS2 SS3;
   Test H=Drug E=Patient(Drug);

   Run;
   Quit;
```

SAS OUTPUT FOR ANALYSES OF TABLE 11.22 DATA:

Split-Plot ANOVA of Table 11.15 Data 1

Change From Baseline

DRUG	PATIENT	WK2	WK4	WK6	WK8
Standard	1	4	-5	-16	-9
Standard	2	-2	-3	-6	-4
Standard	5	-4	-3	-11	-11
Standard	9	-3	-3	-7	-7
Standard	13	0	-7	-17	-6
Standard	15	-3	-7	-5	-7
Standard	17	-3	-6	-9	-5
Standard	18	-3	-4	-1	-7
New	3	-2	-1	-16	-7
New	4	-6	-8	-10	-13
New	6	-3	-7	-9	-9
New	8	-8	-5	-4	-17
New	10	-5	-14	-11	-15
New	11	2	-13	-16	-20
New	12	-7	-4	-15	-17
New	14	-5	-5	-8	-12
New	16	0	-11	-14	-10

Split-Plot ANOVA of Table 11.22 Data 2

Change From Baseline

General Linear Models Procedure
Class Level Information

Class	Levels	Values
WEEK	4	2 4 6 8
DRUG	2	New Standard
PATIENT	17	1 2 3 4 5 6 8 9 10 11 12 13 14 15 16 17 18

Number of observations in data set = 68

Split-Plot ANOVA of Table 11.22 Data 3

Change From Baseline

General Linear Models Procedure

Dependent Variable: CHANGE

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	22	1087.35457516	49.42520796	3.35	0.0003
Error	45	663.27777778	14.73950617		
Corrected Total	67	1750.63235294			

R-Square	C.V.	Root MSE	CHANGE Mean
0.621121	-51.69625	3.83920645	-7.42647059

Source	DF	Type II SS	Mean Square	F Value	Pr > F
WEEK	3	669.69117647	223.23039216	15.15	0.0001
DRUG	1	196.16013072	196.16013072	13.31	0.0007
PATIENT(DRUG)	15	171.72222222	11.44814815	0.78	0.6951
WEEK*DRUG	3	49.78104575	16.59368192	1.13	0.3487

Source	DF	Type III SS	Mean Square	F Value	Pr > F
WEEK	3	654.72222222	218.24074074	14.81	0.0001
DRUG	1	196.16013072	196.16013072	13.31	0.0007
PATIENT(DRUG)	15	171.72222222	11.44814815	0.78	0.6951
WEEK*DRUG	3	49.78104575	16.59368192	1.13	0.3487

Tests of Hypotheses using the Type III MS for PATIENT(DRUG) as an error term

Source	DF	Type III SS	Mean Square	F Value	Pr > F
DRUG	1	196.16013072	196.16013072	17.13	0.0009

Note: Type II SS corresponds to results in Table 11.25 However Type III SS is technically more appropriate with the unequal numbers of patients in each Drug group. The slight difference between the Type II and Type III results is only in the Sum of Squares (SS) and, therefore, the Mean Square for Week. The evaluations of interest, Drug and Week*Drug, are equivalent for both Type II and Type III results.

```
/* SAS PROGRAM TO ANALYZE TABLE 12.9 DATA */


Options LS=95 PS=58 Nodate Pageno=1;

Title1 'Determination of Variance Components for Table 12.9 Results';

Data A;
Input Batch $ Tablet Assay1 Assay2 Assay3;

Cards;
A       1       50.6       50.5       50.8
A       2       49.1       48.9       48.5
A       3       51.1       51.1       51.4
B       1       50.1       49.0       49.4
B       2       51.0       50.9       51.6
B       3       50.2       50.0       49.8
C       1       51.4       51.7       51.8
C       2       52.1       52.0       51.4
C       3       51.1       51.9       51.6
D       1       49.0       49.0       48.5
D       2       47.2       47.6       47.6
D       3       48.9       48.5       49.2
;

Proc Print;
Id Batch;
Var Tablet Assay1 Assay2 Assay3;

Data B;                        /* Format Data for Analyses */
Set A;
Array A[3] Assay1 Assay2 Assay3;
Do I=1 to 3;
Assay=A[I];
Output;
End;

Proc Varcomp;
Class Batch Tablet;
Model Assay=Batch Tablet(Batch);

Run;
Quit;
```

SAS OUTPUT FOR ANALYSES OF TABLE 12.9 RESULTS:

Determination of Variance Components for Table 12.9 Results 1

BATCH	TABLET	ASSAY1	ASSAY2	ASSAY3
A	1	50.6	50.5	50.8
A	2	49.1	48.9	48.5
A	3	51.1	51.1	51.4
B	1	50.1	49.0	49.4
B	2	51.0	50.9	51.6
B	3	50.2	50.0	49.8
C	1	51.4	51.7	51.8
C	2	52.1	52.0	51.4
C	3	51.1	51.9	51.6
D	1	49.0	49.0	48.5
D	2	47.2	47.6	47.6
D	3	48.9	48.5	49.2

Determination of Variance Components for Table 12.9 Results 2

Variance Components Estimation Procedure
Class Level Information

Class	Levels	Values
BATCH	4	A B C D
TABLET	3	1 2 3

Number of observations in data set = 36

Determination of Variance Components for Table 12.9 Results 3

MIVQUE(0) Variance Component Estimation Procedure

SSQ Matrix

Source	BATCH	TABLET(BATCH)	Error	ASSAY
BATCH	243.00000000	81.00000000	27.00000000	438.18750000
TABLET(BATCH)	81.00000000	99.00000000	33.00000000	198.62250000
Error	27.00000000	33.00000000	35.00000000	68.70750000

Variance Component	Estimate ASSAY
Var(BATCH)	1.55990741
Var(TABLET(BATCH))	0.69527778
Var(Error)	0.10416667

Note: Variance due to error is the between-assay variance component

```
/* SAS PROGRAM TO ANALYZE TABLE 13.8, DAY 1 DATA TO CONSTRUCT TABLE 13.10 */

Options ls=95 ps=58 nodate pageno=1;
Title1 'Regression Analysis of Table 13.8 Day 1 Results';

Data A;
input X Y1 Y2;  /* Concentration is X, Peak Areas are Y1 & Y2 */
Keep X Y Wt;
Wt = (1/X)**2;   /* Weight by inverse of concentration squared */
Y=Y1;
Output;
Y=Y2;
Output;
Label X = Conc        (X);
Label Y = Peak Area   (Y);
Label Wt = Weight     [1/(X*X)];

Cards;          /* data in order: Conc(X), Rep1(Y1), Rep2(Y2) */
0.05  0.003 0.004
0.20  0.016 0.018
1.00  0.088 0.094
10.00 0.920 0.901
20.00 1.859 1.827
;

Proc Print label;
ID X;
Var Y Wt;

Proc Reg; /* Fit Calibration Line to (X,Y) pairs */
model Y = X;
Weight Wt;

Proc GLM;  /* Analysis to obtain Within Duplicates SS */
Class X;
Model Y=X;
Weight Wt;

Run;
Quit;
```

SAS OUTPUT FOR ANALYSES OF TABLE 13.8, DAY 1 RESULTS:

Regression Analysis of Table 13.8 Day 1 Results 1

Conc (X)	Peak Area (Y)	Weight [1/(X*X)]
0.05	0.003	400.000
0.05	0.004	400.000
0.20	0.016	25.000
0.20	0.018	25.000
1.00	0.088	1.000
1.00	0.094	1.000
10.00	0.920	0.010
10.00	0.901	0.010
20.00	1.859	0.003
20.00	1.827	0.003

Regression Analysis of Table 13.8 Day 1 Results 2

The REG Procedure
Model: MODEL1
Dependent Variable: Y Peak Area (Y)

Weight: Wt Weight [1/(X*X)]

Analysis of Variance

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	1	0.05689	0.05689	1652.71	<.0001
Error	8	0.00027537	0.00003442		
Corrected Total	9	0.05716			

Root MSE	0.00587	R-Square	0.9952
Dependent Mean	0.00453	Adj R-Sq	0.9946
Coeff Var	129.52287		

Parameter Estimates

Variable	Label	DF	Parameter Estimate	Standard Error	t Value	Pr > |t|
Intercept	Intercept	1	-0.00109	0.00024393	-4.46	0.0021
X	Conc (X)	1	0.09154	0.00225	40.65	<.0001

Regression Analysis of Table 13.8 Day 1 Results 3

The GLM Procedure

Class Level Information

Class	Levels	Values
X	5	0.05 0.2 1 10 20

Number of observations 10

Regression Analysis of Table 13.8 Day 1 Results 4

The GLM Procedure

Dependent Variable: Y Peak Area (Y)

Weight: Wt Weight [1/(X*X)]

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	4	0.05689338	0.01422334	262.34	<.0001
Error	5	0.00027109	0.00005422		
Corrected Total	9	0.05716446			

R-Square	Coeff Var	Root MSE	Y Mean
0.995258	162.5539	0.007363	0.004530

Source	DF	Type I SS	Mean Square	F Value	Pr > F
X	4	0.05689338	0.01422334	262.34	<.0001

Source	DF	Type III SS	Mean Square	F Value	Pr > F
X	4	0.05689338	0.01422334	262.34	<.0001

Notes on How to Construct Table 13.10 from SAS Output Pages:

- Intercept and Slope are given on output page 2 under Parameter Estimates.
- Slope DF, SS, MS & F are those listed for Model at top of page 2.
- Error and Total DF, SS & MS (error) are listed at top of page 2.
- Within (duplicates) DF, SS and MS are those listed for Error on page 4.
- Deviations from Regression DF = DF Error (page 2) - DF Error (page 4).
- Deviations from Regression SS = SS Error (page 2) - SS Error (page 4).

```
/* Sas Program to Analyze Table 15.3 Data as Shown in Table 15.4  */

Options ls=90 ps=60 nodate pageno=1;
Title1 'Wilcoxon Signed Rank Test of Paired Tmax Results';

Data A;
Input Subject TmaxA TmaxB;
Diff=TmaxB-TmaxA;              /* calculate the B-A difference */
AbsDiff=Abs(Diff);             /* obtain absolute value of difference */
Dsign=Sign(Diff);               /* determines sign of the difference */
If Diff=0 Then Do;             /* exclude zero differences from analysis */
    AbsDiff=.;
    Dsign=.;
  end;
Label Diff=Difference (B-A);
Label AbsDiff=Absolute Value of Difference;
Label Dsign=Sign;

Cards;
1  2.5  3.5
2  3.0  4.0
3  1.25 2.5
4  1.75 2.0
5  3.5  3.5
6  2.5  4.0
7  1.75 1.5
8  2.25 2.5
9  3.5  3.0
10 2.5  3.0
11 2.0  3.5
12 3.5  4.0
;

Proc Print Label;
ID Subject;
Var TmaxA TmaxB Diff AbsDiff Dsign;

Proc Rank;                  /* rank results by absolute value of difference */
Var AbsDiff;                /* variable AbsDiff will now contain the rank */

Proc Means N Sum;           /* obtain ranksums by sign */
Title3 'Rank Sums for Using Exact Tables';
Var AbsDiff;
Class DSign;
output out=mnsum Sum=;

Data B;
Set mnsum;
If _Type_=0;
N=_Freq_;                    /* get number in analysis */
```

```
Data C;
Set mnsum;
If _Type_=1 and DSign>0;    /* get Ranksum for positive sign */
R=AbsDiff;                  /*AbsDiff has Rank Sum  */

Data D;                     /* calculate large sample approximation */
Title3 'Normal Approximation for Large Samples';
Merge B C;
Z=(Abs(R-N*(N+1)/4))/Sqrt(N*(N+0.5)*(N+1)/12);
pval=2*(1-Probnorm(Z));
Label pval=p-value;

Proc Print Label;
ID N;
Var R Z pval;

Run;
Quit;
```

SAS Output for Analyses Shown in Table 15.4:

Wilcoxon Signed Rank Test of Paired Tmax Results 1

Subject	Tmax A	Tmax B	Difference (B-A)	Absolute Value of Difference	Sign
1	2.50	3.5	1.00	1.00	1
2	3.00	4.0	1.00	1.00	1
3	1.25	2.5	1.25	1.25	1
4	1.75	2.0	0.25	0.25	1
5	3.50	3.5	0.00	.	.
6	2.50	4.0	1.50	1.50	1
7	1.75	1.5	-0.25	0.25	-1
8	2.25	2.5	0.25	0.25	1
9	3.50	3.0	-0.50	0.50	-1
10	2.50	3.0	0.50	0.50	1
11	2.00	3.5	1.50	1.50	1
12	3.50	4.0	0.50	0.50	1

Wilcoxon Signed Rank Test of Paired Tmax Results 2

Rank Sums for Using Exact Tables

The MEANS Procedure

Analysis Variable : AbsDiff Values of AbsDiff Were Replaced by Ranks

Sign	N Obs	N	Sum
-1	2	2	7.0000000
1	9	9	59.0000000

```
                    Wilcoxon Signed Rank Test of Paired Tmax Results                3

                        Normal Approximation for Large Samples

                           N      R        Z         p-value

                          11     59     2.31168     0.020795
```

```
/* Sas Program to Produce Table 15.7 and Confidence Intervals  */


Options ls=90 ps=58 nodate pageno=1;
Title1 'Nonparametric Confidence Intervals for Table 15.6 Cmax Ratios';

Data A;
input Subject CmaxA CmaxB;
Ratio=CmaxB/CmaxA;  /* Calculate Cmax Ratio B/A */

Cards;          /* data */
1     135   102
2     179   147
3     101   385
4     109   106
5     138   189
6     135   105
7     158   130
8     156   125
9     174   144
10    147   133
11    145   114
12    147   167
;

Proc Print;
ID Subject;
Var CmaxA CmaxB ratio;

Data B;      /* Creates a one-record file of the ratios for each Subject */
Keep Sub1-Sub12 Geomean;     /* Variables Sub1-Sub12 contain the ratios */
Array Rat[12] Sub1-Sub12;
Product=1;
Do I=1 to 12;
Set A;
Product=Product*ratio;    /* multiplies Product by ratio for Subject I */
Rat[I]=ratio;             /* captures ratio for Subject I */
end;
Geomean=Product**(1/12);    /* computes geometric mean ratio for subjects */
```

```
Data C;        /* Pairing of the ratios */
Set B;
Keep Pair Geomean Geomn;
Array First[12] Sub1-Sub12;   /* array for first ratio in pair */
Array Second[12] Sec1-Sec12;  /* array for second ratio in pair */
Do I=1 to 12;
 Second[I]=First[I];           /* copy ratios to second array */
end;
Do fst=1 to 12;          /* pair ratio of each subject with itself and with*/
  Do sec=fst to 12;   /* that of each subject number higher than it*/
  Geomn=Sqrt(First[fst]*Second[sec]); /* geometric mean for paired subjs */
  Pair=compbl(fst||','||sec);
  Output;
  end;
end;
Label Geomn=Sorted Geometric Mean Ratio;
Label Pair=Subjects;

Proc Sort;          /* Sorts paired Geometric Mean Ratios */
By Geomn;

Proc Print Label;
Var Pair Geomn;

Data D;
Keep Geomean CI95Lo CI90Lo CI90Hi CI95Hi;
Array CI[4] CI95Lo CI90Lo CI90Hi CI95Hi;
Z=1;
Do I=1 to 78;
Set C;
If I=14 or I=18 or I=61 or I=65 then
    do;                    /* capture geomn vals for CI limits */
    CI[Z]=geomn;
    Z=Z+1;
  end;
end;
Label Geomean=Geometric Mean Ratio;
Label CI90Lo = 90% CI Lower Limit;
Label CI90Hi = 90% CI Upper Limit;
Label CI95Lo = 95% CI Lower Limit;
Label CI95Hi = 95% CI Upper Limit;

Proc Print Label;
ID Geomean;
Var CI95Lo CI90Lo CI90Hi CI95Hi;
Attrib Geomean CI95Lo CI90Hi CI90Lo CI95Hi Format=F6.3;

Run;
Quit;
```

SAS Output for Analyses Shown in Table 15.7 (Table 15.6 data):

Nonparametric Confidence Intervals for Table 15.6 Cmax Ratios 1

Subject	Cmax A	Cmax B	Ratio
1	135	102	0.75556
2	179	147	0.82123
3	101	385	3.81188
4	109	106	0.97248
5	138	189	1.36957
6	135	105	0.77778
7	158	130	0.82278
8	156	125	0.80128
9	174	144	0.82759
10	147	133	0.90476
11	145	114	0.78621
12	147	167	1.13605

Nonparametric Confidence Intervals for Table 15.6 Cmax Ratios 2

[Partial Page Shown]

Obs	Subjects	Sorted Geometric Mean Ratio
1	1, 1	0.75556
2	1, 6	0.76659
3	1, 11	0.77073
4	6, 6	0.77778
5	1, 8	0.77808
6	6, 11	0.78198
7	11, 11	0.78621
8	1, 2	0.78771
9	1, 7	0.78845
10	6, 8	0.78944
11	1, 9	0.79075
12	8, 11	0.79371
13	2, 6	0.79921
14	6, 7	0.79996
15	8, 8	0.80128
16	6, 9	0.80230
17	2, 11	0.80353
18	7, 11	0.80429
19	9, 11	0.80663

Nonparametric Confidence Intervals for Table 15.6 Cmax Ratios 3

Obs	Subjects	Sorted Geometric Mean Ratio
53	10, 12	1.01383
54	1, 5	1.01724
55	5, 6	1.03209
56	5, 11	1.03767
57	5, 8	1.04757
58	4, 12	1.05109
59	2, 5	1.06053
60	5, 7	1.06154
61	5, 9	1.06463
62	5, 10	1.11316
63	12, 12	1.13605
64	4, 5	1.15407
65	5, 12	1.24736
66	5, 5	1.36957
67	1, 3	1.69708
68	3, 6	1.72186
69	3, 11	1.73116
70	3, 8	1.74768
71	2, 3	1.76930
72	3, 7	1.77098
73	3, 9	1.77614
74	3, 10	1.85711
75	3, 4	1.92535
76	3, 12	2.08099
77	3, 5	2.28487
78	3, 3	3.81188

Nonparametric Confidence Intervals for Table 15.6 Cmax Ratios 4

Geometric Mean Ratio	95% CI Lower Limit	90% CI Lower Limit	90% CI Upper Limit	95% CI Upper Limit
1.006	0.800	0.804	1.065	1.247

```
/* Sas Program to Analyze Table 15.8  */

Options ls=90 ps=60 nodate pagno=1;
Title1 'Dissolution Results at 30 Minutes';
Title3 'Wilcoxon Rank Sum Test for Difference Between Two Independent Groups';

Data A;
input App $ Diss;
label App=Apparatus;
label Diss=Amount Dissolved;
cards;      /* Data from Table 15.8*/
O     53
.
.
M     56 ;

Proc Rank;              /* Rank Dissolution Data */
Var Diss;
Ranks Rank;

Proc Print Label;      /* Displays Ranks for Data */
ID App;
Var Diss Rank;

Proc Means Sum;        /* Obtain Rank Sums by apparatus */
Var Rank;
Class App;
Output out=mn Sum=Sum;

Data B;          /* Captures Rank Sums and numbers of data values */
Array Num[2] n1 n2;
Array T[2] t1 t2;
Do I= 1 to 3;
Set mn;
If _Type_=1 then
     do;
       Num[I-1]=_Freq_;
       T[I-1]=Sum;
     end;
end;
I=1;
if n2<n1 then I=2;
Z=Abs(T[I]-Num[I]*(n1+n2+1)/2)/Sqrt(n1*n2*(n1+n2+1)/12);  /* Z-statistic */
pval=2*(1-probnorm(z));                /* p-value for normal approximation */
label pval=p-value;

Proc Print label;
ID n1;
var n2 t1 t2 z pval;

Run;
Quit;
```

SAS OUTPUT FOR TABLE 15.8:

Dissolution Results at 30 Minutes 1

Wilcoxon Rank Sum Test for Difference Between Two Independent Groups

Apparatus	Amount Dissolved	Rank for Variable Diss
O	53	3.0
O	61	14.0
O	57	9.0
O	50	1.0
O	63	17.0
O	62	15.5
O	54	4.0
O	52	2.0
O	59	12.5
O	57	9.0
O	64	18.5
M	58	11.0
M	55	5.5
M	67	21.0
M	62	15.5
M	55	5.5
M	64	18.5
M	66	20.0
M	59	12.5
M	68	22.0
M	57	9.0
M	69	23.0

Dissolution Results at 30 Minutes 2

Wilcoxon Rank Sum Test for Difference Between Two Independent Groups

The MEANS Procedure

Analysis Variable : Rank Rank for Variable Diss

Apparatus	N Obs	Sum
M	12	170.5000000
O	11	105.5000000

Dissolution Results at 30 Minutes 3

Wilcoxon Rank Sum Test for Difference Between Two Independent Groups

n1	n2	t1	t2	Z	p-value
12	11	170.5	105.5	1.63096	0.10290

```
/* Sas Program to Analyze Table 15.10  */

Options ls=90 ps=60 nodate pagno=1;
Title1 'Kruskal-Wallis Test (One-Way ANOVA)';

Data A;
input @@ t1-t29;
keep cmpnd Time;
array v[29] t1-t29;
do i=1 to 29;
cmpnd='H';                          /* compound = High Dose */
if i<10 then cmpnd='C';            /* compound = Control, first 9 elements */
if i>9 and i<20 then cmpnd='L';    /* compound = Low dose, elements 10-20 */
time=v[i];
output;                /* creates 29 records of two variables: cmpnd time */
end;
cards;     /* data */
8 1 9 9 6 3 15 1 7
10 5 8 6 7 7 15 1 15 7
3  4 8 1 1 3 1  6 2  2
;

proc nparlway wilcoxon;
class cmpnd;
var time;     /* if sample sizes are small, add statement: Exact Wilcoxon */
              /* to obtain exact tests for the treatment comparison */
run;
quit;
```

SAS OUTPUT:

```
                    Kruskal-Wallis Test (One-Way ANOVA)                    1

                     N P A R 1 W A Y  P R O C E D U R E

                Wilcoxon Scores (Rank Sums) for Variable TIME
                      Classified by Variable CMPND

                                 Sum of      Expected       Std Dev        Mean
CMPND            N             Scores      Under H0     Under H0         Score

C                9          149.500000         135.0   21.0479748   16.6111111
L               10          191.000000         150.0   21.6247384   19.1000000
H               10           94.500000         150.0   21.6247384    9.4500000

                      Average Scores Were Used for Ties


            Kruskal-Wallis Test (Chi-Square Approximation)

            CHISQ =  6.9981       DF =  2       Prob > CHISQ = 0.0302
```

```
/* Sas Program to Analyze Table 15.11  */

Options ls=90 ps=60 nodate pagno=1;
Title1 'Friedman Test (Two-Way ANOVA) on Tablet Hardness Data';

Data A;
input @@ t1-t20;
keep press form hardness;
array v[20] t1-t20;
do i=1 to 20;
if i<6 then press='A';          /* press is A for first 5 hardness values */
if i>5 and i<11 then press='B';   /* press is B for values 6 through 10 */
if i>10 and i<16 then press='C';  /* press is C for values 11 through 15 */
if i>15 then press='D';           /* press is C for values 15 through 20 */
form=i-5*Int(i/5.1);             /* determines formulation from counter i */
hardness=v[i];
output;            /* creates 20 records of two variables: press hardness */
end;
cards;               /* data */
7.5 8.2 7.3 6.6 7.5
6.9 8.0 7.9 6.5 6.8
7.3 8.5 8.0 7.1 7.6
7.0 7.9 7.6 6.4 6.7
;

proc print;
id form;
var press hardness;

proc freq;              /* Friedman Test */
tables form*press*hardness/ noprint cmh2 scores=rank;
footnote1 'Friedman Chi-Square is given in Statistic 2';

proc sort data=a;
by form;
footnote1 "  ";

proc rank;          /* Ranks press results (hardness) within each
formulation */
var hardness;
by form;

proc Anova;            /* Modified Test */
Title1 'Modified Friedman Test (Two-Way ANOVA) on Tablet Hardness Data';
class form press;
model hardness=form press;
means press/LSD;     /* Performs multiple pairwise comparisons of Press
means */

run;
quit;
```

SAS OUTPUT TABLE 15.11:

Friedman Test (Two-Way ANOVA) on Tablet Hardness Data 1

FORM	PRESS	HARDNESS
1	A	7.5
2	A	8.2
3	A	7.3
4	A	6.6
5	A	7.5
1	B	6.9
2	B	8.0
3	B	7.9
4	B	6.5
5	B	6.8
1	C	7.3
2	C	8.5
3	C	8.0
4	C	7.1
5	C	7.6
1	D	7.0
2	D	7.9
3	D	7.6
4	D	6.4
5	D	6.7

Friedman Test (Two-Way ANOVA) on Tablet Hardness Data 2

SUMMARY STATISTICS FOR PRESS BY HARDNESS
CONTROLLING FOR FORM

Cochran-Mantel-Haenszel Statistics (Based on Rank Scores)

Statistic	Alternative Hypothesis	DF	Value	Prob
1	Nonzero Correlation	1	0.864	0.353
2	Row Mean Scores Differ	3	9.720	0.021

Total Sample Size = 20

Friedman Chi-Square is given in Statistic 2

Modified Friedman Test (Two-Way ANOVA) on Tablet Hardness Data 3

Analysis of Variance Procedure
Class Level Information

Class	Levels	Values
FORM	5	1 2 3 4 5
PRESS	4	A B C D

Number of observations in data set = 20

Modified Friedman Test (Two-Way ANOVA) on Tablet Hardness Data 4

Analysis of Variance Procedure

Dependent Variable: HARDNESS VALUE OF HARDNESS REPLACED BY RANK

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	16.20000000	2.31428571	3.16	0.0389
Error	12	8.80000000	0.73333333		
Corrected Total	19	25.00000000			

R-Square	C.V.	Root MSE	HARDNESS Mean
0.648000	34.25395	0.85634884	2.50000000

Source	DF	Anova SS	Mean Square	F Value	Pr > F
FORM	4	0.00000000	0.00000000	0.00	1.0000
PRESS	3	16.20000000	5.40000000	7.36	0.0047

Modified Friedman Test (Two-Way ANOVA) on Tablet Hardness Data 5

Analysis of Variance Procedure

T tests (LSD) for variable: HARDNESS

NOTE: This test controls the type I comparisonwise error rate not the experimentwise error rate.

Alpha= 0.05 df= 12 MSE= 0.733333
Critical Value of T= 2.18
Least Significant Difference= 1.1801

Means with the same letter are not significantly different.

T Grouping	Mean	N	PRESS
A	3.8000	5	C
A			
B A	2.8000	5	A
B			
B C	2.0000	5	B
C			
C	1.4000	5	D

Notes on Modified Friedman Test Output:

Page 4 Press row is comparison across presses. P-value is Friedman Test.
Page 5 Least Significant Difference is for mean; for Rank Sum: 5 * 1.18 = 5.90.
Press mean C is significantly greater than means for B & D.
Press mean A is significantly greater than mean for D.

```
/* Sas Program to Produce Quade's Test Analysis shown in Table 15.12  */

Options ls=90 ps=60 nodate pagno=1;
Title1 'Quade Test for Randomized Block Design on Data of Table 15.11';

Data A;
input @@ t1-t20;
keep press form rn hardness;
array v[20] t1-t20;
do i=1 to 20;
if i<6 then press='A';          /* press is A for first 5 hardness values */
if i>5 and i<11 then press='B';   /* press is B for values 6 through 10 */
if i>10 and i<16 then press='C';  /* press is C for values 11 through 15 */
if i>15 then press='D';           /* press is D for values 15 through 20 */
form=i-5*Int(i/5.1);     /* determines tablet formulation from counter i */
hardness=v[i];
z=form;
rn=range(v[z],v[z+5],v[z+10],v[z+15]); /* determines range for each form */
rn=round(rn,0.01);
output;
end;
cards;                   /* data */
7.5 8.2 7.3 6.6 7.5
6.9 8.0 7.9 6.5 6.8
7.3 8.5 8.0 7.1 7.6
7.0 7.9 7.6 6.4 6.7
;

proc sort data=A;
by form press;

Data B1;             /* creates one record for each formulation containing
range */
set A;
keep form rn;
if press="A";

proc rank data=B1 out=B2;    /* rank the tablet formulations by range */
var rn;
ranks q;              /* store ranks for each formulation in variable q */

data C;
set B2;            /* creates records of formulation ranks for each press */
press="A"; output;
press="B"; output;
press="C"; output;
press="D"; output;

proc sort data=C;
by form press;
```

```
proc rank data=A out=A2;  /* rank hardness of each form within press */
var hardness;               /* replace hardness value by its rank */
by form;

data d;
merge A2 C;                /* Merge hardness and formulation ranks */
by form press;
keep press form rn q hardness;
hardness=q*(hardness-5/2);      /* Quade's test using formulation ranks q */
label rn=range;
label q=rank;

proc print label;           /* Produces Table 15.12 */
id form;
var press hardness rn q;

proc Anova;                 /* Quade's test using modified hardness ranks */
class form press;
model hardness= form press;
means press/LSD;            /* multiple paired comparisons of press means */

run;
quit;
```

SAS OUTPUT:

Quade Test for Randomized Block Design Applied Data of Table 15.11 1

FORM	PRESS	VALUE OF HARDNESS REPLACED BY RANK	range	rank
1	A	2.25	0.6	1.5
1	B	-2.25	0.6	1.5
1	C	0.75	0.6	1.5
1	D	-0.75	0.6	1.5
2	A	0.75	0.6	1.5
2	B	-0.75	0.6	1.5
2	C	2.25	0.6	1.5
2	D	-2.25	0.6	1.5
3	A	-5.25	0.7	3.5
3	B	1.75	0.7	3.5
3	C	5.25	0.7	3.5
3	D	-1.75	0.7	3.5
4	A	1.75	0.7	3.5
4	B	-1.75	0.7	3.5
4	C	5.25	0.7	3.5
4	D	-5.25	0.7	3.5
5	A	2.50	0.9	5.0
5	B	-2.50	0.9	5.0
5	C	7.50	0.9	5.0
5	D	-7.50	0.9	5.0

Quade Test for Randomized Block Design Applied Data of Table 15.11 2

Analysis of Variance Procedure
Class Level Information

Class	Levels	Values
FORM	5	1 2 3 4 5
PRESS	4	A B C D

Number of observations in data set = 20

Quade Test for Randomized Block Design Applied Data of Table 15.11 3

Analysis of Variance Procedure

Dependent Variable: HARDNESS VALUE OF HARDNESS REPLACED BY RANK

Source	DF	Sum of Squares	Mean Square	F Value	Pr > F
Model	7	156.30000000	22.32857143	2.36	0.0919
Error	12	113.70000000	9.47500000		
Corrected Total	19	270.00000000			

R-Square	C.V.	Root MSE	HARDNESS Mean
0.578889	9999.99	3.07814879	0

Source	DF	Anova SS	Mean Square	F Value	Pr > F
FORM	4	0.00000000	0.00000000	0.00	1.0000
PRESS	3	156.30000000	52.10000000	5.50	0.0131

```
Quade Test for Randomized Block Design Applied Data of Table 15.11          4

                    Analysis of Variance Procedure

                T tests (LSD) for variable: HARDNESS

NOTE: This test controls the type I comparisonwise error rate not the
      experimentwise error rate.

              Alpha= 0.05  df= 12  MSE= 9.475
                 Critical Value of T= 2.18
              Least Significant Difference= 4.2417

Means with the same letter are not significantly different.

        T Grouping              Mean       N  PRESS

                A              4.200       5  C
                A
          B     A              0.400       5  A
          B
          B                   -1.100       5  B
          B
          B                   -3.500       5  D
```

Note on Analysis: Press Mean C does not share a grouping letter with presses B and D, indicating C is significantly different than these two presses at the 5% level of significance.

```
/* Sas Program to Perform Quade Nonparametric ANCOVA on Table 15.13 Data */

Options ls=90 ps=60 nodate pagno=1;
Title1 'Quade Nonparametric Covariance Analysis on Table 15.13 Data';

Data A;
input Method$ Assay Material;

Cards;
I       98.0       98.4
I       97.8       98.6
I       98.5       98.6
I       97.4       99.2
II      97.6       98.7
II      95.4       99.0
II      96.1       99.3
II      96.1       98.4
;
```

```
proc rank data=A out=A2;        /* rank assay and material */
var Material Assay;
ranks Rx Ry;                    /* material ranks in Rx, Assay ranks in Ry */

Proc Standard mean=0 out=B;     /* Centers Ranks about 0; puts results in B*/
Var Rx Ry;

Proc Reg noprint data=B;    /* Regression of Assay ranks on Material ranks */
model Ry = Rx;
Output out=C r=resid;           /* Residuals in C */

Data D;               /* Gets Method, Assay, Material, Ry, Rx & Residuals */
merge A B C;

Proc Print;
Var Assay Material Ry Rx Resid;
Sum Resid;
By Method;

proc Anova;                       /* ANOVA on regression residuals */
class Method;
model resid= Method;

run;
quit;
```

SAS OUTPUT:

```
            Quade Nonparametric Covariance Analysis on Table 15.13 Data              1

---------------------------------------- METHOD=I ----------------------------------------

                 OBS    ASSAY    MATERIAL     RY      RX      RESID

                   1     98.0       98.4      2.5    -3.0    1.05488
                   2     97.8       98.6      1.5    -1.0    1.01829
                   3     98.5       98.6      3.5    -1.0    3.01829
                   4     97.4       99.2     -0.5     2.5    0.70427
                                                             -------
               METHOD                                        5.79573


---------------------------------------- METHOD=II ----------------------------------------

                 OBS    ASSAY    MATERIAL     RY      RX      RESID

                   5     97.6       98.7      0.5     0.5    0.74085
                   6     95.4       99.0     -3.5     1.5   -2.77744
                   7     96.1       99.3     -2.0     3.5   -0.31402
                   8     96.1       98.4     -2.0    -3.0   -3.44512
                                                             --------
               METHOD                                        -5.79573
                                                             ========
                                                              0.00000
```

```
                Quade Nonparametric Covariance Analysis on Table 15.13 Data              2

                                Analysis of Variance Procedure
                                   Class Level Information

                                  Class     Levels    Values

                                  METHOD         2    I II

                                Number of observations in data set = 8
```

```
                Quade Nonparametric Covariance Analysis on Table 15.13 Data              3

                                Analysis of Variance Procedure

Dependent Variable: RESID   Residual

Source                   DF        Sum of Squares          Mean Square   F Value     Pr > F

Model                     1           16.79525301          16.79525301      6.63     0.0420

Error                     6           15.19102748           2.53183791

Corrected Total           7           31.98628049

                  R-Square                 C.V.            Root MSE          RESID Mean

                  0.525077              9999.99            1.59117501          0.00000000


Source                   DF             Anova SS          Mean Square   F Value     Pr > F

METHOD                    1           16.79525301          16.79525301      6.63     0.0420
```

```
/* Sas Program to Analyze Table 15.16  */

Options ls=90 ps=60 nodate pagno=1;
Title1 'Patients Categorized by Disease Severity and Treatment';

Data A;
input Trtment$ Severe$ Count;

cards;      /* data */
A Very      13
B Very      19
A Moderate  24
B Moderate  20
A Mildly    18
B Mildly    12
;

Proc Freq order=data;          /* order of Severity should be as entered */
Tables Trtment*Severe/nofreq nopercent norow nocol nocum expected;
                                                  /*expected values */
```

```
                                        /*frequency table & stats*/
Tables Trtment*Severe/ chisq nopercent norow nocol nocum;
Weight Count;                           /*data are counts per cell*/

run;
quit;
```

SAS Output:

Patients Categorized by Disease Severity and Treatment 1

TABLE OF TRTMENT BY SEVERE

TRTMENT SEVERE

Expected	Very	Moderate	Mildly	Total
A	16.604	22.83	15.566	
B	15.396	21.17	14.434	
Total	32	44	30	106

TABLE OF TRTMENT BY SEVERE

TRTMENT SEVERE

Expected	Very	Moderate	Mildly	Total
A	13	24	18	55
B	19	20	12	51
Total	32	44	30	106

STATISTICS FOR TABLE OF TRTMENT BY SEVERE

Statistic	DF	Value	Prob
Chi-Square	2	2.541	0.281
Likelihood Ratio Chi-Square	2	2.553	0.279
Mantel-Haenszel Chi-Square	1	2.334	0.127
Phi Coefficient		0.155	
Contingency Coefficient		0.153	
Cramer's V		0.155	

Sample Size = 106

```
/* Sas Program to Analyze Table 15.21  */

Options ls=90 ps=60 nodate pagno=1;
Title1 "Fisher's Exact Test for Carcinoma in Drug- and Placebo-Treated Animals";

Data A;
input Trtment$ Carcnoma$ Count;
cards;                          /* data */
Placebo Present 0
Placebo Absent  12
Drug    Present 5
Drug    Absent  9
;

Proc Freq order=data;     /* Trtment order in table should be as entered */
Tables Trtment*Carcnoma/nopercent norow nocol nocum exact; /*table & stats*/
Weight Count;            /* data are counts for each table cell */

run;
quit;
```

SAS OUTPUT:

Fisher's Exact Test for Carcinoma in Drug- and Placebo-Treated Animals 1

TABLE OF TRTMENT BY CARCNOMA

TRTMENT CARCNOMA

Frequency	Absent	Present	Total
Placebo	12	0	12
Drug	9	5	14
Total	21	5	26

STATISTICS FOR TABLE OF TRTMENT BY CARCNOMA

Statistic	DF	Value	Prob
Chi-Square	1	5.306	0.021
Likelihood Ratio Chi-Square	1	7.208	0.007
Continuity Adj. Chi-Square	1	3.256	0.071
Mantel-Haenszel Chi-Square	1	5.102	0.024
Fisher's Exact Test (Left)			1.000
(Right)			0.030
(2-Tail)			0.042
Phi Coefficient		0.452	
Contingency Coefficient		0.412	
Cramer's V		0.452	

Sample Size = 26
WARNING: 50% of the cells have expected counts less
than 5. Chi-Square may not be a valid test.

Note: Fisher's Exact Test (2-Tail) is correct test.

REFERENCES

1. Halvorson M, Young M. Running Microsoft Office 2000 Professional, Part III Microsoft Excel. Washington: Microsoft Press, Redmond, 1999.
2. SAS Institute Inc. SAS® Language Reference, Version 6, 1st ed., Cary, NC: SAS Institute Inc., 1990.
3. SAS Institute Inc. SAS/STAT® User's Guide, Version 6, 4th ed., Volumes 1 and 2. Cary, NC: SAS Institute Inc., 1990.

Appendix IX
An Alternative Solution to the Distribution of the Individual Bioequivalence Metric*

The Office of Generic Drugs (OGD) of the Federal Drug Administration (FDA) has recently published statistical guidelines for determination of bioequivalence [1], see above. Included in that publication is a statistical approach to determining individual bioequivalence (IB), as recommended by Hyslop et al. [1]. Herewith, is a description of an alternative approach. The probability density function (PDF) of the IB metric is determined and used to construct a decision rule for acceptance. The acceptance criterion is based on an upper 95% confidence interval for the metric, defined as 2.4948. Here is shown the derivation here for the reference-scaled metric. However, with minor modifications, this approach is also applicable to the constant denominator metric and to population bioequivalence described in the FDA guidance [1]. The following has been described in chapter 11, but is repeated here for the sake of continuity.

The reference-scaled metric is defined as

$$\phi = [(\mu_t - \mu_r)^2 - \sigma_d^2 + \sigma_t^2 - \sigma_r^2]/\sigma_r^2, \tag{IX.1}$$

or, equivalently as

$$\phi = [(\mu_t - \mu_r)^2 + \sigma_d^2 + \sigma_t^2]/\sigma_r^2 - 1. \tag{IX.2}$$

Here, μ_t is the mean of the parameter for the test product, μ_r is the mean of the parameter for the reference product, σ_d^2 = subject-product interaction variance, σ_t^2 = within-subject test variance, σ_r^2 = within-subject reference variance.

For a four-period replicate design as described by Hyslop and in the FDA guidance [1,2], we can also define [3]

$$\sigma_i^2 = \sigma_d^2 + 0.5\sigma_t^2 + 0.5\sigma_r^2, \tag{IX.3}$$

where σ_i^2 is the variance of $(\mu_t - \mu_r)$. Combining equations (IX.2) and (IX.3),

$$\phi = [(\mu_t - \mu_t)^2 + \sigma_i^2 + 0.5\sigma_i^2]/\sigma_r^2 - 1.5. \tag{IX.4}$$

The parameter estimates, $\overline{X}_t \overline{X}_r$, S_i^2, S_t^2 and S_r^2, are computed using a mixed-effects linear model as described in the FDA guidance [1].

The analysis in the recent guidance is approximate, has reasonably good properties [1,2], and is relatively simple to calculate. It appears to agree well with the results of the previously used bootstrap simulation approach.

The following derivation results in a more direct approach to estimating the upper confidence interval. The idea is to derive the PDF of the metric. Once the PDF is known, the cumulative probability distribution function (CDF), the 95% confidence interval, as well as other parameters of interest can be easily determined.

*Abstracted from a paper submitted to the Journal, *Drug Development and Industrial Pharmacy*, Marcel Dekker.

IX.1 DERIVATION AND RESULTS

In principle, the PDF of ϕ can be determined if the joint distributions of the random variables $\overline{X}_t$, $\overline{X}_r$, S_i^2, S_t^2 and S_r^2 are known. In general, this would be a formidable task. However, under the usual assumption of statistical independence of these variables [2], it is quite feasible to compute the PDF of ϕ . Further assumptions include [1] that the random variables $\overline{X}_t$ and $\overline{X}_r$ are Gaussian after the usual logarithmic transformation, and [2] that the variances are distributed as $\sigma_i^2\chi^2/\text{d.f}$. With these assumptions, which are similar to those made by Hyslop [2], the PDF of ϕ can be derived as shown below. In the derivation, we have used the formulae for computing the PDF of the sum of two independent variables and the PDF of the ratio of two independent variables. These may be found in Ref.[4].

For ease of notation, define the following random variables:

$$Y = (\overline{X}_t - \overline{X}_r)^2$$
$$Z = S_i^2$$
$$U = 0.5S_t^2$$
$$V = S_r^2$$

In terms of these, define further the intermediate variables,

$$W = Y + Z$$
$$G = W + U$$

The metric may then be expressed as

$$\phi = \frac{G}{V} - 1.5.$$

Since $\overline{X}_t$ and $\overline{X}_r$ are both Gaussian, their difference is also Gaussian. Let the mean and standard deviation of $(\bar{X}_t - \bar{X}_r)$ be μ and σ , respectively. Then the PDF of Y, $p(y)$ is given by

$$p(y) = \frac{1}{\sigma\sqrt{2\pi}} \exp\left(-\frac{y+\mu^2}{2\sigma^2}\right) \frac{1}{\sqrt{y}} \cosh\left(\frac{\mu\sqrt{y}}{\sigma^2}\right) y \geq 0$$

Let $q(z)$ be the PDF of Z. Since Y and Z are independent, the PDF of W, $r(w)$, is given by the convolution of $p(y)$ and $q(z)$. Thus

$$r(w) = \int_0^w p(y)q(w-y)dy$$

Similarly, if $s(u)$ is the PDF of U, then the PDF of the variable G, $f(g)$, is given by

$$f(g) = \int_0^g r(w)s(g-w)dw$$

Finally, let a(m) be the PDF of ϕ. If t(v) is the PDF of V, then

$$a(m) = \int_0^w vt(v)f[(m+1.5)v]dv$$

A program was written in MATLAB [5] to evaluate $a(m)$ using numerical integration to compute the various integrals in the above derivation. If the parameters defining the distributions of X_t, X_r, etc. were known, this would be an exact solution. In the absence of such

Table IX.1 Comparison of Results of Convolution Method to Hyslop Method for the Parameter Values Shown

N	Mean	Difference	S^2_i	S^2_t	S^2_r	Hyslop[a]	Convolution[b]
122[c]		0	0.02	0.02	0.0125	−0.028	2.185
		0	0.02	0.02	0.01	−0.001	2.46
		0	0.02	0.03	0.01	+0.005	3.065
		0.2	0.12	0.12	0.065	+0.023	3.175
26[d]		0.05	0.12	0.1	0.085	−0.008	2.43
		0.05	0.198	0.02	0.1075	+0.0004	2.50
		0.05	0.08	0.049	0.05	+0.005	2.68
		0.2	0.12	0.12	0.095	+0.0205	2.96
16		0.05	0.05	0.05	0.05	−0.0085	2.24
		0.05	0.02	0.02	0.02	−0.0014	2.41
		0.05	0.05	0.1	0.05	+0.0296	3.395
		0.05	0.03	0.02	0.02	+0.0623	3.725
12		0.05	0.02	0.02	0.01	−0.0014	2.79
		0.05	0.02	0.022	0.03375	−0.0118	2.46
		0	0.05	0.04	0.0475	+0.0144	3.56
		0.07	0.05	0.04	0.0475	+0.0222	3.175

[a] Hyslop method passes for negative values.
[b] Convolution passes for values less than 2.498.
[c] Sequence sizes are 30,30,30,32.
[d] Sequence sizes are 6,6,6,8.

knowledge, an approximate solution is obtained by using the observed values of the means and variances as the parameter values. Clearly, this solution would approach the exact solution with large sample sizes. With the sample sizes usually used in BE studies, we expect that the solution should be reasonably good. A preliminary spot check of the results and decisions comparing this new approach to that of Hyslop is shown in Table IX.1. Examples are shown where the decisions are borderline.

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3. Ekbohm G. Melander, H. The subject-by-formulation interaction as a criterion for inter-changeability of drugs. Biometrics 1989; 45:1249–1254.
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Matlab Program to Compute CDF of Metric

EXAMPLE

Data from Replicate Design with 8 subjects

A. mean of xt-xr is the estimated difference between the means of Test and Reference = -0.1715

B. std err of xt-xr is the standard error of (A) = 0.295

C. si^2 is the estimated interaction variance = 0.0871

D. sr^2 is the estimated within subject variance of the reference = 0.06605

E. st^2 is the estimated within subject variance of the test = 0.0729

Matlab Program

```
clear
global degfree
global mean
%These variables are used to compute chisq/df distributions
%using chidf.m
%
mtr=-.01715              % mean of xt-xr
str=0.295                % std err of xt-xr
msi=0.0871               % si^2
msr=0.06605              % sr^2
mst=0.0729              % st^2
%mit=msi+.5*mst          % mean of si^2 + .5 st^2
%sit=sqrt(ssi^2+ (.5*sst)^2)
```

```
%
%Note: si^2, sr^2 and st^2 are distributed as sig^2 chi^2/d.f
%      where the degrees of freedom are 6.
%      Therefore the mean = sig^2
%      sig^2 is, of course, unknown. We approximate it by the sample
%      estimate
%      we need the distribution of
%          [(xt-xr)^2 + si^2 + .5st^2 ] / sr^2 -1.5
%prob density of (xr-xt)^2 is ptr2
%prob density of si^2 is psi (deg of free =6)
%prob density of sr^2 is psr
%prob density of st^2 is pst
%prob density of si^2+.5st^2 is pit
%prob density of denominator is pden (= prob density of sr^2)
%prob density of numerator is pnum
%prob density of metric is pmetric
%
xtr2max=0.15
xchimax=0.4
deltr=.00005
ntr2=1+round(xtr2max/deltr)
nchi=1+round(xchimax/deltr)
xtr=linspace(0.,xtr2max,ntr2);
xchi=linspace(0.,xchimax,nchi);
ctr=(1/(str*sqrt(2*pi)))*exp(-mtr^2/(2*str^2));
ptr2(1)=2*ctr/sqrt(deltr);

for i=2:ntr2
   xdel=xtr(i);
```

```
   xsqrt=sqrt(xdel);
   ptr2(i)=ctr*exp(-xdel/(2*str^2))*(1/xsqrt)*cosh(mtr*xsqrt/str^2);
end
sumtr2=deltr*ones(1,ntr2)*ptr2'
ptr2=ptr2/sumtr2;
plot (xtr,ptr2)
title('prob density of (xt - xr)^2')
text(.03,250,'xt-xr is gaussian')
text(.03,225,['mu= ' num2str(mtr), ',   sigma= ', num2str(.129)])
iplot=0

if(iplot==1)
   print -dwin
end
%
mean=msi
degfree=6
psi=chidf(xchi);
sumpsi=deltr*ones(1,nchi)*psi'
plot (xchi,psi)
title('prob density of si^2')
text(.3,5,['sig^2= ' num2str(msi)])
text(.3,4,['df =   ' int2str(degfree)])

if(iplot==1)
   print -dwin
end
mean=msr
degfree=6
```

```
psr=chidf(xchi);
sumpsr=deltr*ones(1,nchi)*psr'
plot(xchi,psr)
title('prob density of sr^2')
text(.3,8,['sig^2= ' num2str(msr)])
text(.3,7,['df =    ' int2str(degfree)])

if(iplot==1)
   print -dwin
end
mean=mst*.5
degfree=6
pst=chidf(xchi);
sumpst=deltr*ones(1,nchi)*pst'
plot(xchi,pst)
title('prob density of .5*st^2')
text(.3,8,['sig^2= ' num2str(mst)])
text(.3,7,['df =    ' int2str(degfree)])

if(iplot==1)
   print -dwin
end
%
psist= deltr*conv(psi,pst);
[junk,npl]=size(psist)
xpl=linspace(0.,2.*xchimax,npl);
plot(xpl,psist)
title('prob density of si^2+.5st^2')
sumsist=deltr* ones(1,npl)*psist'
```

```
if(iplot==1)
   print -dwin
end
pnum=deltr*conv(psist,ptr2);
[junk,nplnum]=size(pnum)
xnum=linspace(0.,2.*xchimax+xtr2max,nplnum);
for i=1:nplnum
   cumnum(i)=deltr*ones(1,i)*pnum(1:i)';
end

plot(xnum,pnum)
sumnum=deltr*ones(1,nplnum)*pnum'
title('prob density of numerator')

if(iplot==1)
   print -dwin
end
maxplot=15.
nplot=301
xmetric=linspace(-1.5,maxplot,nplot);
for i=1:nplot
   factor=xmetric(i)+1.5;
   for k=1:nchi
      index=round((factor*xnum(k)/deltr)+1);
      if(index > nplnum)
         index=nplnum;
      end
      integrand(k)=xnum(k)*psr(k)*pnum(index);
```

```
      cumint(k)=psr(k)*cumnum(index);
   end
   pmetric(i)=deltr*ones(1,nchi)*integrand';
   cumplot(i)=deltr*ones(1,nchi)*cumint';
end
plot(xmetric,pmetric)
title('prob density of metric')
summetric=cumplot(nplot)
%summetric=(maxplot/(nplot-1))*ones(1,nplot)*pmetric'

if(iplot==1)
   print -dwin
end
nstop95=1
nstop90=1
for i=1:nplot
%     cumplot(i)= (maxplot/(nplot-1))*ones(1,i)*pmetric(1:i)';
      if cumplot(i)>.90 & nstop90 > 0
         cum90=xmetric(i);
         nstop90=0
      end
      if cumplot(i)>.95 & nstop95 > 0
         cum95=xmetric(i);
         nstop95=0
      end
end
iplot=1
plot(xmetric,cumplot)
title('cumulative distribution of ratio')
```

```
text(10,.5,['90% is at  ' num2str(cum90)])
text(10,.4,['95% is at  ' num2str(cum95)])

if(iplot==1)
   print -dwin
end
%distribution of chi^2/d.f. when mean is not unity
function y=chidf(x)
global degfree
global mean
n=degfree;
n2=n/2;
n2m=n2-1;
u=degfree*x/mean;
y=(n/mean)* (1/((2^n2)*gamma(n2)))* u.^n2m.*exp(-u/2);
end
```

Appendix X
Some Statistical Considerations and Alternate Designs and Considerations for Bioequivalence

X.1 PARALLEL DESIGN IN BIOEQUIVALENCE

The great majority of bioequivalence studies measure drug in body fluids, such that products can be compared within an individual using crossover designs. In some rare circumstances, this approach is either not possible or impractical. For example, drugs with long half-lives may not be amenable to a crossover design or studies where a clinical endpoint is required in patients because of insufficient blood concentrations. In these cases a parallel design may be used.

In parallel designs comparative products are not given to the same patient. Patients are randomly assigned to one of the test products. In this discussion, we will use examples where two products are to be compared, a test and reference product. Typically, a random device is used to assign product to patients as they enter the study, with an aim of having equal numbers of patients in each product group. For a bioequivalence study, it would be expected that patients would all be entered together, each patient assigned a number. If more patients are needed that can be accommodated at one site, a multicenter study may be necessary. Randomization schemes for parallel studies have been described in the literature [1]. Note that for these designs, the number of observations in each group needs not be identical; dropouts do not invalidate any of the remaining data.

Endpoints in clinical studies can be "continuous" data or discrete. For example, the endpoint could be treadmill time to angina, or a local treatment for ulcers, where the endpoint is dichotomous, that is, success or failure. We will discuss the analysis of both kinds of studies.

Another problem with parallel studies is how to construct a test comparing products. For numerical data, one should consider whether or not to transform the data. The usual bioequivalence study uses a log transform of the pharmacokinetic parameters. In clinical studies, it is not obvious if the clinical result should be transformed. In general, a transformation is not necessary, but may depend on the nature of the resulting data. For dichotomous data, we have a different problem when comparing outcomes.

The analysis will be illustrated using the following hypothetical data. The study is for a drug taken orally that is absorbed, but is in such low concentrations in the blood that an acceptable analysis is not available. The study looks for a clinical endpoint that can be measured objectively. The drug is given once daily for seven days. The endpoint is the average time it takes for patients to fall asleep. A parallel study is used because of the potential for carryover of a physiological or psychological nature. At first, the data are considered to be approximately normal, and no transformation is needed. The study design is single blind, with the evaluator being blinded, as is typical for the usual bioequivalence crossover studies. The results of the study are as follows:

Product	*N*	Average	Variance
Test	24	0.980	0.228
Reference	26	0.949	0.213

Without a (log) transformation, the confidence interval computation is more complicated than that for the usual crossover design with a log transformation. The ratio of test/reference is not normally distributed. Before the log transformation requirement was initiated, an approximate confidence interval was computed as described by FDA and the literature [1]. However,

presently, the FDA is recommending use of Fieller's method for computing confidence intervals. We will calculate the confidence interval using both of these methods for the sake of illustrating the methods and comparing the results.

X.1.1 Old FDA Method

$$\frac{\text{Confidence interval}(1) = [(\text{Average test} - \text{average reference}) \pm t(\text{d.f.}0.1) * \text{sqrt}(\text{variance} * (1/N1 + 1/N2))]}{\text{Average test}}$$

Where the t value is from the t distribution with appropriate degrees of freedom at the (one-sided) 5% level. The variance, in this case would be the pooled variance from the two groups. The computations for the numerator are the same as that computed for a 90% confidence interval in a two independent group t test.

In this example, the point estimate (Test/Reference) is 103.3% with a lower and upper 90% confidence interval equal to 92.3% and 114.3%, respectively (see Table X.1 for raw data and calculations).

One could also use a log transformation if appropriate. Of course, there should be some documentation of the rationale for a transformation. Using a log transform the results are 103.1 with a lower and upper 90% confidence interval equal to 91.8% and 115.8%, respectively

Table X.1 Data for Parallel Design Study (Clinical Endpoint)

Subject	Test	Subject	Reference
1	0.82	1	0.83
2	0.54	2	1.22
3	1.01	3	1.14
4	1.4	4	0.88
5	0.89	5	0.95
6	1	6	1.4
7	0.76	7	1.1
8	1.23	8	0.84
9	0.87	9	0.99
10	0.99	10	0.61
11	1.1	11	0.68
12	1.15	12	1.03
13	0.76	13	0.79
14	0.65	14	1.09
15	1.25	15	0.91
16	1.11	16	1.22
17	0.77	17	1.1
18	0.63	18	0.89
19	0.98	19	1.17
20	1.32	20	0.58
21	1.26	21	1.11
22	0.94	22	0.75
23	0.99	23	0.95
24	1.11	24	1.03
		25	0.88
		26	0.54
	Test		Reference
Average	0.9804167		0.949231
Standard deviation	0.2281967		0.213353
Variance	0.0520737		0.045519
Point estimate =		1.032853863	
t =		1.677224191	
Pooled variance =		0.048660009	
Upper level		114.3170257	
Lower level		92.2537469	

Table X.2 Data For Parallel Design Study Transformed to Logarithms

Subject	Test	Log	Subject	Ref	Log
1	0.82	−0.19845	1	0.83	−0.186329578
2	0.54	−0.61619	2	1.22	0.198850859
3	1.01	0.00995	3	1.14	0.131028262
4	1.4	0.336472	4	0.88	−0.127833372
5	0.89	−0.11653	5	0.95	−0.051293294
6	1	0	6	1.4	0.336472237
7	0.76	−0.27444	7	1.1	0.09531018
8	1.23	0.207014	8	0.84	−0.174353387
9	0.87	−0.13926	9	0.99	−0.010050336
10	0.99	−0.01005	10	0.61	−0.494296322
11	1.1	0.09531	11	0.68	−0.385662481
12	1.15	0.139762	12	1.03	0.029558802
13	0.76	−0.27444	13	0.79	−0.235722334
14	0.65	−0.43078	14	1.09	0.086177696
15	1.25	0.223144	15	0.91	−0.094310679
16	1.11	0.10436	16	1.22	0.198850859
17	0.77	−0.26136	17	1.1	0.09531018
18	0.63	−0.46204	18	0.89	−0.116533816
19	0.98	−0.0202	19	1.17	0.157003749
20	1.32	0.277632	20	0.58	−0.544727175
21	1.26	0.231112	21	1.11	0.104360015
22	0.94	−0.06188	22	0.75	−0.287682072
23	0.99	−0.01005	23	0.95	−0.051293294
24	1.11	0.10436	24	1.03	0.029558802
			25	0.88	−0.127833372
			26	0.54	−0.616186139
		Test			Reference
	Point estimate =	1.032854			1.03123
	t =	1.677224			
	Pooled variance =	0.05942			
	Upper level	115.775	(log) 0.146479		
	Lower level	91.8533	(log) −0.08498		

(see Table X.2 for raw data and calculations). This result is similar to that for the untransformed data, a result of the relatively low coefficient of variation.

X.1.2 Fieller's Method

Fieller's method can be used to compute confidence intervals for the ratio of two normally distributed variables. There are assumptions when using Fieller's method that include the assumption of normality. Also the value of the denominator in Fieller's equation must show the reference product average to be "statistically significant" when compared to zero. In most cases, the results of this approach should give similar conclusions as the old FDA method above.

The method is described in an FDA document [2], which is duplicated below.

X.1.2.1 Fieller's Calculation for Crossover data (Correlated Values)

For an example of this calculation, see Ref. [2].

$$\frac{[(\text{Average test/average reference}) - G(\sigma - \text{RT}/\sigma - \text{RR}) \pm (1/\text{average reference}) \times \text{Sqrt}(K * \sigma - \text{RR}/n]}{(1 - \text{G})}$$

$$G = \frac{t^2 * \sigma - \mathrm{RR}}{n * \text{average reference}^2}$$

$$K = \left(\frac{\text{Average test}}{\text{average reference}}\right)^2 + (1 - G)(\sigma - \mathrm{TT}) + \left(\frac{\sigma - \mathrm{RT}}{\sigma - \mathrm{RR}}\right) * \left(\frac{G * \sigma - \mathrm{RT}}{\sigma - \mathrm{RR} - 2} * \frac{\text{Average test}}{\text{Average reference}}\right)$$

$$\sigma - \mathrm{TT} = \text{Variance test}$$

$$\sigma - \mathrm{RR} = \text{Variance reference}$$

$$\sigma - \mathrm{RT} = \sum \frac{(\text{test} - \text{average test})(\text{reference} - \text{average reference})}{n - 1}$$

X.1.2.2 Fieller's Calculation for Independent Data

If the two groups are independent as in the above example, the term that relates to the correlation of the data for the two groups, $\sigma - \mathrm{RT}$, is considered to be zero, and is not included in the equation. Applying the data in Table X.1 without a transformation, the calculations are as follows:

$$\text{Interval} = [(\text{Average test/average reference}) \pm (1/\text{average reference}) \times \text{Sqrt}(K * \sigma - \mathrm{RR}/n)]/(1 - G)$$

$$G = t^2 * \sigma - \mathrm{RR}/(n * \text{average reference}^2)$$

$$K = (\text{Average test/average reference}^2 + (1 - G)(\sigma - \mathrm{TT}/\sigma - \mathrm{RR}) - (2 * \text{Average test/average reference})$$

	Test		Reference
Average	0.9804167		0.949231
Standard deviation	$\sigma - \mathrm{TT} =$ 0.2281967		$\sigma - \mathrm{RR} =$ 0.213353
Pooled variance		0.04866	

$$G = 0.0054659$$

$$K = 2.204524409$$

$$\text{Upper interval} = 1.09866168$$

$$\text{Lower interval} = 0.967046045$$

X.2 OUTLIERS

An outlier is an observation far removed from the bulk of the observations. A more detailed discussion and statistical detection of outliers, as well as their treatment can be found in a number of references [1].

For crossover studies and parallel studies, the detection of an outlier using common statistical methods is straightforward. Using an appropriate statistical model, a single statistical outlier can be identified. Although this alone may be sufficient to suspect an anomaly, usually

it would be more definitive if other evidence is available to verify that the suspected datum is indeed "mistaken." A more creative approach is possible in the case of replicate designs (see below). In these situations, we have estimates of within-subject variability that can be used to identify outliers. For example, if the within-subject variance for a given treatment (omitting the subject with the suspected outlier) is 0.04, and the two values for the log-transformed parameter for the suspected data are 3.8 and 4.9 (corrected for period effects if necessary and meaningful), we may perform an F test comparing variances for the suspect data and the remaining data. The F ratio is

$$\frac{0.61}{0.04} = 15.3.$$

If the degrees of freedom for the denominator ($N - 1$, where N is the number of subjects including the outlier) is 25, an F value of 15.3 is highly significant ($P < 0.01$). One may wish to correct the significance level, although there is no precedent for this approach. An alternative analysis could be an ANOVA with and without the suspected outlier. An F test with 1 d.f. in the numerator and appropriate d.f. in the denominator would be

$$\frac{[\text{SS (all data)} - \text{SS (without outlier data)}]}{1}.$$

Another approach that has been used is to compare results for periods 1 and 2 versus periods 3 and 4 in a 4 period fully replicated design.

Of course, if there are is an obvious cause for the outlier, a statistical justification is not necessary. However, further evidence, even if only suspicious, is helpful.

If an outlier is detected, as noted above, the most conservative approach is to find a reason for the outlying observation, such as a transcription error, or an analytical error, or a subject who violated the protocol, and so on. In these cases, the data may be reanalyzed with the corrected data, or without the outlying data if due to analytical or protocol violation, for example.

If an obvious reason for the outlier is not forthcoming, one may wish to perform a new small study, replicating the original study, including the outlying subject along with a number of other subjects (at least 5 or 6) from the original study. The results from the new study can be examined to determine if the data for the outlier from the original study is anomalous. The procedure here is not fixed, but should be reasonable, and makes sense. One can compare the test to reference ratios for the outlying subject in the two studies, and demonstrate that the data from the new study show the outlying subject is congruent with the other subjects in the new study, for example.

X.3 DICHOTOMOUS OUTCOME

Studies with a dichotomous outcome (e.g., cured or not cured) are, typically, clinical studies on patients. They may be parallel or crossover studies. An example of a crossover study with a dichotomous outcome would be an application of a patch or topical product studying sensitivity or evidence of a pharmacodynamic response. It would be difficult to compare products based on a ratio for crossover designs with a dichotomous outcome. Statistical tests for such designs would fall in the category of a McNemar test, where only those results that are different for the two products are considered in the analysis. Thus, the results that are "positive" for both products, or "negative" for both products would not be considered in the analysis. Thus far, no regulatory requirements have been issued for bioequivalence for such designs.

Parallel designs for bioequivalence using dichotomous outcomes are not uncommon. These studies usually use patients with the "disease." The results are analyzed using either the binomial distribution or the normal approximation to the binomial, where the outcome may be cured or not cured. The FDA guidances suggest that the confidence interval for the difference of the proportion of "successes" (or "failures") between the products be within ±20% for equivalence. Some criteria may be based on a one-sided 95% confidence interval in the case of noninferiority studies. Proposals have been made to modify the ±20% window for equivalence depending on the observed proportion [3].

For example, consider the following example:

Test product	160/200 successes = 80%
Reference product	170/200 successes = 85%

The confidence interval for the difference in proportion of successes is calculated as

$$(85 - 80) \pm \text{sqrt}\left(P0 * Q0 * \left(\frac{1}{N1} + \frac{i}{N2}\right)\right) = 5 \pm 1.96 * \text{sqrt}\left(0.825 * 0.175 * \left(\frac{2}{200}\right)\right) = 5 \pm 7.4.$$

This result would pass the ± 20% requirements. The interval is −2.4% to 7.4%.

X.4 STEADY STATE STUDIES

Steady state (SS) studies have been used to study bioequivalence for some drug products, for example, controlled release products and highly variable products. SS is approximately attained after about 5 drug half-lives. For example, if the half-life is 8 hours, the drug should be administered for about 40 hours; for example, five single doses given at 8-hour intervals. At SS, theoretically, C_{max}, C_{min}, and the AUC during a dosing interval remain constant. In particular, the relative amount of drug absorbed is measured by the AUC over the dosing interval at SS. SS studies are now discouraged by the FDA. One reason given for this proposal is that the variability is reduced in SS studies, resulting in a less sensitive test for showing differences. This lowering of the variability, however, could be useful from a practical point of view to compare highly variable drug products. Thus, there is some controversy about the use and utility of SS studies.

The design of SS studies are typically crossover studies with multiple dosing. Two groups of patients are entered into the study similar to the usual two-treatment, two-period design. However in the SS design, multiple dosing is administered, using the usual dosing schedule, for a sufficient period of time to attain SS. One would estimate the total number of doses needed based on a package insert, literature or available experimental results.

SS is achieved if the PK parameters remain constant with a given multiple dosing regimen. Typically, dosing should be administered for at least three or more consecutive days. Appropriate dosage administration and sampling should be carried out to document SS. The trough concentration data should be analyzed statistically to verify that SS was achieved prior to Period 1 and Period 2 pharmacokinetic sampling.

According to the FDA Guidance [4,5], the following parameters should be measured:

a. Individual and mean blood drug concentration levels.
b. Individual and mean trough levels ($C_{min\ ss}$).
c. Individual and mean peak levels ($C_{max\ ss}$).
d. Calculation of individual and mean steady state $AUC_{interdose}$ ($AUC_{interdose}$ is AUC during a dosing interval at steady state).
e. Individual and mean percent fluctuation.

$$\left[= 100 * \frac{C_{max\ ss} - C_{min\ ss}}{C_{average\ ss}}\right]$$

f. Individual and mean time to peak concentration.

The log-transformed AUC and C_{max} data during the final dosing interval should be analyzed statistically using analysis of variance. The 90% confidence interval for the ratio of the geometric means of the pharmacokinetic parameters (AUC and C_{max}) should be within 80% to 125%. Fluctuation for the test product should be evaluated for comparability with the fluctuation of the reference product.

X.5 BIOEQUIVALENCE STUDIES PERFORMED IN GROUPS

Bioequivalence studies are usually performed at a single site, where all subjects are recruited and studied as a single group. On occasion, more than one group is required to complete a study. For example, if a large number of subjects are to be recruited, the study site may not be large enough to accommodate the subjects. In these situations, the study subjects are divided into two cohorts. Each cohort is used to assess the comparative products individually, as might be done in two separate studies. Typically, the two cohorts are of approximately equal size. Another example of a study that is performed in groups is the so–called "Add-on" study. In Canada, if a study fails because it was not sized sufficiently, an additional number of subjects may be studied so that the combined, total number of subjects would be sufficient to pass the study based on results of the initial failing study. This reduces the cost to the pharmaceutical company, which, otherwise, would have to repeat the entire study with a larger number of subjects.

It is not a requirement that each group separately pass the confidence interval requirement. The final assessment is based on a combination of both groups. The totality of data is analyzed with a new term in the analysis of variance (ANOVA), a Treatment × Group interaction term. This is a measure (on a log scale) of how the ratios of test to reference differ in the groups. For example, if the ratios are very much the same in each group, the interaction would be small or negligible. If interaction is large, as tested in the ANOVA, then the groups cannot be combined. However, if at least one of the groups individually passes the confidence interval criteria, then the test product would be acceptable. If interaction is not statistically significant ($P > 0.10$), then the confidence interval based on the pooled analysis will determine acceptability. It is an advantage to pool the data, as the larger number of subjects results in increased power and a greater probability of passing the bioequivalence confidence interval, if the products are truly bioequivalent.

In Canada, a second statistical test (in addition to the test for interaction) is required when an Add-on group is studied. Each group is analyzed separately in the usual manner. The residual variances from the two separate groups are compared using an F test. If the variances are significantly different, the groups cannot be pooled and the product will probably fail. Note that the second group is studied only if the original study failed because of lack of size. It is possible that the Add-on study could pass on its own, and in this case, the test product would be acceptable. This second test comparing variances seems rather onerous, because an analysis is possible for the combined groups with unequal variance. However, it may be the intention of the Canadian HPB to trade the benefit of the add-on design for unnecessarily more stringent regulatory requirements. An intensive study of the appropriateness and properties of add-on designs is being investigated by FDA and industry personnel in the United States at the time of this writing. A final finding is forthcoming.

An interesting question arises if more than two groups are included in a bioequivalence study. As before, if there is no interaction, the data should be pooled. If interaction is evident, at least one group is different from the others. Usually, it will be obvious which group is divergent from a visual inspection of the treatment differences in each group. The remaining groups may then be tested for interaction. Again, as before, if there is no interaction, the data should be pooled. If there is interaction, the aberrant group may be omitted, and the remaining groups tested, and so on. In rare cases, it may not be obvious which group or groups are responsible for the interaction. In that case, more statistical treatment may be necessary, and a statistician should be consulted. In any event, if any single group or pooled groups (with no interaction) passes the bioequivalence criteria, the test should pass. If a pooled study passes in the presence of interaction, but no single study passes, one may still argue that the product should pass, if there is no apparent reason for the interaction. For example, if the groups are studied at the same location under the identical protocol, and there is overlap in time among the treatments given to the different groups, as occurs often, there may be no obvious reason for a significant interaction. Perhaps, the result was merely due to chance, random variation. One may then present an argument for accepting the pooled results.

The following statistical models have been recommended for analysis of data in groups:

Model 1: GRP SEQ GRP∗SEQ SUBJ(GRP∗SEQ) PER(GRP) TRT GRP∗TRT
If the GRP∗TRT term is not significant ($P > 0.10$), then reanalyze the data using Model 2.
Model 2: GRP SEQ GRP∗SEQ SUBJ(GRP∗SEQ) PER(GRP) TRT

X.6 REPLICATE STUDY DESIGNS

Replicate studies in the present context are studies in which individuals are administered one or both products on more than one occasion. For purposes of bioequivalence, either three or four period designs are recommended. The two treatment four-period design is the one most used. FDA [1] gives sponsors the option of using replicate design studies for all bioequivalence studies. Replicate studies may provide information on within-subject variance of each product separately, as well as potential product × subject interactions, although these analyses are not required by FDA.

The FDA recommends that submissions of studies with replicate designs be analyzed for average bioequivalence. The following (Table X.3) is an example of the analysis of a two treatment four-period replicate design to assess average bioequivalence. The design has each of two products, balanced in 2 sequences, ABAB and BABA, over four periods. Table X.1 shows the results for C_{max} for a replicate study. Eighteen subjects were recruited for the study and 17 completed the study. An analysis using the usual approach for the TTTP design, as discussed above, is not recommended. The FDA [1] recommends use of a mixed model approach as in SAS PROC MIXED (11). The recommended code is

Table X.3 Results of a Four-Period, Two-Sequence, Two-Treatment, Replicate Design (C_{max})

Subject	Product	Sequence	Period	C_{max}	Ln(C_{max})
1	Test	1	1	14	2.639
2	Test	1	1	16.7	2.815
3	Test	1	1	12.95	2.561
4	Test	2	2	13.9	2.632
5	Test	1	1	15.6	2.747
6	Test	2	2	12.65	2.538
7	Test	2	2	13.45	2.599
8	Test	2	2	13.85	2.628
9	Test	1	1	13.05	2.569
10	Test	2	2	17.55	2.865
11	Test	1	1	13.25	2.584
12	Test	2	2	19.8	2.986
13	Test	1	1	10.45	2.347
14	Test	2	2	19.55	2.973
15	Test	2	2	22.1	3.096
16	Test	1	1	22.1	3.096
17	Test	2	2	14.15	2.650
1	Test	1	3	14.35	2.664
2	Test	1	3	22.8	3.127
3	Test	1	3	13.25	2.584
4	Test	2	4	14.55	2.678
5	Test	1	3	13.7	2.617
6	Test	2	4	13.9	2.632
7	Test	2	4	13.75	2.621
8	Test	2	4	13.25	2.584
9	Test	1	3	13.95	2.635
10	Test	2	4	15.15	2.718
11	Test	1	3	13.15	2.576
12	Test	2	4	21	3.045
13	Test	1	3	8.75	2.169
14	Test	2	4	17.35	2.854
15	Test	2	4	18.25	2.904
16	Test	1	3	19.05	2.947
17	Test	2	4	15.1	2.715
1	Reference	1	2	13.5	2.603
2	Reference	1	2	15.45	2.738
3	Reference	1	2	11.85	2.472
4	Reference	2	1	13.3	2.588

Table X.3 *Continued*

5	Reference	1	2	13.55	2.606
6	Reference	2	1	14.15	2.650
7	Reference	2	1	10.45	2.347
8	Reference	2	1	11.5	2.442
9	Reference	1	2	13.5	2.603
10	Reference	2	1	15.25	2.725
11	Reference	1	2	11.75	2.464
12	Reference	2	1	23.2	3.144
13	Reference	1	2	7.95	2.073
14	Reference	2	1	17.45	2.859
15	Reference	2	1	15.5	2.741
16	Reference	1	2	20.2	3.006
17	Reference	2	1	12.95	2.561
1	Reference	1	4	13.5	2.603
2	Reference	1	4	15.45	2.738
3	Reference	1	4	11.85	2.472
4	Reference	2	3	13.3	2.588
5	Reference	1	4	13.55	2.606
6	Reference	2	3	14.15	2.650
7	Reference	2	3	10.45	2.347
8	Reference	2	3	11.5	2.442
9	Reference	1	4	13.5	2.603
10	Reference	2	3	15.25	2.725
11	Reference	1	4	11.75	2.464
12	Reference	2	3	23.2	3.144
13	Reference	1	4	7.95	2.073
14	Reference	2	3	17.45	2.859
15	Reference	2	3	15.5	2.741
16	Reference	1	4	20.2	3.006
17	Reference	2	3	12.95	2.561

```
PROC MIXED;
CLASSES SEQ SUBJ PER TRT;
MODEL LNCMAX = SEQ PER TRT/DDFM = SATTERTH;
RANDOM TRT/TYPE = FA0(2) SUB = SUBj G;
REPEATED/GRP = TRT SUB = SUBJ;
LSMEANS TRT;
ESTIMATE 'T VS. R' TRT 1 − 1/CL ALPHA = 0.1;
RUN;
```

The abbreviated output is shown in Table X.4.

Table X.4 Analysis of Data from Table X.1 for Average Bioequivalece

ANALYSIS FOR LN-TRANSFORMED CMAX

The MIXED Procedure

Class Level Information

Class	Concentrations	Values
SEQ	2	1 2
SUBJ	17	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
PER	4	1 2 3 4
TRT	2	1 2

Table X.4 (Continued)

Covariance Parameter Estimates (REML)

Cov Parm	Subject	Group	Estimate
FA(1,1)	SUBJ		0.20078553
FA(2,1)	SUBJ		0.22257742
FA(2,2)	SUBJ		-0.00000000
DIAG	SUBJ	TRT 1	0.00702204
DIAG	SUBJ	TRT 2	0.00982420

Tests of Fixed Effects

Source	NDF	DDF	Type III F	Pr > F
SEQ	1	13.9	1.02	0.3294
PER	3	48.2	0.30	0.8277
TRT	1	51.1	18.12	0.0001

ESTIMATE Statement Results

Parameter	TVS. R					
Alpha = 0.1		**Estimate**	**Std Error**	**DF**	**t**	**Pr > |t|**
		0.09755781	0.02291789	51.1	4.26	0.0001
			Lower	**0.0592**		**Upper 0.1360**

Least Squares Means

Effect	TRT	LSMEAN	Std Error	DF	t	Pr > |t|
TRT	1	2.71465972	0.05086200	15	53.37	0.0001
TRT	2	2.61710191	0.05669416	15.3	46.16	0.0001

ANALYSIS FOR LN-TRANSFORMED CMAX

REFERENCES

1. Bolton S, Bon C. Pharmaceutical Statistics, 4th ed. Rockville, MD: Marcel Dekker, 2004.
2. Guidance, Topical Dermatologic Corticosteroids: In Vivo Bioequivalence, Issue Date June 2, 1995, FDA.
3. Statistical Considerations for Clinical Trials in Developing Antimicrobial Drugs, Anti-infective Drug Products Advisory Committee, July 29, 1998, Daphne Lin, Ph.D., CDER/OFB/DBIV.
4. Guidance for Industry, Bioavailability and Bioequivalence Studies for Orally Administered Drug Products, Genereal Considerations, CDER, 2003.
5. Guidance for Industry, Clozapine Tablets: In Vivo Bioequivalence and In Vitro Dissolution Testing, Center for Drug Evaluation and Research (CDER), June 2005.

Answers to Exercises

CHAPTER 1

1. (a) Tablet hardness, blood concentration of drug, creatinine in urine
   (b) Number of patients with side effects, bottles with fewer than 100 tablets, white blood cell count
   (c) Any continuous variable, rating scale
   (d) Race, placebo group in clinical study, number of bottles of syrup that are cloudy
2. None (This is a simple linear transformation; the C.V. is unchanged.)
3.

Interval	Frequency
−99.5 to −83.5	1
−83.5 to −67.5	2
−67.5 to −51.5	10
−51.5 to −35.5	16
−35.5 to −19.5	26
−19.5 to −3.5	34
−3.5 to +12.5	33
12.5 to 28.5	24
28.5 to 44.5	8
44.5 to 60.5	2

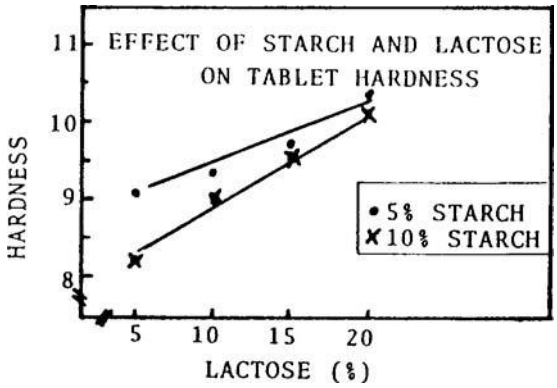
4. −10.27
5. Approximately 82% between 95 and 105 mg (0.91–0.09); approximately 9% above 105 mg
6. (a) Mean = −12.65, $S = 31.68$; (b) $\bar{X} = -7$, $S = 30.48$ (read data in columns). Differences probably not significant. The last set is more precise but the standard deviations are virtually identical (the variability is probably not different in the two sets of data).
7. Median = −16 = (−13 − 19)/2; range = 46 to − 64 = 110
8. (a) Median = −16 as in Problem 7; range = 100 to − 64 = 164
   (b) Mean = −8.5, $S = 40.09$, $S^2 = 1607$
10. Probably not unbiased
11. $\sigma = \sqrt{2/3} = 0.816, \bar{S} = 0.6285$
13. $\sqrt{\Sigma(X - \bar{x})^2/(N-1)} = \sqrt{(0.0001 + 0 + 0.0001)/2} = 0.01$. The s.d. of 2.19; 2.20, and 2.21 is also 0.01. If a constant is added to each value (the constant added here is 1), the s.d. is unchanged. Standard deviation depends on differences among the values, not the absolute magnitude.
14. (a) 101.875; (b) 4.79; (c) 22.98; (d) 4.79/101.875 = 0.047; (e) 14; (f) 101.5
15. $\Sigma N_i X_i^2 = 1(90.5)^2 + 6(70.5)^2 + \cdots + 16(29.5)^2 + 3(49.5)^2 = 137{,}219$
    $\Sigma N_i X_i = 1(-90.5) + 6(-70.5) + \cdots + 16(29.5) + 3(49.5) = -1658$
    $\Sigma N_i = 156$
    $S^2 = [137{,}219 - (-1658)^2/156]/155 = 771.6$
    $S = 27.79$
16. 16.167, 9.865, 7.009

17. $\bar{X}_w = (2 \times 3 + 5 + 7 + 3 \times 11 + 14 + 3 \times 57)/10 = 17.9$

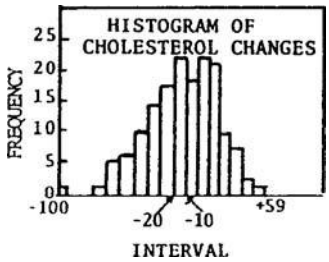
$$S_w^2 = \frac{7149 - 3204.1}{9} = 438.3$$

CHAPTER 2

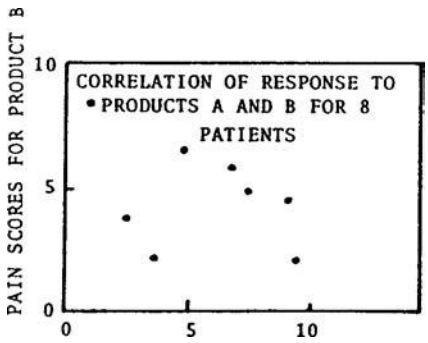
1.



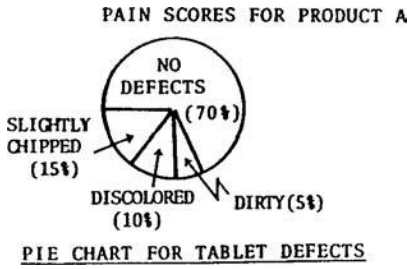
2.



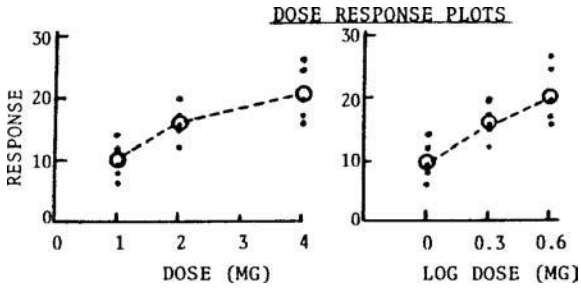
3.



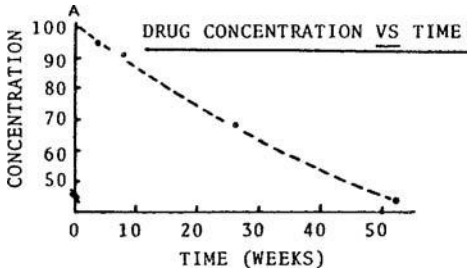
4.

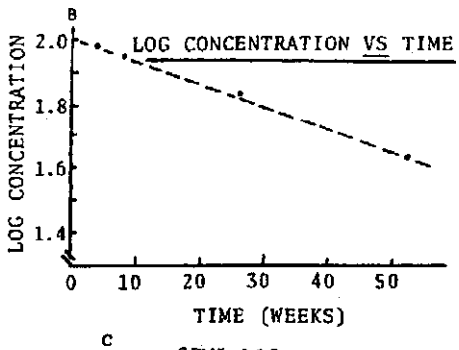


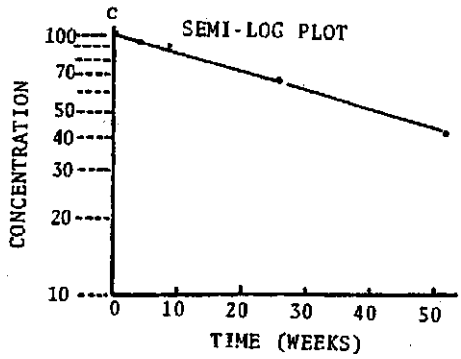
5.


DOSE RESPONSE PLOTS
RESPONSE
30
20
10
0
0 1 2 3 4
DOSE (MG)
0 0.3 0.6
LOG DOSE (MG)

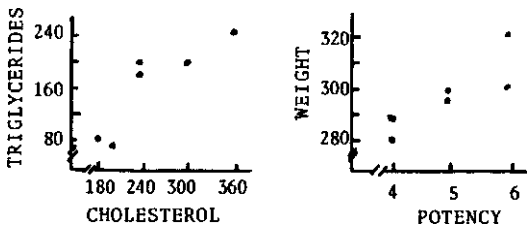
6.


A
DRUG CONCENTRATION VS TIME
CONCENTRATION
100
90
80
70
60
50
0 10 20 30 40 50
TIME (WEEKS)


B
LOG CONCENTRATION VS TIME
LOG CONCENTRATION
2.0
1.8
1.6
1.4
0 10 20 30 40 50
TIME (WEEKS)

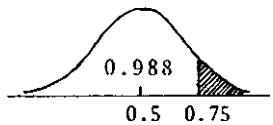

C
SEMI-LOG PLOT
CONCENTRATION
100
70
50
40
30
20
10
0 10 20 30 40 50
TIME (WEEKS)

7.


TRIGLYCERIDES
240
160
80
180 240 300 360
CHOLESTEROL
WEIGHT
320
300
280
4 5 6
POTENCY

CHAPTER 3

1. Larger sample, more representative, blinded, less bias, etc.
2. All patients with disease who can be treated by antibiotic
3. Preference for new formulation among 24 panelists; number of broken tablets in sample of 100; race of patients in clinical study
4. 50,000 specked, but 20,000 are also chipped. Therefore, 30,000 are only specked. Probability of speck or chip is 0.06 (60,000 tablets have either a speck or a chip).
5. (a) $P(A \text{ and } B) = P(A|B)P(B)$. Let A = high blood pressure and B = diabetic. Then $P(A \text{ and } B) = (0.85)(0.10) = 0.085$.
   (b) If independent, $P(A) = P(A|B)$; $0.25 \neq 0.85$; they are not independent.
6. $(0.75)^2(0.25)^2 = 0.35163 \times 6 = 0.21094$. There are 6 ways of choosing 2 patients out of 4 $\binom{4}{4}$.
7. $(0.6)^3(0.4)^3 = 0.013824 \times 20 = 0.276$. There are 20 ways of choosing 3 patients out of 6 $\binom{6}{4}$.
8. 0.3697
9. (a) Approximately 0.8; (b) 0.2
10. $Z = (170 - 215)/35 = 1.29$; probability = approximately 0.10
11. $Z = (60 - 50)/5 = 2, P(X \leq 60) = 0.977$; $Z = (40 - 50)/5 = -2$, $P(X \leq 40) = 0.023$; $P(40) \leq X \leq 60) = 0.977 - 0.023 = 0.954$
12. Not necessarily; the patient may have a cholesterol value in the extremes of the normal distribution.
13. $Z = (137 - 140)/2.5 = -1.2$, probability $\leq Z = 0.115$; $Z = (142 - 140)/2.5 = 0.8$, probability $\leq Z = 0.788$; $P(137 \leq Z \leq 142) = 0.788 - 0.115 = 0.673$
14. $Z = (280 - 205)/45 = 1.67$; probability = 0.952; probability $Z > 280 = 1 - 0.952 = 0.048$
15. There are 36 equally likely possibilities, of which one is 2.
16. Yes! The order of heads and tails is not considered in the computation of probability.
17. $P(0 \text{ defects}) = \binom{20}{0}(0.01)^0(0, 99)^{20} = 0.818$; $P(1 \text{ defect}) = \binom{20}{1}$ $(0.01)^1(0.99)^{19} = 0.165$; $P(0 \text{ or } 1 \text{ defect}) = 0.818 + 0.165 = 0.983$
18. $\binom{10}{1}(0.5)^1(0.5)^9 = 0.0098$
19. $\binom{4}{2}(0.01)^2(0.99)^2 = 0.00059$. The probability is small; and two of four cures can be considered unlikely. The probability of this event plus equally likely or less likely events (three of four and four of four cures) is close to 0.00059. Thus, we conclude that the new treatment is effective.
20. $\sqrt{(0.01)(0.99)20} = 0.445$; $\sqrt{(0.01)(0.00)/20} = 0.022$ (Problem 17)
    $\sqrt{(0.01)(0.99)4} = 0.199$; $\sqrt{(0.01)(0.99)/4} = 0.497$ (Problem 19)
21. $S = \sqrt{(0.5)(0.5)/20} = 0.112$; $Z = (0.75 - 0.5)/0.112 = 2.24$; $P(Z > 2.24) = 1 - 0.988 = 0.012$



Drug is a promising candidate. The probability of observing such a large response is small if the true proportion of responses is 50%.

22. $P(0 \text{ defects}) = 0.99^{30} = 0.7397$; $P(1 \text{ defect}) = (30)(0.01)(0.99)^{29} = 0.2242$;
    $P(0 \text{ or } 1 \text{ defect}) = 0.7397 + 0.2242 = 0.9639$; $P(\text{more than } 1 \text{ defect}) = 1 - 0.9639 = 0.0361$
23. $85 = 35 + 50 + 50 - 20 - 15 - 25 + P(ABC)$; $P(ABC) = 10\%$

CHAPTER 4

1. Starting at the upper left corner,* going down in Table IV.1. Even numbers to A. Patients assigned to A: 1, 2, 3, 5, 6, 8, 13, 14, 15, 16, 17, and 19.

* We started at the upper left and read down for convenience and for the purpose of illustration. Otherwise, the starting point should be random.

2. Start as in Problem 1. If the number is 1 to 3, assign to A; 4 to 6, assign to B; 7 to 9, assign to C; do not count zeros.

Patient	Random number	Treatment
1	4	B
2	8	C
3	2	A
4	5	B
5	8	C
6	4	B
7	9	C
8	2	A
9	1	A
10	5	B
11	5	B
12	5	B
13	4	B
14	6	B (8 B's)
15	8	C
16	3	A
17	9	C
18	3	A
19	8	C
20	8	C
21	9	C (8 C's)
Remaining patients (22, 23, 24) given A		

(May also randomize in groups of three; e.g., the first three patients are B, C, A—random numbers 4 and 8 refer to B and C.)

3. Start as above in Table IV.1. Use two-digit numbers between 1 and 30: 28, 24, 14, 6, 17, 29.
5. Placebo: 1, 2, 4, 5, 7, 8, 9, 10, 12, 18; Drug: 3, 6, 11, 13, 14, 15, 16, 17, 19, 20.
6. Take 20 tablets at a specific time every hour, all at the same time each hour (e.g., on the hour). Take 20 tablets each hour, but randomize the time the 20 are taken; e.g., first hour, take the sample at 5 min past the hour; second hour, take at 25 min past the hour; etc. Take tablets, one every 3 min during each hour. Take tablets at random times during each hour.
7. (see also Problem 3) 44, 8, 28, 55, 88
10. $\bar{X} = 300.7$

CHAPTER 5

1. $Z = (49.8 - 54.7)/2 = -2.45$; $= 0.0071$
2. $103 \pm 2.58(2.2)/\sqrt{10} = 103 \pm 1.8 = 101.2$ to 104.8
3. (a) $5.95 \pm 2.57(1.16/\sqrt{6} = 5.95 \pm 0.17$
   (b) $0.024 \pm 1.96\sqrt{(0.024)(0.976)/500} = 2.4 \pm 1.34\%$
   (c) $(0.83 - 0.50) \pm 1.06\sqrt{(0.83)(0.17)}$ >sh> $60 + (0.50)(0.50)/50 = 0.33 \pm 0.17$
4. (a) $Z = |498 - 502|/(5.3/\sqrt{6} = 1.85$; not significant, $\alpha = 0.05$; two tailed test
   (b) $t = (5.08 - 4.86)/\sqrt{0.095(2/5} = 1.13$; not significant at 5% level
   (c) $T = 4/\sqrt{(15.2)/6} = 2.51$; $t_5 = 2.57$; just misses significance at 5% level; two-tailed test.
5. (a) 0.098, larger
   (b) 0.350 and 0.261, average s.d. $= 0.305$, pooled s.d. $= 0.308$
6. (a) $\bar{X} = 10.66$, s.d. $= 0.932$
   (b) $\bar{X} = 9.66$, s.d. $= 0.4696$. $t_{18} = 1/(0.738\sqrt{2/10} = 3.03$; difference is significant
   (c) Approximate test: $Z = (0.7 - 0.2)/\sqrt{(0.45)(0.55)(2/10)} = 2.24$; significant. Chi-square test with correction $= 3.23$; not quite significant.
   (d) $0.45 \pm 1.96\sqrt{(0.45)(0.55)(1/20)} = 0.45 \pm 0.22$

7. Paired t test; 3 d.f.; $\alpha = 0.05$; two tailed test
   (a) $t = 0.07\sqrt{0.0039/4} = 2.23$; not significant
   (b) $0.07 \pm 3.18(0.0627)/\sqrt{4} = 0.07 \pm 0.10$
8. (a) Paired t test, 11 d.f.; $t = 0.5/(0.612/\sqrt{12} = 2.83$; significant at 5% level
   (b) $0.5 \pm 2.2(0.612/\sqrt{12} = 0.5 \pm 0.39$
9. $9/60$ and $6/65 = 15/125 = 0.12$; $80/1000$ and $57/1000 = 137/2000 = 0.685$
10. $t = (16.7 - 15)/(3.87/\sqrt{10}) = 1.39$; 10% level, one-sided test, this is significant
11. Chi-square $= (3.5)^2(2/12 + 2/88) = 2.32$; not significant
12. $Z = (|0.05 - 0.028| - 1/400)/\sqrt{(0.028)(0.972)/200} = 1.67$; not significant. $0.05 \pm 1.96\sqrt{(0.95)(0.05)/(200)} = 0.5 \pm 0.03$; $10 \pm 1.96\sqrt{(0.95)(0.05)(200)} = 10 \pm 6$
13. (a) $50 \pm 1.96\sqrt{(0.01)(0.99)(5000)} = 50 \pm 13.79$ in 5000 for 1,000,000 tablets; $10{,}000 \pm 2758$
   (b) $(0.01 - 0.02)/\sqrt{(0.02)(0.98)/5000} = -5.05$; P #of 0.001;
   very unlikely $1.96\sqrt{(0.01)(0.99)/N} = 0.001$, $N = (1.96)^2(0.99)(0.01/10) = 38{,}032$
14. Chi-square $= (4.5)^2(1/35.45 + 1/24.55 + 1/29.55 + 1.20.45) = 3.07$; not significant at 5% level. $(40/60 - 25/50) \pm 1.96\sqrt{(0.67)(0.33)/60 \pm (0.5(0.5)/50} = 0.167 \pm 0.183$
15. $Z = (|0.75 - 0.5| - 1/80)/\sqrt{(0.5)(0.5)/40} = 3.0$; $P < 0.05$
16. $Z = (|0.45 - 0.2| - 1/40)/\sqrt{(0.8)(0.2)/20} = 2.51$; $P < 0.05$; $0.45 \pm 2.58\sqrt{(0.45)(0.55)/20} = 0.45 \pm 0.287$
17. Chi-square $= (3.5)^2(1/13.85 + 1/86.15 + 1/13.15 + 1/81.85) = 2.10$; not significant
18. $(1.8)^2(1/7.2 + 1/7.8 + 1/52.8 + 1/57.2) = 0.98$
19.

80	920
57	943

   $= 2\times2$ table

   $\chi^2 = 11^2(1/68.5 + 1/931.5 + 1/68.5 + 1/931.5) = 3.79$; just misses significance at 5% level
20. $F_{9,9} = 0.869/0.220 = 3.94$, $P < 0.10$ (Table IV.6). This is a two-sided test. A ratio of 3.18 is needed for significance at the 10% level.
21. Correct $\chi^2 = 3.79$; d'Agostino $= 2.04$
22. $\chi^2 = 28.6135 - 20.8591 = 7.75$ ($P < 0.05$)
23. $\sigma^2 = \dfrac{9 \times 5}{0.711} = 63.29$ $\sigma = 7.96$
24. $\sigma^2 = \dfrac{(7.8)^2}{18.49} = 95$ $\sigma = 9.7$

CHAPTER 6

1. $2(5/10)^2(1.96 + 0.84)^2 + 0.25(1.96)^2 =$ approximately 5 per group
2. $2(5/10)^2(1.96 + 0.84)^2 =$ approximately 4 per group
3. $[(0.8 \times 0.2 + 0.9 \times 0.1)/(0.1)^2](1.96 + 1.28)^2 =$ approximately 263 per group
4. $[(0.5 \times 0.5 + 0.5 \times 0.5)/(0.2)^2](1.96 + 1.28)^2 =$ approximately 132 per group
5. $(1.96)^2(0.5 \times 0.5)/(0.15)^2 =$ approximately 43
   $(1.96)^2(0.2)(0.8)/(0.15)^2 =$ approximately 28
6. $(10/10)^2(1.96 + 2.32)^2 + 2 =$ approximately 21 tablets
7. (a) $Z_\beta = (3/5)\sqrt{19/2} - 1.96 = -0.11$; power is approximately 46%
   (b) $Z_\beta = (3/5)\sqrt{49/2} - 1.96 = 1.01$; power $= 84\%$
8. $(10/3)^2(1.96 + 1.28)^2 =$ approximately 117
9. $Z_\beta = (0.2/0.25)\sqrt{10} - 1.96 = 0.57$; power is approximately 71%
10. $2(12/10)^2(1.96 + 1.65)^2 + 0.25Z_\alpha^2 =$ approximately 39
11. $Z_\beta = (15/40)\sqrt{16} - 1.96 = -0.46$; power $=$ approximately 0.32
12. $(1.96)^2(0.90)(0.10)/(0.05)^2 = 138.2 =$ approximately 139
13. $N = 2(5/6)^2(1.96 + 1.28)^2 + 0.25(1.96)^2 = 15.5 =$ approximately 16
14. 23 tablets per formulation

CHAPTER 7

1. (a) $b = 40/10 = 4; a 12 - (4)(3) = 0$
   (b) $S^2_{y,x} = (164 - 16.10)/3 = 1.33; S^2_b\ 1.33/10 = 0.133$
   $t = 4/\sqrt{0.133} = 10.95$; significantly different from 0
   (c) $|4 - 5|/\sqrt{0.133} = 2.74$; d.f. $= 3$; not significant, 3.18 needed for significance
   (d) 3 hr; $Y = 4X = 12 \pm 3.18\sqrt{1.33}\sqrt{1/5 + 0.10} = 10.36$ to 13.64.
   5 hr; $Y = 4X = 20 \pm 3.18\sqrt{1.33}\sqrt{1/5 + 4/10} = 17.16$ to 22.84
   (e) $Y = 4(20) = 80 \pm 3.18\sqrt{1 + 1/5 + (20 - 3)^2/10} = 80 \pm 20.1$
   (f) $b = \sum Xy / \sum X^2 = 220/55 = 4$
2. (a) $a = -0.073; b = 0.2159$
   (b) $S^2_{y,x} = 0.003377; S^2_a = 0.001848; -1.69$(3 d.f.); not significant; may be due to interfering impurity
   (c) $C = 7.98$; confidence limits are 7.43 to 8.64; see Eq. (7.17)
3. (a) $b = 27/41.2 = 0.655, a = 100 - 0.655(200.4) = -31.3$
   (b) $Y = -31.3 + 0.655)(200) = 99.74$
   (c) $99.74 \pm 3.18\sqrt{0.0102}\sqrt{1/5 + (200 - 200.4^2/41.2} = 99.74 \pm 0.46$
4. (a) 0.9588
   (b) $t_{10} = 10.7$; r is significantly different from 0 at 5% level
5. $r = 0.6519; t_8 = 1.84/0.76 = 2.43$, significant at 5% level
6. $r = -0.93135; t_7 = 6.77$, significant at 5% level
7. $r = 0.2187; F = 6.54/1.067 = 6.135$
   $r_{ds} = (6.135) - 1)/\sqrt{(6.135) + 1)^2 - 4(0.2187^2)6.135} = 0.728$
   $t_8 = 0.728\ \sqrt{8}/\sqrt{1 - 0.728^2} = 3.00;\ p < 0.05$; drug B is less variable
8. $Y = -3.90082 + 0.99607X$; predicted values: 0.10049 ($X = \ln 5$); 0.20043 ($X = \ln 10$), 0.49928 ($X = \ln 25$), 0.99584 ($X = \ln 50$), 1.98626 ($X = \ln 100$).
9. (a) $C = 2.5482 - 0.01209t$; (b) 24.66 mos; (c) 23.27 mos; (d) 23.55 mos.
10. $a = 0.5055$

CHAPTER 8

1. For significance at the 5% level, t(8 d.f.) ≥ 2.31 (two-sided test) A vs. $B : t = (101.2 - 99.4)/S_p\sqrt{1/5 + 1/5} = 2.84 (P < 0.05)$; $S_p = 1.0$. A vs. $C : t = (101.6 - 101.2)/(1.58\sqrt{1/5 + 1/5}) = 0.40$. B vs. $C : t = (101.6 - 99.4)/(1.67\sqrt{1/5 + 1/5}) = 2.08$
2.

Source	d.f.	MS	F
Between treatments	2	0.167	0.039
Within treatments	3	4.33	

   Treatments are not significantly different.
3. Pooled error term from ANOVA table (Table 8.3) $= 2.10$
   A vs. $B : t = 1.8/\sqrt{2.10(2/5)} = 1.96$
   A vs. $C : t = 0.44$
   B vs. $C : t = 2.40\ (P < 0.05)$
   Pooled error results in different values of t. This is appropriate if F is significant and/or tests are proposed a priori (use pooled error, i.e., WMS).
4. (a) H_0: $\mu_1 = \mu_2 = \mu_3 = \mu_4$; H_a: $\mu_i \neq \mu_j$; $\alpha = 0.05$
   (b) Fixed
   (c)

Source	d.f.	MS	F
Between analysts	3	2.89	5.78 (<0.05)
Within analysts	8	0.50	

   $\text{LSD} = 2.31\sqrt{0.5(2/3)} = 1.33$
   A differs from B, C, and D; B differs from C and D

(d) Tukey test: $4.53\sqrt{0.5(3)} = 1.85$; only analysts A and C differ at 5% level Scheffé test: $\sqrt{0.5(3)4.07(1/3 + 1/3)} = 2.02$; none of the analysts differ at 5% level

5. H_0: $\mu_i = \mu_j$; H_a: $\mu_i \neq \mu_j$; $\alpha = 5\%$

(a)

Source	d.f.	MS	F
Between clinics	6	16.425	8.21 ($P < 0.05$)
Within clinics	13	2	

(b) Yes

(c) Fisher's LSD method (for example) at the 5% level
$\text{LSD} = 2.16\sqrt{2(1/3 + 1/3)} = 2.49$
Clinic 1 ≠ clinics 2, 5, 7; clinic 2 ≠ clinics 3, 5, 6; clinic 3 ≠ clinics 5, 7; clinic 4 ≠ clinic 5; clinic 5 ≠ clinics 6, 7; clinic 6 ≠ clinic 7 For comparisons to clinic 7,
$\text{LSD} = 2.16\sqrt{2(1/3 + 1/2)} = 2.79$

6. (a) Drugs fixed; (b) Machines fixed; (c) formulations fixed; (d) Machines random; (e) Clusters chosen at random

7. H_0: $\mu_1 = \mu_2 = \mu_3; \alpha = 0.05$

Source	d.f.	MS	F
Between batches	2	115.2	10.26 ($P < 0.05$)
Within batches	12	11.24	

t test shows that batch 3 is different from batches 1 and 2; e.g., batch 1 vs. batch 3: $t_{12} = (20.33 - 11.8)/\sqrt{11.24(1/6 + 1/5}$

8. (a)

Source	d.f.	MS	F
Row	5	1679.0	
Column	2	8.22	0.34 ($P > 0.05$)
Error	10	23.96	

(b)

Source	d.f.	MS	F
Row	5	52.99	
Column	2	26.06	5.37 ($P < 0.05$)
Error	10	4.86	($F_{2,10} = 4.10$ for $\alpha = 0.05$)

(c) Averages of drugs are: placebo = −0.33, drug 1 = −3.67, and drug 2 = −4.17. Tukey test: $3.88\sqrt{4.86/6} = 3.49$; therefore, drug 2 is different from placebo. Newman–Keuls test: Drugs 1 and 2 different from placebo ($P < 0.05$). Dunnett test: Drug 1 and drug 2 different from control ($P < 0.05$).

9. (a) If the six presses comprise all of the presses, the presses are fixed. Hours are fixed (i.e., each hour of the run is represented).

Source	d.f.	MS	F
Hour	4	11.95	6.76 ($P < 0.05$)
Presses	5	2.45	1.38 ($P > 0.05$)
Error	20	1.77	

(b) Presses are not significantly different (5% level)

(c) "Hours" are significantly different.

(d) Assume no interaction

(e) Use Tukey test: $4.23\sqrt{1.77/6} = 2.30$; hour 3 is significantly different from hours 1, 2, and 5.

10.

Source	d.f.	MS	F
Rows	2	7.06	2.05
Columns	2	16.89	4.91 ($P < 0.05$)
Interaction	4	3.03	0.88
Within	9	3.44	

($F_{2,9} = 4.26$ for significance at 5% level.)

"Presses" are significant. "Interaction" is not significant. Interaction means that differences between presses depend on the hour at which tablets are assayed.

11. Average results: $A = 2.90$, $B = 6.50$, $C = 6.07$
If "sites" are random, use CR as error term.
$5.04\sqrt{22.66/24} = 4.90$ (no significant differences).
If "sites fixed," use within error.
$3.4\sqrt{3.215/24} = 1.24$ A is lower than B and C)

12. ANOVA Table:

Source	d.f.	Sum-Squares	Mean Square
C	2	14.29167	7.145834
B	2	9.125	4.5625
Error	3	7.083334	2.361
Total (Adj)	7	30.5	

13. ANOVA Table:

Source	d.f.	Sum-Squares	Mean Square	F-Ratio	Prob > F
A (Method)	1	6.438E-04	7.438E-04	7.15	0.0369
Error	6	5.406E-04	9.010E-05		
Total (Adj)	7	1.184E-03			

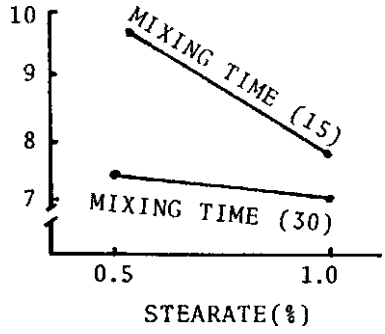
Method average
1.9921655
2.974223
$P = 0.0366$ from ANCOVA

CHAPTER 9

1. ANOVA Table:

Source	d.f.	MS	F
Stearate	1	1.56	5.21
Mixing time	1	1.82	6.1
Stearate X mixing time	1	0.72	2.41

Mixing time and stearate are significant at 5% level. Interaction is not significant.



2.

Low starch, low stearate	Low starch, high stearate
0.475	0.487
0.421	0.426
Av. = 0.448	Av. = 0.4565

High starch − low starch = 0.4565 − 0.4480 = 0.0085

3. ANOVA:

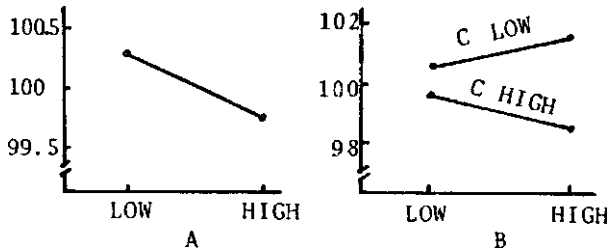
Source	d.f.	MS	F
a	1	0.66	14.0*
b	1	0.06	1.3
ab	1	0.03	—
c	1	7.41	158**
ac	1	0.10	—
bc	1	3.25	69**
abc	1	0.01	—

*$P < 0.05$; **$P < 0.01$.

Error = (0.03 + 0.10 + 0.01)/3 = 0.047; d.f. = 3

(a) a, c, bc

(b)



(c) When C is low, as B is increased, recovery is increased.
When C is high, as B is increased, recovery is decreased.

4. Synergism (or antagonism) would be evidenced by a significant AB interaction. If the effects are additive, we would expect an increase of 12 for the AB combination beyond placebo (4 from A and 8 from B). This is close to the observed increase of 14 (35 − 21) for AB. The combination of A and B work better than either one alone, but the evidence for synergism is not strong.

5. Weigh (1), ab, ac, bc: empty, a and b together, a and c together, b and c together.

Source	d.f.	MS	F
A	1	2014	21.3[a]
B	1	356	3.8
AB	1	14	0.2
C	1	45	0.5
AC	1	741	7.9[b]
BC	1	121	1.3
ABC	1	36	—
D	1	5704	60.5[a]
AD	1	114	1.2
BD	1	226	2.4
ABD	1	128	—
CD	1	0.02	0
ACD	1	10	—
BCD	1	10	—
ABCD	1	271	—
Total	15	9806	

Estimate of error = 94.3

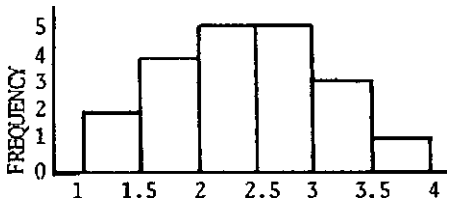
[a] $P < 0.01$

[b] $P < 0.05$

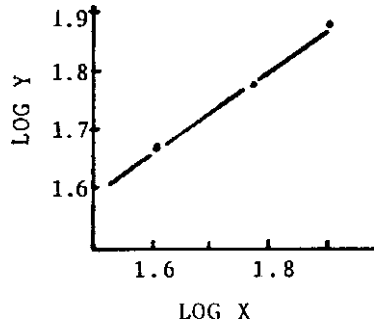
AC interaction is significant: at low C, the A effect is 52.2 − 43.3; i.e., changing from low to high level of A has little effect when C is at the low level. At high C, the A effect is 62.4 − 26.4.

CHAPTER 10

1. 1.00, 1.11, 1.60, 1.64, 1.74, 1.80, 2.06, 2.16, 2.30, 2.34, 2.36, 2.57, 2.70, 2.90, 2.90, 2.99, 3.10, 3.12, 3.18, 3,66



2. $\log Y = -0.127 + 1.068 \log X$
$\log 47 = -0.127 + 1.068 \log X$
$\log X = 1.685$
$X = 48.4\,\text{mg}$



3. $\bar{R} = 1.066, S = 0.281; (0.066)/(0.089) = 0.75$ (not significant at 5% level). The t test for log B − log A is identical except for sign as the t test for log A − log B. This example shows the problems of using ratios. The average of A/B is not (in general) the reciprocal of B/A.
4. $(62 - 54)/(62 - 47) = 8/15 = 0.533$. This is an outlier according to the Dixon test. We probably should not omit this value without further verification. The outlier could be due to analytical error and/or the presence of tablets with unusual high potency.
5. Winsorized, 50.7; using all values, 51.4.
6. $t = [2.8 - 0.6]/[1.732\sqrt{1/5 + 1/5}] = 2.01$.
(Note the difference between the variances of the two groups.)
Use a square-root transformation:
Process 1: mean = 1.4363, s.d. = 0.960
Process 2: mean = 0.6, s.d. = 0.548
$t = [1.4363 - 0.6]/[0.782\sqrt{1/5 + 1/5}] = 1.69$

CHAPTER 11

1. (b)
$$t = \sqrt{\frac{107.2 - (-3.05)}{1983.9(1/20 + 1/20)}} = 7.83 (t^2 = F)$$

2.

Source	d.f.	MS	F	
Subjects	11	5.19		
Treatment	1	0.04	0.005	Treatments are not significantly different.
Order	1	2.04	0.25	
Error	10	8.04		

3.

Source	d.f.	MS	F	
Subjects	11	16.41		
Treatments	1	155	13.19	($P < 0.01$)
Order	1	177	9.96	($P < 0.05$)
Error	10	11.75		

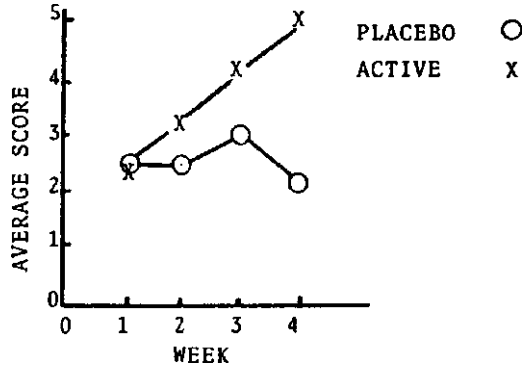
$(22.3 - 17.3) \pm 2.23\sqrt{11.75(1/12 + 1/12)} = 5 \pm 3.12$

Grizzle analysis: Residual effect $= \dfrac{(245)^2+(230)^2}{12} - \dfrac{(475)^2}{24} = 9.375$;
within MS $= 17.11$; $F_{1,10} = 9.375/17.11 = 0.55$; not significant at 5% level

4. $\overline{A/B} = 1.334, S^2 = 0.238$; $t = (1.334 - 1.0)/\sqrt{0.238(1/12)} = 2.37$; $P < 0.05$.
5. $\overline{\log X} = 0.0954265$; antilog $= 1.246$; $S^2 = 0.0309$; $t = 1.88$ (not significant; assume no order effect); $0.0954 \pm 2.20\sqrt{0.031(1/12)} = -0.016$ to 0.207; antilogs: 0.96 to 1.61
6. Two-way ANOVAS:

	Placebo		Active		Combined ANOVA	
Source	d.f.	MS	d.f.	MS	d.f.	MS
Patients	5	2.866	5	2.742	10	2.804
Weeks	3	1.055	3	7.264	3	3.91
Patients × weeks	15	0.956	15	0.897	30	0.926
Drugs	1				1	15.1875
Drugs × weeks	3				3	4.41

For "drugs," $F_{1,10} = 15.1875/2.804 = 5.416 (P < 0.05)$; for "drugs × weeks," $F_{3,15} = 4.41/0.926 = 4.76 P < 0.05$). From the accompanying plot and the F test for interaction, the active effect increases with time while the placebo is relatively constant.



7. $N = 2(55/60)^2(1.96 + 1.28)^2 + 1 \approx 19$
8. $|-4.75 + 7.6| / (3.433\sqrt{1/8 + 1/9}) = 1.71 (P > 0.05)$
10. Suppose that we start in column 5 in the Blocks of 6 section of Table 11.1. We can equate numbers 1 and 2 to Treatment A, 3 and 4 to Treatment B, and 5 and 6 to Treatment C. The assignments are as follows:
From Table 11.1

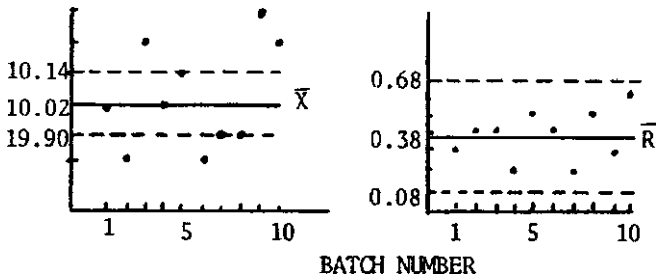
3	2	5	1	5
2	1	2	6	6
1	3	3	5	4
5	5	4	2	3
6	6	1	3	2
4	4	6	4	1

Subject	Treatment	Subject	Treatment	Subject	Treatment
1	B	13	C	25	C
2	A	14	A	26	C
3	A	15	B	27	B
4	C	16	B	28	B
5	C	17	A	29	A
6	B	18	C	30	A
7	A	19	A		
8	A	20	C		
9	B	21	C		
10	C	22	A		
11	C	23	B		
12	B	24	B		

11. A = 3, B = 2. The effect of A in Period 2 = 3 (Direct effect) + 2 (carryover) + 3 (period) = 8. The effect of B in Period 2 is 2 + 2 + 3 = 7. A − B = 8 − 7 = 1.
12. $N = 2(0.8)(1 - 0.8)\{(1.65 + 1.28)/0.16\}^2 = 108$ per group.

CHAPTER 12

1. $\bar{X} = 9.95$; limits are $9.95 \pm 1.88(0.10) = 9.95 \pm 0.19$
   $\bar{R} = 0.10$; for $N = 2$, limits are 0 to $(3.27)(0.10) = 0.33$
2. $\sigma = \sqrt{0.02(0.98)/1000} = 0.004427$; $3\sigma = 0.0133$; $0.02 \pm 3\sigma = 0.0067$ to 0.0333
3. $\bar{X}$ control chart is centered at 47.6 with limits $47.6 \pm 1.02(1.2) = 47.6 \pm 1.22$. R chart has a target of 1.2 with lower limit of 0 and upper limit of $2.57(1.2) = 3.1$ (see Table IV.10).
4. $P = 1\%$; accept if 0 or 1 rejects. Probability 0 rejects $= 0.99^{100} = 0.366$.
   P(1 reject) $= 0.370$; P(batch rejected) $= 1 - 0.736 = 0.264$.
5. $\bar{X} = 10.02$; limits : $10.02 \pm 0.31(0.38) = 10.02 \pm 0.12$
   $R = 0.38$; limits: lower is $0.22(0.38) = 0.08$; upper is $1.78(0.38) = 0.68$
   Many means are out of limits. Either find cause or, if not possible, use moving average if means are well within official limits.



6. $p = 50/100{,}000 = 0.005 =$ probability of reject; $q = 0.9995$; therefore, probability of passing batch $= 0.9995^{100} = 0.951$
7.

Source	d.f.	MS
Between	3	483.3
Within	8	87.83

Between-analyst component = (483.3 − 87.83)/3 = 131.8; within-analyst component = 87.83
Three analysts perform four essays:

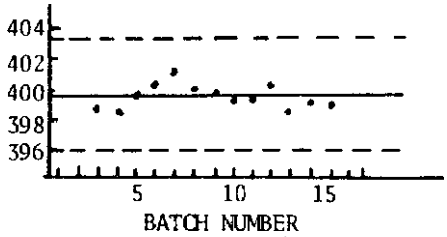
$$S^2 = \frac{4(131.8) + 87.83}{12} = 51.3$$

Four analysts perform two assays:

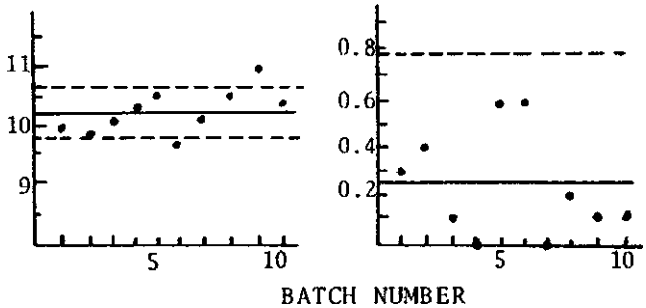
$$S^2 = \frac{2(131.8) + 87.83}{8} = 43.9$$

Cost is $24 for both procedures. The latter procedure (four analysts) is more precise.

8. Limits are $399.6 \pm 1.02(3.48) = 399.6 \pm 3.55$



9. $\bar{X} = 10.21, \bar{R} = 0.24, \bar{S} = \sqrt{0.052} = 0.23$
   Limits for $\bar{X} = 10.21 \pm 1.88(0.24) = 10.21 \pm 0.45$
   Limits for $\bar{R} = 0$ to $3.27(0.24) = 0$ to 0.78



10. $N = 4$; limit $= 2.28, \bar{R} = 2.28(12.5) = 28.5$ (0 is lower limit)
11. 6.25 vs. 3.8
13. (a) $90 + 1.71(0.3/2 + 0.5 + 4/20)^{1/2} = 91.58$
    $110 - 1.71(0.3/2 + 0.5 + 4/20)^{1/2} = 108.42$
    (b) $90 + 1.71(0.3 + 0.5 + [4/20]/2)^{1/2} = 91.62$
    $110 - 1.71(0.3 + 0.5 + [4/20]/2)^{1/2} = 108.38$
    Consider the advantages and disadvantages of different kinds of replication.

CHAPTER 13

1. $\bar{R} = 3.375$; upper limit $= 3.375 \times 2.57 = 8.7$
2. $\bar{X} = 106.5$; $\bar{R} = 5.4$; limits $= 106.5 \pm 1.02(5.4) = 106.5 \pm 5.5$
3. $S_1^2 = 15.67$; $S_2^2 = 2.83$; $S_3^2 = 3.94$
   $\bar{S}^2 = 7.48$
   $X_2^2 = 72.440 - 61.958 = 10.482 (P < 0.05)$
4. $\bar{R} = 2.38$; upper limit $= 2.38 \times 3.27 = 7.78$
5. $\bar{X} = 102.4$; $\bar{R} = 3.3$; limits $= 102.4 \pm 3(3.3)/1.128 = 102.4 \pm 8.8$

CHAPTER 15

1. $t = 0.583/0.6685\sqrt{1/12} = 3.02$; $P < 0.05$; parametric t test shows significance
2. (a) 9 of 12 comparisons are higher for B: not significant
   (b) (b) $t = 0.5/(0.61\sqrt{1/12}) = 2.83$; $P < 0.05$
3. Σ Ranks for $A = 11$(or 67); Σ ranks for $B = 67$; $N = 12$, $\alpha = 0.05$
   $$Z = \frac{|67 - 12(13)/4|}{\sqrt{12(12.5)(13)/12}} = 2.20;\ P < 0.05$$
4. Use the Wilcoxon signed-rank test. $\sum R = 13.5$ (or 22.5); $P > 0.05$ (not significant).
5. Use the Wilcoxon rank sum test.
   $$Z = \frac{|74 - 10(10 + 10 + 1)/2|}{\sqrt{10(10(10 + 10 + 1)/12}} = 2.34;\ P < 0.05$$
   $$t = \frac{4.35 - 2.09}{\sqrt{3.816(1/10 + 1/10)}} = 2.59;\ P < 0.05$$

6. Use the Kruskal-Wallis test. Sum of ranks = 63.5, 40.5, and 16.
$\chi_2^2 = \frac{12}{15(16)}(1133.3) - 3(15+1) = 8.67;\ P < 0.05$
There is a significant difference (batch 3 has lowest dissolution).
7. Sum of ranks = 31, 21.5, and 19.5.
$\chi_2^2 = \frac{12}{36(3+1)}(31^2 + 21.5^2 + 19.5^2) - 3(12)(4) = 6.29;\ P < 0.05$
The standard has the highest C_{max} (standard is greater than B, $P < 0.05$; see Ref. 2).
8.

	0	1	2	Total
A	50(38.9)	50(61.1)	75(75)	175
B	20(31.1)	60(48.9)	60(60)	140
Total	70	110	135	315

$X_2^2 = 11.69$; $P < 0.01$. The distribution of scores for *A* and *B* is different.

9.

		Capping		
		Yes	**No**	**Total**
Specks	Yes	13(1.8)	45(56.2)	58
	No	18(29.2)	924(912.8)	942
	Total	31	969	1000

(a) $S_1{}^2 = 73.7$ (corrected); $P \ll 0.01$; not independent
(b) $Z = \frac{|0.714 - 0.5| - 1/126}{\sqrt{0.5(0.5)/63}} = 3.27;\ P < 0.01$
The difference is significant at the 1% level.
10. The probability of the fourfold table is 0.0304:
$\frac{12!5!14!21!}{0!12!5!9!26!} = 0.0304$
The only least likely table has five tumors in the controls and zero tumors in the treated group. This table has a probability of 0.012.4. Therefore, the probability of the given table + more unlikely tables is $0.0304 + 0.01204 = 0.0421$. The χ^2 test (corrected) is equal to 3.98, which is equal to $P = 0.0460$.
11. The median is 303.25. There are nine runs. According to Table IV.14, fewer than 6 or more than 15 runs are needed for significance at the 5% level. Therefore, the sequence is not significantly nonrandom for both one- and two-sided tests.
14. $\chi^2 = 5.44 (P < 0.05)$
15.

Source	**d.f.**	**Sum-Squares**	**Mean Square**
A (Treatment)	1	2.485E-04	2.485E-04
B (Subject)	11	.637813	.057983
Error	11	1.138684	.1035167
Total (Adj)	23	1.776746	

90%C.I. : $(4.9615 - 4.9551) \pm 1.8\sqrt{0.1035167/6} = 0.0064 \pm 0.2364 = 0.795$ to 1.275
16. Sequence 1: $P_1 + T_1 - P_2 - T_2$
Sequence 2: $P_1 + T_2 - P_2 - T_1$
Seq. 1 − Seq. 2 = $2(T_P - T_2)$
17. Sequence: $\frac{|73 - 8(8+9+1)/2|}{\sqrt{8 \times 9(8+9+1)/12}} = 0.096 P > 0.5$
Period: $\frac{|54 - 8(8+9+1)/2|}{\sqrt{8 \times 9(8+9+1)/12}} = 1.73 P < 0.10$

18. Answer: $p = 0.012$

Source	d.f.	Sum-Squares	Mean Square	F-Ratio	Prob > F
A (Press)	3	.9815	.3271667	5.64	0.012
B (Formula)	4	5.288004	1.322001		
AB	12	.6959966	5.79E-02		
Total (Adj)	19	6.965501			

19.

Source	d.f.	Sum-Squares	Mean Square
Formulation	4	0	0
Press	3	156.3	52.1
Error	12	113.7	9.475
Total (Adj)	19	270	

$$\text{LSD}_{\bar{X}} = 2.18\sqrt{9.475\left(\frac{1}{5}+\frac{1}{5}\right)} = 4.244$$
$$\text{Sum} = 5 \times 4.244 = 21.22$$

CHAPTER 16

1. (a) $'X_1 = 0; 'X_2 = 1; 'X_3 = 0; Y = 10.725 + 2.225 = 12.95$
   (b) $'X_1 = 1; 'X_2 = 1; 'X_3 = 0.6; Y = 15.36$
2. See Eq. (16.4). $'X_1 = (1-1)/1 = 0; 'X_2 = (0.5-0.5)/0.5 = 0; 'X_3 = (2.5-2.5)/2.5 = 0$
3. $Y = (9.7 + 7.2 + 8.4 + 4.1)/4 + (-9.7 + 7.2 - 8.4 + 4.1)X_1/4 + (-9.7 - 7.2 + 8.4 + 4.1)X_2/4 + (9.7 - 7.2 - 8.4 + 4.1)X_1X_2/4 = 7.35 - 1.7X_1 - 1.1X_2 - 0.45X_1X_2$
4. $A' = (8.75 - 7.5)/2.5 = 0.5; B' = (100 - 75)/25 = 1.0; Y = 7.35 - 1.7(0.5) - 1.1(1) - 0.45(0.5) = 5.725$
5. $Y = 19.75 + 4.25(St) + 3.25(M) - 2.25(M)(St)$. Note: M and St are coded. One possibility is $(St) = -0.23$ and $(M) = -1$. This is equivalent to 15 min of mixing and 0.539% stearate, for a 15-min dissolution time.
6. $Y + 10A + 15B + 30AB$; let $B = 1 - A. Y = 10A + 15(1-A) + 30A(1-A) = -30A^2 + 25A + 15$; $dY/dA = -60A + 25 = 0$; $A = 0.417 = 41.7\%$
7. (a) $Y = 292A + 5.6B + 50.4C - 492.8AB - 186.8AC - 49.6BC + 54.6ABC$
   (b) 100% B is 5.6 min. Combinations between 50 and 100% B and 0 and 50% A may give a fast dissolution (e.g., 0.6 of B and 0.4 of A = less than 2 min).
   (c) There are many combinations. For example, 35% of A and 65% of C results in a dissolution of approximately 92 min.

Index

Pharmaceutical Science

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