STATISTICAL SIMULATION OF PATIENT COMPLIANCE

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ABSTRACT

Patient compliance is one of the important factors which effect patient outcome in therapeutic trials. As the methods of measuring patient compliance have been developed, the impact of compliance on therapeutic regimen performance could be studied.

In this project, patient compliance measures are defined and compliance distributions are introduced. The two are combined from the two sources to improve both the knowledge of drug-outcome combinations and compliance information has been simulated in the case of therapeutic trials.

The study of compliance effects on patient outcome was approached in two ways; looking at the fixed compliance effects upon the entire dose-response curve, and looking at the compliance measure as a variable effect on dose-response outcome of patients, the latter by means of statistical simulation.

It was shown that patient compliance information affected patient outcome in terms of the achievement of the therapeutic goal. Also, the results of this project support what should be said about the basis of drug-outcome combinations and prescriptions, when we mention patient compliance. Another result is that Compliance-Response-outcome chains were obtained in terms of percentages to respond from simulation of some common design models used in therapeutic trials.

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I believe that God works through the use of medical means for healing, as well as through the simple faith in Him.

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INTRODUCTION

Compliance with prescribed therapy or medications has effects on the outcome of clinical trials. Compliance studies have been done and compliance-improvement strategies have been developed. However, quantitative information about patient compliance has not been given in enough detail in the reports of clinical trials that appear in the medical literature.

The description of the measure of compliance used in compliance study or report about compliance impact on clinical trials would play a very important part in a compliance study. Also, more detailed information would be preferable. Compliance information helps the physicians(or clinicians) to understand the results of clinical trials and to adjust the therapeutic regimen, and to encourage their patients in order to improve patients outcome.

In this view, the definition of patient compliance is given and compliance distributions of patients groups are studied in this project, and compliance impact, especially, on therapeutic trials is studied.

Goldsmith(Ref.(6) Ch.19, 1979) proposed a measure of patient compliance, presented some possible compliance distributions, and studied the effect of these differing distributions, and studied the effects on the conduct and outcome of clinical trials. This project is extending the compliance study done by Goldsmith.

In chapter 1, compliance concepts and measurement are introduced.

In chapter 2, compliance data patterns are shown and statistical

distributions are considered, and the goodness of fit between data and statistical distributions are tested.

In chapter 3, how compliance impacts on therapeutic trials is studied. Dose-Response curve construction as normal cumulative distribution function and statistical compliance distribution functions are given in chapter 2 to aid in obtaining theoretical data and simulate the compliance-dose-response outcome chain and the compliance-response outcome curves.

CHAPTER 1

COMPLIANCE MEASUREMENT

1.1 COMPLIANCE CONCEPTS

Compliance is defined as the extent to which a person's behavior(in terms of taking medications, following diets, or executing lifestyle changes) coincides with medical or health advice. Under the given medical or health program, some patients do cooperate with the given treatment and others fail to follow it. Thus the study of compliance problems is seen as a means of assisting those who are seeking health and the benefits of modern medicine but who, for whatever reason, have difficulty sticking with the treatments in use.

It is appropriate to keep in mind that the doctor-patient interaction that determines the relative success of therapy in terms of outcome depends as much on the physician's or clinician's compliance as on that of the patient. They must know what is considered appropriate and proper and, comply with current expert opinion and provide such care.

In this project, attention is focused on the question of patient compliance in taking medications.

Compliance information becomes available under the following conditions(Ref.(6) Ch.1).

1. The diagnosis must be correct; otherwise...the remainder of the exercise is futile.

2. The therapy must do more good than harm. Unless the clinical efficacy of the therapy has been clearly established, patients who undergo compliance modification will simply be exposed to increased treatment hazards, rather than treatment benefits. For the same reason, neither the illness nor the proposed therapy can be trivial.

3. It must be established that the patient is an informed, willing partner in the execution of any maneuver designed to alter compliance behavior.

For the investigation of compliance, some specific things are to be established; study plan, sample selection and specification, description of the illness and description of the therapeutic regimen, completeness of the definition of compliance and the adequate measurement of compliance.

1.2 METHODS OF MEASURING COMPLIANCE

The specific methods available for measuring compliance and in particular those for measuring compliance with medications have been developed. The following methods have been explored(Ref.(6), Ch.3).

Ways of measuring medication compliance

A. Direct methods

1. blood levels

2. urinary execretion of

    a. medication

    b. metabolite

    c. marker(tracer)

B. Indirect methods

1. therapeutic or preventive outcome

2. 'impression' of physician(predictability)

3. patient interview

4. filling of prescription

5. pill count

Here, we are going to look at several methods of measuring medication compliance.

1.2.1. Direct Methods

For accuracy, it is essential to use direct methods, but the available methods are not without difficulties. The problems are twofold: first, there are the technical aspects of the test itself, including its sensitivity and specificity as a method of detection; second, there are the conceptual questions of how to define or classify a patient as a complier or a noncomplier.

(1) Urine Test

A method for detecting penicillin in the urine of patients on oral prophylaxis against rheumatic fever is one of the examples. A filter paper strip is dipped into the urine of the patient who is

supposed to be taking penicillin and the end of the paper strip is cut off and applied to an agar plate streaked with Sarcina Lutea, an organism highly sensitive to penicillin. When penicillin is present in the urine, it diffuses out into the surrounding medium and inhibits the growth of the organism.

In carrying out such a test, it is important that one know the absorption and excretion pattern of the agent. For example, when children were administered oral penicillin in a monitored hospital setting, almost 100% of the patients had positive urine tests for about four or five hours following ingestion of the penicillin.

It is therefore critical that if a urinary test for penicillin compliance is to be used in nonhospital populations, it be carried out during the period when penicillin could be detected in the urine. A test carried out beyond this period would produce negative results even for true compliers.

(2) Blood Level

A trace of sodium bromide in a liquid antacid can be employed in patients with peptic ulcers. The prescribed regimen includes the drug containing bromide as sodium bromide. Therefore patients who take the prescribed medication would ingest bromide and a sample of blood obtained by the clinician would show blood bromide levels measured by the technique of Kaplan and Schnert.

Normally, the blood contains bromide derived from diet. When the observations were taken on control patients with peptic ulcers who had no history of taking medication containing bromide, the mean blood bromide level was 1.02 mg per 100 ml with S.D. 0.52 and the interval

was 0.2 to 2.0 mg per 100 ml. This level could fluctuate. It has been shown that the therapeutic levels are 75 or 100 mg per 100 ml(Ref.(17)).

1.2.2 INDIRECT METHODS

(1) Bottle or Pill Count

A count of pills used or bottles of medication emptied is convenient but is based on the assumption that missing pills or emptied bottles represent consumption and may not be justified.

The adequacy of bottle or pill count for assessing patients intake of medication has not been established. However, some specific methods were employed and their accuracy presented(Ref.(16)).

A bottle count was evaluated in the 2 year follow-up of patients with peptic ulcers. The specific procedure was designed to minimize error in the bottle count method. The count of emptied bottles was made by the man who delivered the medication. He explained to patients that a delivery system was being used because older patients, women, and those without automobiles might be unable to carry the large amounts of medication required. Patients did not appear to question this explanation. The delivery man initially brought a case of medicine containing 36 8 ounce bottles of antacid to the patient's home. He returned at intervals varying from 30 to 60 days and replaced empty bottles which patients were asked to have saved. He recorded the number of empty and full bottles. If some were missing he recorded the number, inquired about their whereabouts, and asked whether they were empty or full.

'Bottles consumed per day' for each of 1,445 observation periods

was number of empty bottles divided by the days.

They added a tracer technique (1.2.1. (2)) for comparison of two methods and showed that the correlation between bottle count and bromide was 0.80 and increased to 0.87 when 10 irregular patients were removed.

(2) Outcome as an Indirect Measure

A frequently used indirect measure of compliance is the outcome of the treatment or preventive regimen. At first glance, outcome would appear to be a reasonable measure of compliance if we have sufficient faith that the recommended regimen, when complied with, is truly effective. Several reports do indeed document a relationship between noncompliance and a lack of preventive or therapeutic effectiveness. For example, in rheumatic fever patients on oral penicillin prophylaxis, antistreptolysin O titers were determined at two-month intervals and correlated with levels of compliance. Although the groups were small, the data suggest that patients complying less than one-third of the time had a higher risk of streptococcal infection than the remaining patients(Ref.(6) Ch.3).

For another example, in patients with epilepsy who were not responding to diphenylhydantoin, noncompliance was a significant problem; when the medication was administered to them under rigidly monitored hospital conditions, adequate blood levels of the drug were achieved and a good therapeutic response resulted (Ref.(11), (6) Ch.3).

There are, however, many conceptual problems in using outcome as a measure of compliance(Ref.(6) Ch.3). The main problem is that patients outcome of recovery can be influenced by external factors other than compliance.

(3) Interview with patients

To measure compliance by asking the patient himself is a more practical method, if only the patient tells the truth. Feinstein and his co-workers(Ref.(3), (6) Ch.3))compared compliance in children on penicillin prophylaxis by interview and pill count. Although there was good agreement between the two methods among those classified as poor compliers, there was a considerable discrepancy among those classified as good compliers. In several other studies, it has been shown that there is little or no evidence that complying patients mispresent themselves as noncompliers, nor is there that those who profess noncompliance at interview are lying(Ref.(6) Ch.3). Thus, although there are serious questions regarding the validity of interview responses, if the only objective of the interview is to identify noncompliers, many can be identified by this indirect measure.

1.3 COMPLIANCE MEASURES

We looked at some adequate techniques for measuring compliance that are acceptable to the given therapeutic regimens. We are now interested in how to make the general definition of compliance measures and how to classify compliers and noncompliers (Ref.(6) Ch.19, Ch.3).

1.3.1. DEFINITION OF THE MEASURE OF COMPLIANCE

Definition: The measure of compliance, denoted by C, is defined as the ratio of the number of prescribed doses of the therapy taken by the patient to the number of doses prescribed for the patient, and expressed as a percentage, i.e.,

$$C = \frac{\text{number of prescribed doses taken by the patient}}{\text{number of doses prescribed for the patient}} \times 100(\%).$$

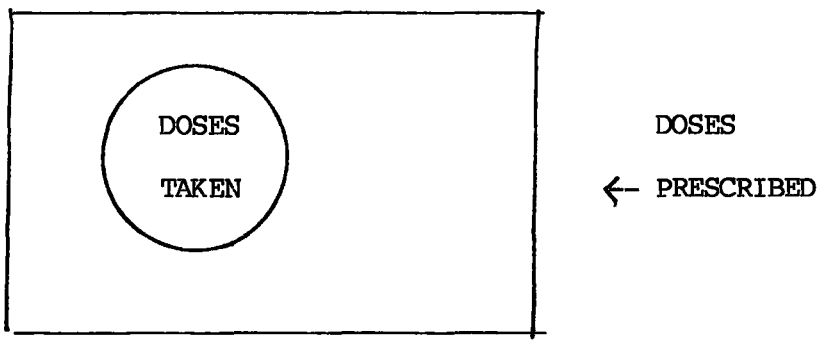
Expressed in this form, the measure of compliance, C, would ordinarily take on values between 0% and 100%, i.e.,

$$0\% \leq C \leq 100\%.$$

Although this measure of compliance is useful, it should be recognized that it does not allow for the possibility of net overconsumption of therapy (i.e., the taking of doses that were not prescribed), nor does it distinguish among the different patterns in which the patient may have consumed the number of 'doses taken'.

The ingredients of this compliance measure can be expressed pictorially with the Venn diagram shown in Figure 1.

Figure 1: Venn diagram



Source: Ref. (6) Ch.19

The rectangular box represents the set of possible doses prescribed for the patients, while the circle represents the set of times that the prescribed doses adhered to by the patients. Clearly, from this representation the set of prescribed doses taken is a subset of the doses prescribed, so that the stated compliance measure are indeed reasonable.

Various modifications of the given definition have been given in the literature. Gordis(Ref.(5),1969), when studying compliance with oral prophylactic penicillin therapy in chidren with prior rheumatic fever, used as their compliance,

$$C = \frac{\text{urine tests positive}}{\text{urine tests done}} \times 100\ (\%).$$

In this case, the number of urine tests done was a substitute for the number of doses prescribed, and a positive urine test served as an indication that the prescribed penicillin therapy had been taken.

Roth (Ref. (16)), when studying compliance with antacid therapy in peptic ulcer prophylatis used as their compliance measure,

$$C = \frac{\text{bottles of antacid consumed}}{\text{bottles of antacid prescribed}} \times 100\ (\%).$$

Here the number of bottles consumed was analagous to the pill count that has been used in other studies.

1.3.2 HOW TO CLASSIFY COMPLIERS AND NONCOMPLIERS

Given a method of compliance measurement and definition of the measure of compliance, how should a patient be classified as a complier or noncomplier? For compliance research, classification of individual patients as a complier or noncomplier is essential. Ideally this could be done on the basis of a biologic rationale such as the level of compliance required to achieve a therapeutic response. But this has not been normally established in compliance investigation. In the next chapter, when we speak of compliers and noncompliers or those in between, it does not imply that the patients achieve the therapeutic goal or not. The important issue is to classify compliers and noncompliers in terms of biological effects.

CHAPTER 2

COMPLIANCE DISTRIBUTIONS

2.1 DATA PATTERNS

Once a measure of individual compliance has been developed, it becomes possible to begin understanding a pattern of compliance of patient populations. Also, it is possible to combine the individual measurements into a distribution. The shape of this distribution must have profound effects upon the design and analysis of therapeutic trials. Though very few studies have reported compliance distributions, we are still able to postulate some possible compliance distributions from those that are available.

Goldsmith(Ref.(6) Ch.19) suggested compliance distributions based on the data reported, as the following:

Gordis (Ref.(5)) reported that 49(36%) of the 136 children in their rheumatic fever prophylaxis study were noncompliers(0% <= C <= 25%), while 43(32%) of the children were intermediate compliers(26% <= C <= 74%) and 44(32%) were said to be compliers(75% <= C <= 100%). Using as the compliance measure the ratio of the urine test positive to the urine tests done, a U-shaped distribution would appear.

Table 2.1: Compliance report of the 136 children in a rheumatic fever prophylaxis study

Noncompliers		Intermediate		Compliers		Total
0 <= C <= 25 (%)		26 <= C <= 74 (%)		75 <= C <= 100 (%)		
Number	%	Number	%	Number	%	Number
49	36.0	43	32.0	44	32.0	136

Source: Ref. (5), 1969
It is displayed as U-shaped distribution in Figure 2.1.
(Source: (6), Ch.19)

Roth (Ref.(16)), in a study of antacid therapy in patients with peptic ulcers, provided enough information to permit the estimation of the compliance distribution. He plotted mean bottle count against mean blood bromide level for the 2 year follow-up period. The correlation between two methods was 0.80, and increases from 0.80 to 0.87 when 10 irregular patients were removed. Average intake of medicine for the 105 patients was 0.31 bottles per day, 54 per cent of the amount prescribed. A bell-shaped distribution results, as shown in Figure 2.2 (Source: Ref.(6) Ch.19). using as the compliance measure the ratio of bottles of antacid consumed to bottles of antacid prescribed.

Table 2.2: Compliance report of 105 patients in a study of antacid therapy

Bottles of antacid consumed per day	f
0.0 <= bottles <= 0.1	6
0.1 < bottles <= 0.2	22
0.2 < bottles <= 0.3	22
0.3 < bottles <= 0.4	31
0.4 < bottles <= 0.5	8
0.5 < bottles <= 0.6	12
0.6 < bottles <= 0.7	1
0.7 < bottles <= 0.9	3
Total	105

f: number of patients.
Source: Ref.(16), 1970

The above distribution can be modified into the following table, when 4 overconsumption-patients are removed. (from correlation plot given by Roth, Caron, and Hsi.(16))

Table 2.3: Compliance report of 101 patients in a study of antacid therapy

(%)	0 <=C <=20	20 < C <=40	40 < C <=60	60 < C <=80	80 < C <=100
Number	10	24	32	21	14
total					101

(Percentage of patients in each cell is almost the same as the number of patients in each cell.) It is plotted in Figure 2.3.

The tuberculosis chemotherapy study of Ireland(Ref.(9)), and the psychomacological rehospitalization study of Mason(Ref.(13)), suggest compliance distributions for INH and phenothiazines that are nearly uniform over the compliance interval. It is shown in Figure 2.4(Source:Ref.(6) Ch.19).

From these examples, it is clear that there are an enormous number of possible shapes for compliance distributions. It is encouraged to report compliance distributions in therapeutic trials and to study the effect of these differing distributions on the conduct and outcome of clinical trials. It may help us to predict compliance tendency in the patients population on the regular medical program, and give the good information for the further therapeutic regimen to the clinicians and patients.

2.2 STATISTICAL DISTRIBUTIONS AND PROPERTIES

2.2.1 NORMAL DISTRIBUTIONS

Definition: A random varible X is **normally** distributed if it has the probability density function:

$$(1|\mathbf{d}\ \mathrm{sq}(2\pi))\exp\left[((x - M)|d)^2|2\right] \qquad (\mathbf{d} > 0) \qquad (1)$$

The probability density function of $U = (X - M)|d$ is:

$$P_U(u) = (\mathrm{sq}(2\pi))^{-1} \exp\ (-u^2|2), \qquad (2)$$

which does not depend on the parameters M, **d**. This is called the **standard form** of the normal distribution. The random variable U is called a **standard**, or unit, normal variable.

Since

$$P(X <= x) = P(U <= (x - M)|d),$$

such probabilities can be evaluated from tables of the cumulative distribution function of U, which is:

$$\Phi(u) = P(U <= u) = (\mathrm{sq}(2\pi))^{-1} \int_{-\infty}^{u} \exp(-x^2|2)\,dx. \qquad (3)$$

Further, it is convenient to have a systematic notation for the quantiles of the distribution of U. We use the system defined by

$$\Phi(U_\alpha) = \alpha \qquad (4)$$

so that $U_{1-\alpha}$ is the upper 100α % point, and $U_\alpha (= -U_{1-\alpha})$ is the lower 100α % point of the distribution.

If U has the unit normal distribution then, since the

distribution is symmetrical about U = 0,

$$E(U) = 0 \tag{5}$$

$$Var(U) = 1 \tag{6}$$

If X has the general normal distribution (1), then

$$X = M + \delta U$$

where U is a unit normal variable. The distribution is symmetrical about X = M; the probability density function has points of inflection at $X = M \pm \delta$.

The arithmetic mean $m = n^{-1}\sum_{j=1}^{n} X_j$ and the standard deviation $s^2 = n^{-1}\sum_{j=1}^{n}(X_j - m)^2$ are jointly sufficient for M and δ^2, sufficient for M alone. For most practical purposes, m is the best estimator for M, whether δ^2 is known or not. It is the maximum likehood estimator.

The only circumstances in which this estimator would not be used are (a) when not all observations are available, or (b) when the accuracy of some values (e.g. outlying values) is doubtful.

The maximum likelihood estimator of δ^2 (M not being known) is

$$s^2 = n^{-1}\sum_{j=1}^{n}(X_j - m)^2 \tag{7}$$

If M is known, the maximum likelihood estimator is

$$n^{-1}\sum_{j=1}^{n}(X_j - M)^2 = s^2 + (m - \delta)^2 , \tag{8}$$

and $S = n(n-1)^{-1} s^2 = (n-1)^{-1}\sum_{j=1}^{n}(X_j - m)^2$ (9)

is an unbiased estimator of δ^2 (Ref. (10)).

As Goodness-of Fit tests, we can use Lilliefor's test when the

individual data are known and the sample size is below n, n = 100,(Ref.(15)), and Chi-square test is most frequently used for grouped-data(Ref.(8)).

2.2.2 BETA DISTRIBUTION

Definition: The family of beta distributions is composed of all distributions with probability density functions of form:

$$P_Y(y) = \frac{1}{B(A,B)} \frac{(y-a)^{A-1}(b-a)^{B-1}}{(b-a)^{A+B-1}} \qquad (10)$$

$$(a <= y <= b)$$

with parameters $A > 0$, $B > 0$.

If $B = 1$, the distribution is sometimes called a **power-function** distribution.

If we make the transformation

$$X = (Y - a) | (b - a)$$

we obtain the probability density function

$$P_X(x) = \frac{1}{B(A,B)} x^{A-1}(1-x)^{B-1} \qquad (0 <= x <= 1). \quad (11)$$

where $B(A,B) = \frac{\Gamma(A)\Gamma(B)}{\Gamma(A+B)}$, $\Gamma(A) = (A-1)!$ when A is an integer.

$$\Gamma(A) = \int_0^\infty y^{A-1}e^{-y}dy$$

when A and B are not integers.

This is the **standard form** of the beta distribution with parameters A, B. It is the form which will be used in most of this chapter and the next Ch.3.2.2.

The probability integral of the distribution (11) up to x is called the incomplete beta function ratio and denoted $I_X(A,B)$, so that

$$I_X(A,B) = \frac{1}{B(A,B)} \int_0^x t^{A-1} (1-t)^{B-1} dt. \qquad (12)$$

The word 'ratio' which distinguishes (12) from the incomplete beta function

$$B_x(A,B) = \int_0^x t^{A-1} (1-t)^{B-1} dt \qquad (13)$$

is often omitted.

The probability, P(X <= x), is provided from Ref.(18.4) for the purpose of the following chapter 2.3.

If X has the standard beta distribution(11), its r th moment about zero is

$$\mu'_r = \frac{B(A+r, B)}{B(A,B)} = \frac{\Gamma(A+r)\,\Gamma(A+B)}{\Gamma(A)\,\Gamma(A+B+r)}$$

$$= \frac{A^{[r]}}{(A+B)^{[r]}} \text{ if r is an integer.}$$

where $y^{[r]} = y(y+1)\ldots(y+r-1)$ is the ascending factorial.

In particular

$$E(X) = (A|(A + B)) \tag{14}$$

$$Var(X) = A\,B\,(A + B)^2\ (A + B + 1)^{-1}. \tag{15}$$

With different parameters, the shape of the beta distributions is determined. If $A > 1$ and $B > 1$, then $P_X(x) \to 0$ as $x \to 0$ or $x \to 1$; if $0 < A < 1$, $P_X(x) \to \infty$ as $x \to 0$, and if $0 < B < 1$, $P_X(x) \to \infty$ as $x \to 1$. If $A = 1$(or 0), $P_X(x)$ tends to a finite non-zero value as $x \to 0$(or 1). If $A > 1$ and $B > 1$, the density function has a single mode(median) at $x = (A - 1)|(A + B - 2)$. If $A < 1$ and $B < 1$, there is an antimode(minimum value) of $P_X(x)$ at this value of x. Such distributions are called U-shaped beta distributions. If $(A - 1)(B - 1)$ is not positive, the probability density function does not have a mode or an antimode for $0 < x < 1$. Such distributions are called J-shaped beta distributions. If $A = B$, the distribution is symmetrical about $x = 1|2$(Ref.(10)).

2.3 GOODNESS OF FIT TESTS

The characteristic for which statistical tests is whether or not the compliance distributions reported in Ch.2.1 are accepted to be the statistical distributions of the null hypothesis tested. The most popular test for the statistical distributions is the chi-square test. We subdivided the given interval, i.e. compliance interval($0 <= c <= 1$; $c = C(\%)|100$) into k subintervals.

The chi-square statistic is defined as follows:

$$Q_{k-1} = \sum_{i=1}^{K} (f_{oi} - f_{ei})^2\ |f_{ei}$$

where $f_{ei} = n \times P_{ei}$ (x: multiplication)
and

n: total number of observations,
k: number of subintervals used in fitting the distribution,
f_{oi} : observed frequency for the i-th subinterval,
P_{ei} : probability of a trial result's being in the i-th subinterval,

f_{ei} : expected frequency for the i-th subinterval.

If the null hypothesis H_o is true, the above statistic has an approximate chi-square distribution with k - 1 degrees of freedom. Since, when H_o is true, n x P_{ei} is the expected value of f_{oi}, one would feel that experimental value of Q_{k-1} should not too large if the null hypothesis were true.

The probabilities of rejecting the hypothesis when it is true, is to be specified by the experimenter. By using Table of Ref.(8) with and k - 1 degrees of freedom, k - 3 degrees of freedom for (2), it is determined whether or not to accept the hypothesis.

Our basic hypothesis being tested are that

(1) U-shaped distribution in the children rheumatic fever prophylaxis is the beta distribution with parameters A = B = 0.5.

(2) Bell- shaped distribution in a study of antacid therapy is the normal distribution.(Here, the subintervals are with the bottles consumed. The sample mean and standard deviation , respectively, 0.31 and 0.21, given by study are used as the estimates to evaluate P_{ei}, and Q_{k-1}. (Q_{k-1} is not minimized by maximum likelihood estimates, in general, and thus its computed value is somewhat greater than it would be if minimum chi-square estimates were used. Hence, when comparing it to a critical value listed in the chi-square table, we do it with k - 3 degrees of freedom.)

(3) Bell- shaped distribution modified in a study of antacid therapy is the beta distribution with parameters A = B = 2.0. (Here, the subintervals are with compliance proportions.)

The following are the results of the chi- square tests.

(1) Compliance	f_{oi}	f_{ei} (= n x P_{ei})
0.00 <= c <= 0.25	49	45.3288 (= 136 x 0.3333)
0.25 < c <= 0.74	43	44.3496 (= 136 x 0.3261)
0.74 < c <= 1.00	44	46.3216 (= 136 x 0.3406)
Total	136	136.0

$$Q_{3-1} = 0.4548$$

This value is less than $Q_{0.95,\ 2} = 5.99$. Therefore, the hypothesis of the beta distribution with parameters A = B = 0.5 is accepted at the 5% level of significance.

(2) Bottles consumed	f_{oi}	f_{ei} (= n x P_{ei})
0.00 <= b <= 0.10	6	9.3240(= 105 x 0.0888)
0.10 < b <= 0.20	22	14.8675(= 105 x 0.1415)
0.20 < b <= 0.30	22	18.9840(= 105 x 0.1808)
0.30 < b <= 0.40	31	19.4145(= 105 x 0.1849)
0.40 < b <= 0.50	8	15.8865(= 105 x 0.1513)
0.50 < b <= 0.60	12	10.4160(= 105 x 0.0992)
0.60 < b <= 0.70	1	5.4600(= 105 x 0.0520)
0.70 < b <= 0.90	3	3.0555(= 105 x 0.0291)
Total	105	97.3180

$$Q_{8-1} = 19.8115$$

This value is greater than $Q_{0.95,\ 8-3} = 11.1$. Therefore, the null

hypothesis of the normality was not accepted at the 5% significance level.

(3) Compliance	f_{oi}	f_{ei} (= n x P_{ei})
0.00 <= c <= 0.20	10	10.400(= 101 x 0.1040)
0.20 < c <= 0.40	24	25.048(= 101 x 0.2480)
0.40 < c <= 0.60	32	29.896(= 101 x 0.2960)
0.60 < c <= 0.80	21	25.048(= 101 x 0.2480)
0.80 < c <= 1.00	14	10.504(= 101 x 0.1040)
Total	101	101.0

$Q_{5-1} = 2.0339.$

This is lesser than $Q_{0.95,\ 4} = 9.49$. Therefore the hypothesis of the beta distribution with parameters A = B = 2.0 is accepted at the 5% level of significance.

CHAPTER 3

COMPLIANCE IMPACT ON THERAPEUTIC TRIALS

3.1 DOSE-RESPONSE CURVE IN THERAPEUTIC TRIALS

When responses are plotted against dose, the points usually fall near a fairly simple curve. At the beginning, we may get linear fashioned or skewed sigmoid-shaped dose-response curves generally, when the response is plotted against dose. One of the most common dose-response curves is sigmoid-shaped, like the one displayed in Figure 3.1, in therapeutic trials, increasing as we proceed to the right. Suppose there is a dose, denoted by D1, below which the response is of no therapeutic value. Also suppose there is a dose, denoted by D2 (D2 > D1), above which the drug becomes toxic to the patient. The dosage interval within which a therapeutic effect will take place is D1 to D2. Thus, the therapeutic effect interval is given from R1 to R2 (R2 > R1), corresponding to D1 and D2. The sigmoid curve can be transformed into one for which the point of inflexion is at the half point. It can be illustrated mathematically.

The doses can be rescaled in terms of standard deviations of the cumulative normal curve. The scale so defined is known as that of

normal eqivalent deviates(N.E.D.) or normits. If we have the positive dose, denoted by X, as a random variable of the continuous type with space A = (x; 0 < x <∞), the standard form U = (X - M)|d gives the scale on N.E.D., where M is the mean dose and d is the standard deviation. And the value of response, P, corresponding to the given dose, x, will be the left side area under the unit normal cumulative curve of X up to x, and found as the following

$$\begin{aligned} P &= P(X <= x) \\ &= P((X - M)|d) <= P((x - M)|d) \\ &= P(U <= u), \end{aligned} \tag{1}$$

where U is the standard normal variable.

In other words, the response corresponding to a positive dose can be expressed in terms of the cumulative density concerning U, which is normal(0,1).

The scales of Y-axis in which P falls could be bromide blood level or blood pressure reduction, whatever is the effect of the drug taken. It would be rescaled on unit interval, considering the usage of the therapeutic trials. For example, the maximum level of the therapeutic effect could be identified with the value of P, P = 0.85, of course, which corresponds to the positive dose or dose on the N.E.D. scale. The N.E.D scaled dose-response curve was displayed in Figure 3.2. Ideally, dose-response outcome curve available to a drug would be unique, provided under monitored conditions.

If various drugs have their own mean dose and standard deviation, it determines the X-axis positive dose scale. And it should be noticed then by the physicians(or clinicians) that those drugs might

have different therapeutic dosage ranges and yet have corresponding therapeutic response intervals. Consequently, for any drug-outcome combination, the prescribing clinician should have a knowledge of the therapeutic interval and should prescribe corresponding dose of drugs for his or her patients.

The actual amount of a drug available to the patient can be influenced both by the compliance of the patient and by the bioavailability of the drug. While not wishing to ignore the importance of the latter, we shall assume in the following contents of this project that it is constant and high. The patients outcome can be influenced also by some other care, i.e. the external factors, in the case which those patients achieved therapeutic goal. The present outcome can be also influenced by whether a medication regimen is for short term or for long term. In the case of long term, the same percentage of patients compliance could bring about different outcomes from that of short term for whether the patient took his or her medications more recently or in the early days of the medical program. In this chapter, we are going to deal with the case which the things mentioned above are not counted. In other words, the case is that the drug taken by patients directly results in the present patients outcome. Also, as long as the clinician's attention is given to patients group that show low compliance and does not achieve the goal of the treatment, and that shows high compliance and does not achieve the goal, our concern in the following chapters would be generally accepted in a compliance study.

3.2 COMPLIANCE EFFECTS UPON THE INTERPRETATION OF DOSE-RESPONSE CURVES

Let us assume a set of patients, each of whom has been prescribed dose, X, of the same drug, in an effort to achieve the corresponding therapeutic effect P. The dose taken by patients, denoted by Z, would be the some portion of the dose prescribed; where

Dose taken = Compliance Measure x Dose Prescribed,

$$X' = c \times X, \tag{2}$$

where $c = C(\%) \mid 100.$ $(0 <= c <= 1)$

The response, denoted by Q, would be taken the value as the following,

Response = f(compliance, dose),

$$\begin{aligned} Q &= P(X <= cx) \\ &= P(X <= x') \\ &= P((X - M) \mid d) <= P((x' - M) \mid d). \\ &= P(U <= u') \end{aligned} \tag{3}$$

Q would take place on the unit interval, and be reduced from P in the most of the cases that patients do not comply with prescription completely.

The following, 3.2.1 and 3.2.2 are given, in an attempt to study the effect of compliance upon the interpretation of dose-response curve, and to put one of the priorities for future research into practice(Ref.(6) Ch.19). The object of the second part is to simulate statistically the compliance-dose-response-outcome chain for the common design models used in therapeutic trials.

3.2.1 THE EFFECTS OF FIXED COMPLIANCE OVER THE ENTIRE DOSE-RESPONSE CURVE

In this situation, the effect of compliance is taken as a constant value over the entire dose-response curve.

Let $x_1, x_2, \ldots, x_n$ be doses of which effects are $P_1, P_2, \ldots, P_n$.

$$P_i = P(X <= x_i) = P(U <= u_i),\ i = 1, 2, \ldots, n, \qquad (4)$$

where X is the random variable of the positive dose, and $u_1, u_2, \ldots, u_n$ are dose scale on N.E.D. $(U = (X - M)/d)$ with the mean dose, M, and standard deviation, d, of drug used.

However, what happens when doses are reduced by patients noncompliance (not taking all doses)? Suppose that patient's compliance is 80%, then c = 0.8 is multiplied by the dose considered , at the beginning, by the clinician. And a reduced effect will be produced that corresponds to the dose taken by his or her patient.

So if

$$x' = 0.8\ x,$$

then $Q = P(X <= x') = P(U <= u')$

where x is dose prescribed, x' is dose taken, and Q is the actual response corresponding to dose, x'. And U is the standard normal variable. Doses available to patients decreased to $x_1', x_2', \ldots, x_n'$ and reduced effects influenced by patient compliance , $Q_1, Q_2, \ldots, Q_n$ will take place as actual responses.

$$Q_i = P(X <= x_i') = P(U <= u_i'),\ i = 1, 2, \ldots, n, \qquad (5)$$

where $u_1', u_2', \ldots, u_n'$ are dose scales on N.E.D. $(U = (X - M)/d)$, mean M and standard deviation, d, of drug used.

Now, we want to explain the effect of a fixed compliance measure over the entire dose-response curve. We are in the situation which the experimental data have not been given in enough detail to see the effect of patient compliance upon patient outcome on dose-response curve with any description of disease and regimen and the perticular patients group. However, computer simulation could be employed to provide artificial data, without any perticular medical or biological description. We are going to see this process and result of it graphically, by means of computer simulation. We may study our subject mainly with a statistical view.

<Simulation to construct dose-response curve>

(1) Dose-response curve

Pseudo-random normal(0,1) deviates are generated by IMSL routine GGNML(Ref.18.5) with sample size, n. Random normal($\underline{M}$, $\mathbf{d}^2$) deviates may be obtained by transforming these pseudo-random standard normal deviates. In the expression of this chapter, pseudo-random normal deviates generated first are $u_1, u_2, \ldots, u_n$, and random normal deviates obtained by transformation are $x_1, x_2, \ldots, x_n$ ($X = M + U\,\mathbf{d}$). Therefore, positive dose scale is determined by the specified mean dose and variance. About the corresponding response to the given dose, IMSL routine MDNOR(Ref.18.5) provides the cumulative normal density at each dose value, $P_1, P_2, \ldots, P_n$. Sample size, n = 600, is used. By connecting all sample points, in algebraic order, $(x_{(1)}, P_{(1)})$, $(x_{(2)}, P_{(2)}), \ldots, (x_{(n)}, P_{(n)})$ (or $(u_{(1)}, P_{(1)})$, $(u_{(2)}, P_{(2)}), \ldots, (u_{(n)}, P_{(n)})$), dose-response curve is constructed, forming cumulative standard normal density curve. For the value of P, we take it on the continuous density

function (MDNOR provides it.) instead of taking it on an empirical distribution function. It means that the normal deviates generated are used only for giving the points to construct continuous cumulative density curve. (Figure 3.2, and curve R in the Figures 3.3 - 3.6)

We are going to look at the effect of compliance upon dose-response curve considered, now. It should be noticed that portion of multiplication in dose scales on N.E.D. is different from that of multiplication in positive dose scales.

(2) Compliance effect upon dose-response curve

As we have noted, compliance measures should be multiplied to the positive dose scale. It implies that the mean dose and standard deviation are needed to be set up(informed) as the parameters to see the effect of compliance on the interpretation of dose-response curve. For the purpose of the study, we take the mean dose and standard deviation, respectively, 0.5 and 0.2, arbitrally(Case 1). As another combination, 5 and 1 are chosen arbitrally(Case 2), for mean and standard deviation. And, the fixed levels of the compliance measure variables are set as c = 0.8(80% compliance) and c = 0.5(50% compliance). So we have 4 different cases for the study; case 1.1(drug case 1 and 80% compliance), case 1.2(drug case 1 and 50% compliance), case 2.1(drug case 2 and 80% compliance), and case 2.2(drug case 2 and 50% compliance). To choose 80% and 50% of compliance measure seems to have a meaning, though it does not mean that those values have to do with the criteria of compliers or noncompliers directly in biological sense. In diastolic blood pressure study by Sackett(Ref.(6) Ch.18), and prognostic stratification done by Feinstein, 80% and 50% level of patients

compliance were shown as the meaningful levels (Ref.(2)). In prognostic stratification series, it was said that 80% of patients compliance makes a clear difference between the control group and treated group, and there is some difference between these two groups, at the level of 50% to 80% of patients compliance. And, lesser than 50% compliance brings no significant difference between the control group and treated group.

For the sample size, n = 600, is taken. On the basis of the equation (5), (6), the new values of the response are taken from the continuous cumulative distribution function (MDNOR), in 4 cases of different compliance measure and different mean dose and standard combinations. Simulated samples of dose(prescribed)-response(expected) and dose(prescribed)-response(actually happening by the compliance effect) data are generated, and response(expected) is drawn against dose(prescribed) as the curve R. Also response(actually happening by patient compliance) is drawn against dose(prescribed) as the curve ER(Figures 3.3-3.6). The plotting was done by computer IPLOT batch job in CYBER(Appendix B). (x_1,P_1), (x_2,P_2),..., (x_{600},P_{600}) are plotted as the curve R, and (x_1,Q_1), (x_2,Q_2),..., (x_{600},Q_{600}) were plotted as the curve ER. Equation (4) is the basis of the our job, and curve ER is plotted for comparision. Dose(prescribed) is plotted against response(actual) to look at the difference between desired effect and reduced effect influenced by compliance at each point of dose scale. Figures 3.3, 3.4 are for the first combination(M=0.5, d=0.2), and Figures 3.5, 3.6 are for the second combination (M=5, d=1). We do not set the therapeutic interval at a specific level at this point.

(3) Results and Summary

Suppose the physician(or clinician) prescribes the dose, x, which causes the effect, P, on the curve R, but the patient does not comply totally with the given regimen. In fact, we are considering 80% of compliance and 50% of compliance. As a result, the patient who takes the drug, 0.8x or 0.5x, would achieve the reduced effect, Q, on the curve ER.

Result 1: In every case, it is shown that the effects are reduced under the influence of 80% of patient compliance or 50% of patient compliance(compare the curve R and ER in the Figures 3.3-3.6).

Result 2: In the Figures, response which is actually happening in case 1.1(80% patients compliance) is greater than the one of the case 1.2(50% compliance) at every point of dose-axis(compare the Figures 3.3 and 3.4). And, actual response in case 2.1(80% patients compliance) is greater than the one of case 2.2(50% patients compliance) at every point of dose-axis(compare the Figures 3.5 and 3.6). It means that different degrees of patient compliance result in different patients outcome, increasing as patients comply with prescription at the higher stage, with the same dose-response outcome combination(prescribed with the same drug and the same regimen). Higher compliance brings about higher effect in the model of the dose-response curve.

Result 3: In the curves ER, we see that the increasing rate of response reduced by patient compliance(80%) in case 1.1 is greater than the one of the case 2.1(compare the Figures 3.3 and 3.5). And, the response reduced by patients compliance(50%) in case 1.2 is increasing

faster than in case 2.2(compare the Figures 3.4 and 3.6). It means that the results are influenced by different mean dose and standard deviation, with the same compliance measures. In other words, the same level of compliance brings about the different effect on dose-response outcome, depending on dose-response outcome combinations of the drug used.

Result 4: The interpretation of this result is given in terms of treatment goal as the following. As long as the reduced response remains within the therapeutic interval, the patient could achieve the therapeutic goal. If there were patients with high compliance(here 80%), who did not achieve the therapeutic goal, the clinician should check whether or not he or she gave an inadequate regimen(vigorous enough or not). For we are studying under the assumption of good pharmacologic effect, the degree of prescription would be checked. If there were the patients with not so high compliance(here 50%), who achieved the therapeutic goal, over medication would cause that result, if the degree of prescription was adequate. However, whenever the clinician routinely prescribes a dosage level higher than the toxic level dose, in an effort to counteract general lack of high compliance, those patients who do comply with the therapy will be exposed to the toxic effects of the drug.

Table 3.1 Compliance and Treatment goal

Compliance	Treatment goal		Toxicity
	Reached	Not reached	
Taking 80% of medications	Patients subgroup(A) ;Fine	Patients subgroup(B) ;Not enough drug(outside therapeutic interval)	Patients subgroup(*) ;Too much drug

Compliance	Treatment goal	
	Reached	Not reached
Taking 50% of medications	Patients subgroup(C) ;Remains in therapeutic interval or overprescribing	Patients subgroup(D) ;outside therapeutic interval

Source : Ref.(6) Ch. 18, 19

Patients subgroups, B and D, require attention of the clinician , and compliance-improvement strategies.

Patients subgroup(*) needs attention and the adjustment of regimen.

(4) Discussion

When the two different drugs are compared in terms of the therapeutic performance, the previous result shows that one of the important factors is the degree of the patient compliance. Suppose drug 1 was tested in patient group G1 of which mean compliance was 80%, and drug 2 was tested in patients group G2 in which patients comply with prescription at the average, 50%, level of compliance. Then, the effect of compliance upon the interpretation of the test result would be profound, no matter what the dose-response-outcome combinations might be. So compliance differences may confound drug differences.

3.2.2 THE EFFECTS OF THE COMPLIANCE MEASURE VARIABLE UPON DOSE-RESPONSE OUTCOME

When we generally study patients compliance, the degrees of compliance of a set of patients may vary on the basis of individual compliance. In other words, patients would comply with prescriptions at different level.

In Ch.2.2, we looked at the compliance measure variables, denoted by c's, which took the values between 0 and 1, i.e., between zero compliance and complete compliance, and their distributions (% or number of patients against compliance measure). The character of

patients group in terms of compliance with clinician's prescription determines what the compliance distribution is like, regardless of what the compliance determinants may be(patient-doctor interaction, regimen type, etc. Ref.(6) Ch.5). For example, the standard form of the beta distribution was one of the most frequently employed to fit theoretical distributions. The two parameters are determined by the character of compliance of the patients group, and results in a special shape of distribution.

When we have the knowledge of the dose-response outcome of the drug used and are informed of the compliance distribution of the patients group, the result of the clinical trial can be analyzed reasonably by combining both sources of information. Here, it is essential that the compliance distributions need to be constructed by the individual compliance measures data.

In this chapter, we fix the value of dose prescribed, which has the therapeutic goal and every patients of a group are prescribed with the same drug and the same regimen, and see the effect of individual compliance measure variables on the outcome of a patients group and the individual patient.

<Simulation procedure>

(1) Physician's(or Clinician's) Prescription

Here is a situation. A therapeutic dosage lies in the interval D1, to D2 (D2 > D1). Suppose the physician prescribes the dose, x_0, which causes the therapeutic effect, P(R1 <= P <= R2; in the therapeutic interval R1 to R2), but the patients do not comply totally with the therapy. They would take their medications at various degrees of

compliance level. In this study, we are going to use the two dose-response outcome curves which are those of the previous chapter 3.2.1 and dose-response outcome combination with mean dose, 0.5, and standard deviation, 0.2, and another combination, 5 and 1. The therapeutic dosage is going to be taken as 0.6(= x_0 = mean dose + 0.5 x standard deviation) which is expected as vigorous as enough, in the first case. On dose-response curve, the corresponding therapeutic effect is 0.69 as normal cumulative density scale given by P(X <= 0.6) (= P(U <= (0.6-0.5)|0.2)) in the case 1; 100% of response, when patients comply with physician's prescription.

In the case 2, dose level , 6.0(= x_0 = mean dose + 1.0 x standard deviation), is going to be prescribed as a therapeutic dosage of which effect is therapeutic enough, P(X <= 6) = 0.84(= P(W <= (6.0 - 5.0)|1.0), on dose-response curve, which is 100% of response when patients take all of drug prescribed.

(2) Compliance information

Individual compliance measure variables of the patients groups will produce compliance distributions. We have not been given this kind of individual compliance measure variables, so far. Thus, theoretical compliance distributions will be given as compliance information in this chapter. In other words, compliance measure variables are given from the given underlying distributions to obtain the numerical compliance measure data individually for the purpose of study.

We suppose that there are 4 different patients groups, and they show compliance distributions differently. As compliance measure variables, simulated samples of observations (form discrete

distributions) are provided by pseudo-random deviates from underlying distributions (as continuous distributions). We are going to use the standard form of the beta distribution as the underlying distributions:

$$P_C(c) = (1/B(A,B))c^{A-1}\ (1 - c)^{B-1} \qquad (0 <= c <= 1),$$

with parameters A > 0, B > 0,

where c is the compliance measure variables, c = C(%)/100 (here C is percentages of compliance defined in chapter 1.3, and is different from C of the above equation.)

Beta(0.5,0.5) is one of U-shaped beta distribution. The case is that the percentage of the patients taking 80% or more up to 100% of medications is about 30%, percentage taking lesser than 80% and bigger than 50% is 20% out of whole patients. Beta(2,2) is symmetric about c = 0.5. This is the case that the first percentage as the same with previous one is 10%, and the second percentage is 40%, out of the whole patients. Beta(1,1) is uniform distribution. Here, the first percentage is 20%, and the second percentage is 30%, out of 100% of patients. Beta(2,0.5) is J-shaped beta distribution. In this case, 60% is the percentage of patients taking 80% or more up to 100% of medications, and 20% of whole patients take lesser than 80% and bigger than 50% of their medications. Above descriptions are from the percentage points of the standard form of the beta distribution, theoretically(Ref 18.4). At this moment, 80% or 50% of dose prescribed does not mean that it has to do with the therapeutic dosage. For whole patients' number, sample size , n = 10, is displayed at first. For each patient group, the compliance measure variables, c_1, c_2,...,c_{10}, are obtained from 4 differently

specified underlying distributions. Simulated samples of observations are recorded in Appendix A (Simulation number 1-10 in each sample of Samples 1-4; Samples 5-8 have the same ones in the second column. They were recorded as percentages with 1 decimal point.), and described statistically as the following(all of the statistical characters were obtained using generated data numbers, not as percentages).

Table 3.2 Compliance Distributions and Statistical Description

Patients group A1: Beta(0.5,0.5) : $\underline{M}$ = 0.5, $\bar{d}$ = 0.13

n	m	s	ku	sk	p
10	0.59	0.17	-1.71	0.15	0.59

Patients group B1: Beta(1, 1) : $\underline{M}$ = 0.5, $\bar{d}$ = 0.08

n	m	s	ku	sk	p
10	0.63	0.12	-1.38	0.64	0.46

Patients group C1: Beta(2, 2) : $\underline{M}$ = 0.5, $\bar{d}$ = 0.05

n	m	s	ku	sk	p
10	0.53	0.05	-0.39	0.81	0.96

Patients group D1: Beta(2, 0.5) : $\underline{M}$ = 0.8, $\bar{d}$ = 0.05

n	m	s	ku	sk	p
10	0.72	0.09	-0.41	-1.30	0.63

$\underline{M}$: population mean
$\bar{d}$: population variance
n : sample size
m : sample mean
s : sample variance(unbiased estimator)
ku : sample kurtosis coefficient
Kurtosis enables us to have an idea about the shape and nature of the hump of a frequency distribution, i.e., tells about flatness or peakedness of the curve.
sk : sample skewness coefficient
Skewness helps in identifying the right or left tails of frequency curve; positive skewed distribution has longer tail toward right, and negative skewed distribution has longer tail toward left.
p : probability of Kolmogorov-Smirnov statistic exceeding z if simulated sample is distributed as beta distribution.(two-sided alternative) The values of p exceed typical significance levels(0.05, 0.10) in the above result, so one would fail to reject the hypothesis of beta distribution.

Table 3.3 Compliance Distributions and Patient subgroup

Patients group	Compliance distribution	a:Taking 80%-100%		b:Taking 50%-80%		c:Not taking or less than 50%	
		f	%	f	%	f	%
A1	c: Beta(0.5,0.5)	5	50	2	20	3	30
B1	c: Beta(1,1)	4	40	3	30	3	30
C1	c: Beta(2,2)	1	10	4	40	5	50
D1	c: Beta(2,0.5)	5	50	2	20	3	30

Percentage of taking is pertaining to taking medications.
f: number of simulation sample in each interval
% : % of simulation sample in each interval.

Also, individual compliance measures data are plotted in Stem-Leaf plots(Appendix A); simulated data have 13 decimal points which values between 0 and 1, however, Stem-Leaf plots describe the compliance measure distributions using only 2 digits as percentage (C(%) = 100 x c, c's are simulated data from underlying distributions.) in every 10% of interval.

We are going to take larger number of patients, n = 50, with replacement, by computer simulation, that their compliance distributions remain as the original distributions. Simulated samples were recorded with simulation number 1-50 in each one of samples, 1-4 and 5-8 in third column as percentage. Table 3.4 describes them as proportions.

Table 3.4 Compliance Distributions and Statistical Description

Patients group A2: Beta(0.5,0.5) :$\underline{M}$ = 0.5, $\mathbf{d}$ = 0.13

n	m	s	ku	sk	p
50	0.46	0.11	-1.34	-0.09	0.42

Patients group B2: Beta(1, 1) :$\underline{M}$ = 0.5, $\mathbf{d}$ = 0.08

n	m	s	ku	sk	p
50	0.48	0.09	-1.29	-0.18	0.77

Patients group C2: Beta(2, 2) : $\underline{M}$ = 0.5, $\mathbf{d}$ = 0.05

n	m	s	ku	sk	p
50	0.49	0.06	-1.18	-0.01	0.80

Patients group D2: Beta(2, 0.5) :$\underline{M}$ = 0.8, $\mathbf{d}$ = 0.05

n	m	s	ku	sk	p
50	0.82	0.04	0.17	-1.00	0.85

As another description, Table 3.5 is given.

Table 3.5 Compliance Distributions and Patient Subgroup

Patients group	Compliance distribution	a:Taking 80%-100%		b:Taking 50%-80%		c:Not taking or less than 50%	
		f	%	f	%	f	%
A2	c: Beta(0.5,0.5)	15	30	7	14	28	56
B2	c: Beta(1,1)	11	22	18	36	21	42
C2	c: Beta(2,2)	7	14	19	38	24	48
D2	c: Beta(2,0.5)	32	64	11	22	7	14

Simulation sample of the compliance measure variables are plotted as Stem-Leaf plot in Appendix A(Stem-Leaf Plots 5-8).

As the next step, we take the larger patients with the sample size, n = 100, with replacement, by computer simulation, that their compliance distributions remain the same as the original distributions. Simulated data were recorded with simulation number 1-100 in each one of samples 1-4 and 5-8 in the third column of simulated samples, in Appendix A.

Table 3.6 Compliance Distributions and Statistical Description

Patients group A3: Beta(0.5,0.5) : $\underline{M}$ = 0.5, $\mathbf{d}$ = 0.13

n	m	s	ku	sk	p
100	0.47	0.13	-1.56	-0.09	0.65

Patients group B3: Beta(1,1) : $\underline{M}$ = 0.5, $\mathbf{d}$ = 0.08

n	m	s	ku	sk	p
100	0.52	0.09	-1.34	0.16	0.55

Patients group C3: Beta(2,2) : $\underline{M}$ = 0.5, $\mathbf{d}$ = 0.05

n	m	s	ku	sk	p
100	0.51	0.06	-0.82	0.18	0.81

Patients group D3: Beta(2,0.5) : $\underline{M}$ = 0.8, $\mathbf{d}$ = 0.05

n	m	s	ku	sk	p
100	0.78	0.05	1.11	-1.44	0.36

As another description, table 3.7 is given.

Table 3.7 Compliance Distributions and Patient Subgroup

Patients group	Compliance distribution	a:Taking 80%-100%		b:Taking 50%-80%		c:Not taking or less than 50%	
		f	%	f	%	f	%
A3	c: Beta(0.5,0.5)	25	25	15	15	60	60
B3	c: Beta(1,1)	23	23	25	25	52	52
C3	c: Beta(2,2)	18	18	35	35	47	47
D3	c: Beta(2,0.5)	64	64	22	22	14	14

Simulated data were described in Stem-Leaf plots as every 10% interval(Stem-Leaf Plots 9-12) in Appendix A.

Above simulated sample data can be switched with another

slightly different subsequences, c_1', c_2',...,c_n', of compliance measure variables from the same underlying distributions, when double precision DSEED of computer program is replaced by different value; here DSEED = 123457.D0 was used.

(3) The effect of compliance measure variables upon dose - response outcome

As we assumed, 0.6(case 1) and 6.0(case 2) are taken as the prescribed doses on positive scale, denoted by X_0. The actual amount of dose available to the patients would be then the following,

$$x_n' = x_0 \times c_n. \qquad (\times: \text{multiplication})$$

The actual response corresponding to dose taken by the patients would be as the following,

$$Q_n = P(X <= x_n') = P(U <= u_n')$$

where $U = (X - 0.5) \mid 0.2$.

$$Q_n = P(X <= x_n') = P(W <= w_n')$$

where $W = (X - 5.0) \mid 1.0$.

Response scale is in between 0 and 0.69 in case 1, and in between 0 and 0.84 in case 2, as the normal cumulative density scale. So, the result is expected on positive(general) dose scale and the part of unit interval(standard). We need understanding here about it.

The results of these process are recorded(response(actual) against dose(taken) in Appendix B(simulated Samples 1 - 8). The 4 different patients groups, regarding the form of distribution, A, B, C, D, both in case 1 and in case 2, with 3 different sample sizes, are displayed. Altogether 4 x 2 x 3 = 24 times simulated sample data were plotted on dose-response curves of which maximum is coming down to 100%

of the therapeutic goal(Figures 3.7 - 3.30).

Patients group	size	drug	simulated sample	Figure
A1	10	case 1	1(n:1-10)	3.7
B1	10	case 1	2(n:1-10)	3.8
C1	10	case 1	3(n:1-10)	3.9
D1	10	case 1	4(n:1-10)	3.10
A2	50	case 1	1(n:1-50)	3.11
B2	50	case 1	2(n:1-50)	3.12
C2	50	case 1	3(n:1-50)	3.13
D2	50	case 1	4(n:1-50)	3.14
A3	100	case 1	1(n:1-100)	3.15
B3	100	case 1	2(n:1-100)	3.16
C3	100	case 1	3(n:1-100)	3.17
D3	100	case 1	4(n:1-100)	3.18
A1	10	case 2	5(n:1-10)	3.19
B1	10	case 2	6(n:1-10)	3.20
C1	10	case 2	7(n:1-10)	3.21
D1	10	case 2	8(n:1-10)	3.22
A2	50	case 2	5(n:1-50)	3.23
B2	50	case 2	6(n:1-50)	3.24
C2	50	case 2	7(n:1-50)	3.25
D2	50	case 2	8(n:1-50)	3.26
A3	100	case 2	5(n:1-100)	3.27
B3	100	case 2	6(n:1-100)	3.28

C3	100	case 2	7(n:1-100)	3.29
D3	100	case 2	8(n:1-100)	3.30

Size: sample size
n: simulation number
Simulated samples: Appendix A
Figures: Appendix B.

(4) Results and summary

Result 1: The main result is that the 4 different compliance distributions' information are reflected on dose-response curve. Dose(taken)-Response(actual) was plotted as Compliance-Dose-Response-Curve in the Figures 3.7-3.30). The two parameters of the beta distributions determine what the therapeutic regimen performances are in various patients groups, reflecting the character of the each underlying compliance distributions; U-shaped distribution, uniform distribution, symmetric distribution, and J-shaped distribution. Also they reflect their statistical characters; mean and variance, kurtosis and skewedness in each beta distribution parameters and each sample size, as we see in the Figures. The 4 different compliance distributions' information are reflected on dose(taken)-response(actual) curve, and we see that the information directly effects upon dose-response-outcome. The case of the parameters, A = 2.0, B = 0.5, shows a good result in the view of the therapeutic effect achievement, comparing with the other cases. And, we can look at the individual patient outcome of each group on Compliance-Dose-Response Curves.

Result 2: If drug employed has the therapeutic effect at the level of 80% up to 100%, patients subgroup (a)(Tables 3.3, 3.5, 3.7)

will be fine, while other patients subgroup (b), (c) need attention of the clinician and compliance-improvement stategies. The various ways to patients compliance-improvement stategies have neen investigated(Ref.(6)). If some patients of subgroup (b), (c), get the therapeutic effect, it implies that the drug used could work in terms of the therapeutic interval, at the level of less than 80% of the prescribed medication. Again, it is emphasized for clinician to know the precise knowledge of drug-response outcome combination and the therapeutic interval of drug considered for regimen. Here, we leave what the therapeutic interval is as an unknown thing. Stem-Leaf plots may be useful to classify patients subgroups in this point of view. While we divided patient groups into three different patient subgroups in the Tables 3.3, 3.5, 3.7, Stem-Leaf Plots give more levels of patient subgroups. In Appendix B, the first column, denoted by d, shows a count of the number of values on that line or on lines toward the nearer edge. The line that contains the median shows a count of values on that line instead, enclosed in parentheses. The second column, of numbers holds the stems. The third part represents the leaves. Each leaf digit represents an individual value. The initial digits of the value are the stem digits which are followed by the leaf digit. Thus a stem of 46 and a leaf of 2 would represent a number like 462, or 46.2, or 0.00462. 1(stem) 2(leaf) represents 12, when leaf digit unit is 1. 1(stem) 2(leaf) represents 120, when leaf digit unit is 10. In the Stem-Leaf Plots of the study here, all of the leaf digit unit is 1(Ref. MINITAB Manual). Stem-Leaf Plots 1, 2, 3, 4, 5, 6, 7, 9 were plotted in every 10th interval(10% of compliance level). In Stem-Leaf Plots 8, 10, 11,

12, the leaves for each stem are stretched over 2 lines(can be more than 2 lines, if needed); '*' and '.' were used for 2 lines, and Stem-Leaf Plots were plotted in every 5th level(5% of compliance level). Plotting was done by computer job(MINITAB) in CYBER.

The analyzer could rearrange Stem-Leaf Plot interval, based on his or her knowledge of the therapeutic interval.

Result 3: We know 100% therapeutic goal and what portion of it patients achieved in the previous Result 1. Also we know 100% therapeutic dosage and what percentage of that medication individual patient took in the previous result. So, compliance(%) - Response(%)-outcome chain can be obtained. It is shown as another chapter, here.

3.2.3 COMPLIANCE-RESPONSE-OUTCOME CHAIN AND FUTHRE RESEARCHES

(1) Compliance(%)-Response(%) Outcome Chain

What percentage of therapeutic goal can be accepted as the therapeutic goal would be useful. Instead of setting the therapeutic interval(if so, here, it would be taken arbitrariy), compliance(%)-response(%)-outcome is found in two cases of different drugs(Response(%) = (Response(expected) |Response(actual)) x 100). Here, the percentage of the response refers to that of unit interval as Y-axis scale of the cumulative normal distribution function. So, our interpretation of response percentage should be rescaled to actual response scale in the actual study.

For example, when bromide blood level test is employed, the relation between compliance(%) and response(%) would be helpful. By

the percentage of achievement, conversely, patients compliance can be measured, except the case that patients achieve the certain goal because of external factors.

Now we see what should be attentioned when we mention patient compliance, though we have unbalanced dose(general)-response(standard) scale. In sigmoid-shaped dose-response curve used in curve used in Ch.3.2.2, response(% out of 100% therapeutic goal) is plotted against compliance(%), using simulated sample with sample size n=600. This compliance-response-outcome chains(as continuous curve) in the Figures 3.31 - 3.34 were obtained in this study, when the individual compliance measure variables were generated from given underlying distributions.

The two parameters of normal density function(i.e., the original dose-response) and dose(prescribed)-response(100%)-outcome combinations and prescription determines the compliance(%)-response(%) curves. Table 3.8 is given for 30% to 100% compliance and corresponing response in every 5% level.

Case 1.1: drug case 1, mean dose, 0.5, standard deviation, 0.2, prescription = mean dose + 0.5 x standard deviation.

Case 1.2: drug case 1, mean dose, 0.5, standard deviation, 0.2, prescription = mean dose + 1.0 x standard deviation.

Case 2.1: drug case 2, mean dose, 5.0, standard deviation, 1.0, prescription = mean dose + 0.5 x standard deviation.

Case 2.2: drug case 2, mean dose, 5.0, standard deviation, 1.0, prescription = mean dose + 1.0 x standard deviation.

Table 3.8 Compliance(%) - Response(%) Outcome

Case 1.1		Case 1.2	
Compliance(%)	Response(%)	Compliance(%)	Response(%)
100	100	100	100
95	92	95	94
90	83	90	88
85	75	85	81
80	66	80	73
75	58	75	65
70	50	70	57
65	42	65	49
60	35	60	41
55	29	55	33
50	23	50	27
45	18	45	21
40	14	40	16
35	10	35	12
30	8	30	9

Case 2.1		Case 2.2	
Compliance(%)	Response(%)	Compliance(%)	Response(%)
100	100	100	100
95	84	95	90
90	69	90	77

85	53	85	64
80	39	80	50
75	27	75	36
70	18	70	26
65	11	65	16
60	6	60	9
55	3	55	5
50	2	50	3
45	1	45	1
40	0	40	1
35	0	35	0
30	0	30	0

From the previous result, we know that compliance-response outcome chains are determined by drug-outcome combination primarily. It implies that doctor's knowledge about drug-outcome and prescription are very important to patient outcome relating to patient compliance. It may be called as the problem of 'doctor compliance'.

(2) Future Research

As future research topic, it was pointed out that how we could use compliance infromation to plan therapeutic trials. (Ref.(6) Ch.19). One of the common planning considerations in a therapeutic trial is the determining the number if patients needed.

To reanalyze completed therapeutic trials, taking compliance into account, would be interesting. And, if needed, new statistical

procedure for incorporating compliance in the planning and analysis of therapeutic trials(Ref.(6) Ch.19).

NOTATION

M : Population mean

m : Sample mean

d : Population variance(in the tables of Chapter 3)

s : Sample variance(in the tables of Chapter 3)

| : Division

<= : greater or equal

sq(n) : Square root of n

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18.1 GGBTR: generates beta pseudo-random deviates in (0,1).

18.2 GGNML: generates normal or Gaussian (0,1) pseudo-random deviates.

18.3 GGUBS: generates uniform (0,1) random number.

18.4 MDBETA: computes the probability, P = P(X <= x), of a random variable having the beta distribution.

18.5 MDNOR: computes the probability, P = P(X <= x), of a random variable having the normal distribution.

18.6 NKS1: tests the hypothesis of equality of the distribution from which a sample is taken and a theoretical distribution, allowing consideration of one or two sided alternatives.

18.8 VSRTA: sorts the elements of a vector into ascending sequence by algebraic value.

APPENDIX A

SIMULATED SAMPLE DATA

AND

STEM - LEAF PLOTS OF SIMULATED COMPLIANCE VARIABLES

Simulated Sample 1

Compliance distribution: Beta(0.5,0.5)

n	Dose Presc.	Compliance (%)	Dose Taken	Response (expected)	Response (actual)	Response (%)
1	0.6	64.4	0.39	0.69	0.29	41.3
2	0.6	99.7	0.60	0.69	0.69	99.6
3	0.6	84.7	0.51	0.69	0.52	74.7
4	0.6	0.1	0.00	0.69	0.01	0.9
5	0.6	89.3	0.54	0.69	0.57	82.6
6	0.6	54.0	0.32	0.69	0.19	27.4
7	0.6	4.9	0.03	0.69	0.01	1.3
8	0.6	85.6	0.51	0.69	0.53	76.2
9	0.6	9.4	0.06	0.69	0.01	1.9
10	0.6	96.0	0.58	0.69	0.65	93.7
11	0.6	0.1	0.00	0.69	0.01	0.9
12	0.6	32.9	0.20	0.69	0.07	9.4
13	0.6	24.4	0.15	0.69	0.04	5.6
14	0.6	93.8	0.56	0.69	0.62	90.2
15	0.6	39.9	0.24	0.69	0.10	14.0
16	0.6	47.8	0.29	0.69	0.14	20.7
17	0.6	98.9	0.59	0.69	0.68	98.3
18	0.6	45.3	0.27	0.69	0.13	18.4
19	0.6	86.5	0.52	0.69	0.54	77.7
20	0.6	99.8	0.60	0.69	0.69	99.7
21	0.6	16.3	0.10	0.69	0.02	3.2
22	0.6	96.5	0.58	0.69	0.65	94.6

23	0.6	72.4	0.43	0.69	0.37	53.7
24	0.6	57.4	0.34	0.69	0.22	31.5
25	0.6	30.3	0.18	0.69	0.06	8.1
26	0.6	2.4	0.01	0.69	0.01	1.1
27	0.6	99.8	0.60	0.69	0.69	99.7
28	0.6	94.9	0.57	0.69	0.64	91.9
29	0.6	6.9	0.04	0.69	0.01	1.6
30	0.6	86.9	0.52	0.69	0.54	78.5
31	0.6	77.7	0.47	0.69	0.43	62.6
32	0.6	92.9	0.56	0.69	0.61	88.6
33	0.6	10.6	0.06	0.69	0.01	2.1
34	0.6	12.0	0.07	0.69	0.02	2.3
35	0.6	2.4	0.01	0.69	0.01	1.1
36	0.6	46.9	0.28	0.69	0.14	19.9
37	0.6	61.0	0.37	0.69	0.25	36.4
38	0.6	9.1	0.05	0.69	0.01	1.9
39	0.6	31.3	0.19	0.69	0.06	8.6
40	0.6	7.0	0.04	0.69	0.01	1.6
41	0.6	18.1	0.11	0.69	0.03	3.6
42	0.6	41.5	0.25	0.69	0.10	15.1
43	0.6	9.9	0.06	0.69	0.01	2.0
44	0.6	0.1	0.00	0.69	0.01	0.9
45	0.6	28.5	0.17	0.69	0.05	7.2
46	0.6	97.3	0.58	0.69	0.66	95.8
47	0.6	18.4	0.11	0.69	0.03	3.7
48	0.6	38.9	0.23	0.69	0.09	13.2

49	0.6	10.1	0.06	0.69	0.01	2.0
50	0.6	76.6	0.46	0.69	0.42	60.8
51	0.6	49.3	0.30	0.69	0.15	22.2
52	0.6	62.5	0.38	0.69	0.27	38.5
53	0.6	62.0	0.37	0.69	0.26	37.7
54	0.6	0.2	0.00	0.69	0.01	0.9
55	0.6	12.9	0.08	0.69	0.02	2.5
56	0.6	98.5	0.59	0.69	0.68	97.7
57	0.6	46.1	0.28	0.69	0.13	19.1
58	0.6	67.0	0.40	0.69	0.31	45.1
59	0.6	45.2	0.27	0.69	0.13	18.2
60	0.6	44.2	0.27	0.69	0.12	17.4
61	0.6	26.7	0.16	0.69	0.04	6.5
62	0.6	0.5	0.00	0.69	0.01	0.9
63	0.6	40.6	0.24	0.69	0.10	14.5
64	0.6	1.6	0.01	0.69	0.01	1.0
65	0.6	3.3	0.02	0.69	0.01	1.2
66	0.6	100.0	0.60	0.69	0.69	100.0
67	0.6	7.8	0.05	0.69	0.01	1.7
68	0.6	43.5	0.26	0.69	0.12	16.8
69	0.6	16.6	0.10	0.69	0.02	3.3
70	0.6	92.7	0.56	0.69	0.61	88.3
71	0.6	9.6	0.06	0.69	0.01	1.9
72	0.6	7.8	0.05	0.69	0.01	1.7
73	0.6	24.2	0.15	0.69	0.04	5.5
74	0.6	95.0	0.57	0.69	0.64	92.1

75	0.6	17.6	0.11	0.69	0.02	3.5
76	0.6	100.0	0.60	0.69	0.69	100.0
77	0.6	26.9	0.16	0.69	0.05	6.5
78	0.6	71.5	0.43	0.69	0.36	52.2
79	0.6	1.2	0.01	0.69	0.01	1.0
80	0.6	76.5	0.46	0.69	0.42	60.6
81	0.6	44.7	0.27	0.69	0.12	17.8
82	0.6	94.3	0.57	0.69	0.63	90.9
83	0.6	77.5	0.47	0.69	0.43	62.3
84	0.6	99.4	0.60	0.69	0.68	99.0
85	0.6	33.3	0.20	0.69	0.07	9.6
86	0.6	4.4	0.03	0.69	0.01	1.3
87	0.6	80.1	0.48	0.69	0.46	66.8
88	0.6	31.6	0.19	0.69	0.06	8.7
89	0.6	44.0	0.26	0.69	0.12	17.2
90	0.6	19.6	0.12	0.69	0.03	4.0
91	0.6	98.3	0.59	0.69	0.67	97.4
92	0.6	12.5	0.08	0.69	0.02	2.4
93	0.6	35.9	0.22	0.69	0.08	11.2
94	0.6	59.2	0.36	0.69	0.23	33.9
95	0.6	94.9	0.57	0.69	0.64	91.9
96	0.6	1.5	0.01	0.69	0.01	1.0
97	0.6	29.2	0.18	0.69	0.05	7.6
98	0.6	5.8	0.03	0.69	0.01	1.4
99	0.6	44.3	0.27	0.69	0.12	17.4
100	0.6	59.3	0.36	0.69	0.24	34.1

Simulated Sample 2

Compliance Distribution: Beta(1, 1)

n	Dose Pres.	Compliance (%)	Dose taken	Response (expected)	Response (actual)	Response (%)
1	0.6	96.6	0.58	0.69	0.65	94.7
2	0.6	26.1	0.16	0.69	0.04	6.2
3	0.6	76.6	0.46	0.69	0.42	60.8
4	0.6	56.9	0.34	0.69	0.21	31.0
5	0.6	84.5	0.51	0.69	0.51	74.3
6	0.6	4.4	0.03	0.69	0.01	1.3
7	0.6	98.7	0.59	0.69	0.68	98.0
8	0.6	60.1	0.36	0.69	0.24	35.2
9	0.6	89.6	0.54	0.69	0.58	83.2
10	0.6	38.1	0.23	0.69	0.09	12.6
11	0.6	1.6	0.01	0.69	0.01	1.0
12	0.6	58.7	0.35	0.69	0.23	33.3
13	0.6	48.9	0.29	0.69	0.15	21.8
14	0.6	16.9	0.10	0.69	0.02	3.3
15	0.6	21.3	0.13	0.69	0.03	4.5
16	0.6	19.7	0.12	0.69	0.03	4.1
17	0.6	9.0	0.05	0.69	0.01	1.9
18	0.6	39.5	0.24	0.69	0.09	13.6
19	0.6	34.6	0.21	0.69	0.07	10.4
20	0.6	14.2	0.09	0.69	0.02	2.8
21	0.6	56.6	0.34	0.69	0.21	30.5

22	0.6	89.9	0.54	0.69	0.58	83.6
23	0.6	28.9	0.17	0.69	0.05	7.4
24	0.6	89.8	0.54	0.69	0.58	83.5
25	0.6	22.6	0.14	0.69	0.03	4.9
26	0.6	4.6	0.03	0.69	0.01	1.3
27	0.6	71.0	0.43	0.69	0.36	51.4
28	0.6	87.3	0.52	0.69	0.55	79.2
29	0.6	3.3	0.02	0.69	0.01	1.2
30	0.6	88.7	0.53	0.69	0.56	81.6
31	0.6	47.9	0.29	0.69	0.14	20.8
32	0.6	68.3	0.41	0.69	0.33	47.2
33	0.6	65.9	0.40	0.69	0.30	43.5
34	0.6	82.6	0.50	0.69	0.49	71.1
35	0.6	46.1	0.28	0.69	0.13	19.1
36	0.6	81.3	0.49	0.69	0.48	68.8
37	0.6	66.0	0.40	0.69	0.30	43.6
38	0.6	16.9	0.10	0.69	0.02	3.4
39	0.6	50.3	0.30	0.69	0.16	23.2
40	0.6	61.6	0.37	0.69	0.26	37.2
41	0.6	68.0	0.41	0.69	0.32	46.6
42	0.6	71.1	0.43	0.69	0.36	51.6
43	0.6	48.5	0.29	0.69	0.15	21.4
44	0.6	5.1	0.03	0.69	0.01	1.4
45	0.6	52.9	0.32	0.69	0.18	26.1
46	0.6	58.1	0.35	0.69	0.22	32.5
47	0.6	72.7	0.44	0.69	0.38	54.3

48	0.6	28.8	0.17	0.69	0.05	7.4
49	0.6	95.4	0.57	0.69	0.64	92.8
50	0.6	4.3	0.03	0.69	0.01	1.3
51	0.6	14.6	0.09	0.69	0.02	2.8
52	0.6	33.1	0.20	0.69	0.07	9.5
53	0.6	91.8	0.55	0.69	0.60	86.9
54	0.6	17.4	0.10	0.69	0.02	3.5
55	0.6	77.7	0.47	0.69	0.43	62.5
56	0.6	47.9	0.29	0.69	0.14	20.9
57	0.6	97.7	0.59	0.69	0.67	96.4
58	0.6	95.2	0.57	0.69	0.64	92.5
59	0.6	10.5	0.06	0.69	0.01	2.1
60	0.6	9.0	0.05	0.69	0.01	1.9
61	0.6	75.7	0.45	0.69	0.41	59.2
62	0.6	88.3	0.53	0.69	0.56	80.9
63	0.6	85.7	0.51	0.69	0.53	76.4
64	0.6	85.0	0.51	0.69	0.52	75.2
65	0.6	87.5	0.53	0.69	0.55	79.5
66	0.6	88.0	0.53	0.69	0.56	80.3
67	0.6	40.2	0.24	0.69	0.10	14.2
68	0.6	61.1	0.37	0.69	0.25	36.5
69	0.6	13.1	0.08	0.69	0.02	2.5
70	0.6	84.0	0.50	0.69	0.51	73.4
71	0.6	79.6	0.48	0.69	0.46	65.8
72	0.6	3.7	0.02	0.69	0.01	1.2
73	0.6	68.8	0.41	0.69	0.33	47.9

74	0.6	16.0	0.10	0.69	0.02	3.1
75	0.6	2.4	0.01	0.69	0.01	1.1
76	0.6	8.8	0.05	0.69	0.01	1.8
77	0.6	56.2	0.34	0.69	0.21	30.1
78	0.6	21.8	0.13	0.69	0.03	4.7
79	0.6	26.6	0.16	0.69	0.04	6.4
80	0.6	14.3	0.09	0.69	0.02	2.8
81	0.6	84.0	0.50	0.69	0.51	73.5
82	0.6	23.3	0.14	0.69	0.04	5.2
83	0.6	97.9	0.59	0.69	0.67	96.7
84	0.6	62.6	0.38	0.69	0.27	38.6
85	0.6	18.6	0.11	0.69	0.03	3.8
86	0.6	54.2	0.33	0.69	0.19	27.6
87	0.6	7.0	0.04	0.69	0.01	1.6
88	0.6	18.9	0.11	0.69	0.03	3.9
89	0.6	7.1	0.04	0.69	0.01	1.6
90	0.6	46.0	0.28	0.69	0.13	19.0
91	0.6	54.0	0.32	0.69	0.19	27.4
92	0.6	57.4	0.34	0.69	0.22	31.6
93	0.6	28.9	0.17	0.69	0.05	7.4
94	0.6	23.1	0.14	0.69	0.04	5.1
95	0.6	11.0	0.07	0.69	0.01	2.2
96	0.6	34.5	0.21	0.69	0.07	10.4
97	0.6	25.6	0.15	0.69	0.04	6.0
98	0.6	37.9	0.23	0.69	0.09	12.5
99	0.6	10.2	0.06	0.69	0.01	2.0

100	0.6	37.3	0.22	0.69	0.08	12.1

Simulated Sample 3

Compliance Distribution: Beta(2, 2)

n	Dose Presc.	Compliance (%)	Dose Taken	Response (expected)	Response (actual)	Response (%)
1	0.6	78.5	0.47	0.69	0.44	63.9
2	0.6	52.2	0.31	0.69	0.18	25.3
3	0.6	69.0	0.41	0.69	0.33	48.3
4	0.6	29.4	0.18	0.69	0.05	7.6
5	0.6	19.7	0.12	0.69	0.03	4.1
6	0.6	94.9	0.57	0.69	0.64	92.0
7	0.6	44.9	0.27	0.69	0.12	18.0
8	0.6	44.4	0.27	0.69	0.12	17.5
9	0.6	40.6	0.24	0.69	0.10	14.5
10	0.6	58.5	0.35	0.69	0.23	33.0
11	0.6	80.8	0.48	0.69	0.47	68.0
12	0.6	85.5	0.51	0.69	0.53	76.1
13	0.6	79.1	0.47	0.69	0.45	64.9
14	0.6	64.4	0.39	0.69	0.29	41.2
15	0.6	52.1	0.31	0.69	0.17	25.3
16	0.6	16.5	0.10	0.69	0.02	3.3
17	0.6	58.7	0.35	0.69	0.23	33.2
18	0.6	74.0	0.44	0.69	0.39	56.3
19	0.6	30.6	0.18	0.69	0.06	8.2

20	0.6	42.0	0.25	0.69	0.11	15.5
21	0.6	51.9	0.31	0.69	0.17	25.0
22	0.6	58.0	0.35	0.69	0.22	32.3
23	0.6	4.4	0.03	0.69	0.01	1.3
24	0.6	60.9	0.37	0.69	0.25	36.2
25	0.6	61.7	0.37	0.69	0.26	37.3
26	0.6	27.1	0.16	0.69	0.05	6.6
27	0.6	9.5	0.06	0.69	0.01	1.9
28	0.6	23.0	0.14	0.69	0.04	5.1
29	0.6	78.7	0.47	0.69	0.44	64.3
30	0.6	17.3	0.10	0.69	0.02	3.4
31	0.6	19.0	0.11	0.69	0.03	3.9
32	0.6	18.7	0.11	0.69	0.03	3.8
33	0.6	40.2	0.24	0.69	0.10	14.1
34	0.6	85.9	0.52	0.69	0.53	76.7
35	0.6	93.0	0.56	0.69	0.61	88.8
36	0.6	38.9	0.23	0.69	0.09	13.2
37	0.6	34.2	0.21	0.69	0.07	10.2
38	0.6	33.2	0.20	0.69	0.07	9.6
39	0.6	57.9	0.35	0.69	0.22	32.2
40	0.6	41.4	0.25	0.69	0.10	15.1
41	0.6	20.2	0.12	0.69	0.03	4.2
42	0.6	9.9	0.06	0.69	0.01	2.0
43	0.6	73.9	0.44	0.69	0.39	56.2
44	0.6	70.3	0.42	0.69	0.35	50.4
45	0.6	45.4	0.27	0.69	0.13	18.4

46	0.6	17.4	0.10	0.69	0.02	3.5
47	0.6	55.5	0.33	0.69	0.20	29.2
48	0.6	84.8	0.51	0.69	0.52	74.9
49	0.6	77.0	0.46	0.69	0.43	61.5
50	0.6	84.1	0.50	0.69	0.51	73.7
51	0.6	91.7	0.55	0.69	0.60	86.6
52	0.6	49.1	0.29	0.69	0.15	22.1
53	0.6	83.8	0.50	0.69	0.51	73.2
54	0.6	45.3	0.27	0.69	0.13	18.3
55	0.6	24.5	0.15	0.69	0.04	5.6
56	0.6	50.8	0.30	0.69	0.16	23.8
57	0.6	24.5	0.15	0.69	0.04	5.6
58	0.6	33.0	0.20	0.69	0.07	9.5
59	0.6	59.9	0.36	0.69	0.24	34.8
60	0.6	31.1	0.19	0.69	0.06	8.5
61	0.6	46.0	0.28	0.69	0.13	19.0
62	0.6	38.5	0.23	0.69	0.09	12.9
63	0.6	58.6	0.35	0.69	0.23	33.2
64	0.6	89.7	0.54	0.69	0.58	83.3
65	0.6	18.9	0.11	0.69	0.03	3.9
66	0.6	51.1	0.31	0.69	0.17	24.1
67	0.6	33.3	0.20	0.69	0.07	9.6
68	0.6	66.3	0.40	0.69	0.30	44.1
69	0.6	10.0	0.06	0.69	0.01	2.0
70	0.6	85.7	0.51	0.69	0.53	76.4
71	0.6	58.7	0.35	0.69	0.23	33.3

72	0.6	73.0	0.44	0.69	0.38	54.7
73	0.6	52.8	0.32	0.69	0.18	26.0
74	0.6	87.5	0.53	0.69	0.55	79.5
75	0.6	4.5	0.03	0.69	0.01	1.3
76	0.6	68.5	0.41	0.69	0.33	47.5
77	0.6	32.0	0.19	0.69	0.06	8.9
78	0.6	86.9	0.52	0.69	0.54	78.5
79	0.6	43.5	0.26	0.69	0.12	16.8
80	0.6	29.8	0.18	0.69	0.05	7.9
81	0.6	86.3	0.52	0.69	0.54	77.4
82	0.6	59.9	0.36	0.69	0.24	34.9
83	0.6	28.9	0.17	0.69	0.05	7.4
84	0.6	24.8	0.15	0.69	0.04	5.7
85	0.6	38.4	0.23	0.69	0.09	12.8
86	0.6	79.8	0.48	0.69	0.46	66.2
87	0.6	57.0	0.34	0.69	0.22	31.1
88	0.6	44.5	0.27	0.69	0.12	17.6
89	0.6	39.9	0.24	0.69	0.10	13.9
90	0.6	54.0	0.32	0.69	0.19	27.4
91	0.6	52.5	0.32	0.69	0.18	25.7
92	0.6	92.4	0.55	0.69	0.61	87.7
93	0.6	97.5	0.59	0.69	0.66	96.2
94	0.6	53.5	0.32	0.69	0.19	26.9
95	0.6	22.2	0.13	0.69	0.03	4.8
96	0.6	5.7	0.03	0.69	0.01	1.4
97	0.6	82.3	0.49	0.69	0.49	70.5

98	0.6	56.0	0.34	0.69	0.21	29.8
99	0.6	53.4	0.32	0.69	0.18	26.7
100	0.6	46.2	0.28	0.69	0.13	19.2

Simulated Sample 4

Compliance Distribution: Beta(2, 0.5)

n	Dose Presc.	Compliance (%)	Dose taken	Response (expected)	Response (actual)	Response (%)
1	0.6	22.1	0.13	0.69	0.03	4.8
2	0.6	58.0	0.35	0.69	0.22	32.4
3	0.6	47.3	0.28	0.69	0.14	20.2
4	0.6	38.6	0.23	0.69	0.09	13.0
5	0.6	100.0	0.60	0.69	0.69	100.0
6	0.6	84.5	0.51	0.69	0.51	74.4
7	0.6	97.1	0.58	0.69	0.66	95.4
8	0.6	99.5	0.60	0.69	0.69	99.2
9	0.6	92.2	0.55	0.69	0.61	87.5
10	0.6	79.1	0.47	0.69	0.45	64.9
11	0.6	94.6	0.57	0.69	0.63	91.4
12	0.6	96.7	0.58	0.69	0.66	94.8
13	0.6	99.9	0.60	0.69	0.66	99.9
14	0.6	85.1	0.51	0.69	0.52	75.4
15	0.6	86.2	0.52	0.69	0.53	77.3
16	0.6	70.0	0.42	0.69	0.34	49.8
17	0.6	83.6	0.50	0.69	0.50	72.8
18	0.6	67.9	0.41	0.69	0.32	46.5

19	0.6	84.8	0.51	0.69	0.52	74.8
20	0.6	81.9	0.49	0.69	0.48	69.8
21	0.6	62.7	0.38	0.69	0.27	38.7
22	0.6	25.6	0.15	0.69	0.04	6.0
23	0.6	98.6	0.59	0.69	0.68	97.9
24	0.6	34.3	0.21	0.69	0.07	10.2
25	0.6	56.7	0.34	0.69	0.21	30.7
26	0.6	99.3	0.60	0.69	0.68	98.9
27	0.6	89.5	0.54	0.69	0.57	82.9
28	0.6	98.9	0.59	0.69	0.68	98.3
29	0.6	54.2	0.33	0.69	0.19	27.7
30	0.6	67.0	0.40	0.69	0.31	45.2
31	0.6	100.0	0.60	0.69	0.69	99.9
32	0.6	79.4	0.48	0.69	0.45	65.5
33	0.6	95.4	0.57	0.69	0.64	92.8
34	0.6	47.9	0.29	0.69	0.14	20.8
35	0.6	97.8	0.59	0.69	0.67	96.5
36	0.6	99.7	0.60	0.69	0.69	99.5
37	0.6	99.7	0.60	0.69	0.69	99.5
38	0.6	81.1	0.49	0.69	0.47	68.4
39	0.6	94.6	0.57	0.69	0.63	91.4
40	0.6	99.2	0.60	0.69	0.68	98.8
41	0.6	95.8	0.57	0.69	0.65	93.3
42	0.6	99.3	0.60	0.69	0.68	99.0
43	0.6	90.8	0.54	0.69	0.59	85.0
44	0.6	75.5	0.45	0.69	0.41	58.9

45	0.6	78.3	0.47	0.69	0.44	63.7
46	0.6	95.7	0.57	0.69	0.64	93.2
47	0.6	100.0	0.60	0.69	0.69	100.0
48	0.6	88.6	0.53	0.69	0.56	81.4
49	0.6	27.2	0.16	0.69	0.05	6.7
50	0.6	89.9	0.54	0.69	0.58	83.7
51	0.6	93.3	0.56	0.69	0.62	89.3
52	0.6	99.7	0.60	0.69	0.69	99.6
53	0.6	43.9	0.26	0.69	0.12	17.1
54	0.6	97.2	0.58	0.69	0.66	95.7
55	0.6	82.1	0.49	0.69	0.49	70.1
56	0.6	94.2	0.57	0.69	0.63	90.8
57	0.6	99.9	0.60	0.69	0.69	99.9
58	0.6	98.8	0.59	0.69	0.68	98.2
59	0.6	38.4	0.23	0.69	0.09	12.9
60	0.6	71.6	0.43	0.69	0.36	52.5
61	0.6	57.6	0.35	0.69	0.22	31.8
62	0.6	90.4	0.54	0.69	0.58	84.4
63	0.6	75.2	0.45	0.69	0.40	58.4
64	0.6	83.6	0.50	0.69	0.50	72.8
65	0.6	99.7	0.60	0.69	0.69	99.5
66	0.6	79.6	0.48	0.69	0.46	65.9
67	0.6	99.1	0.59	0.69	0.68	98.7
68	0.6	99.5	0.60	0.69	0.69	99.2
69	0.6	42.4	0.25	0.69	0.11	15.8
70	0.6	98.7	0.59	0.69	0.68	98.0

71	0.6	85.1	0.51	0.69	0.52	75.3
72	0.6	94.4	0.57	0.69	0.63	91.1
73	0.6	65.4	0.39	0.69	0.30	42.7
74	0.6	97.3	0.58	0.69	0.66	95.9
75	0.6	95.4	0.57	0.69	0.64	92.7
76	0.6	87.7	0.53	0.69	0.55	79.9
77	0.6	59.3	0.36	0.69	0.24	34.1
78	0.6	72.7	0.44	0.69	0.37	54.2
79	0.6	98.0	0.59	0.69	0.67	96.9
80	0.6	20.3	0.12	0.69	0.03	4.2
81	0.6	89.5	0.54	0.69	0.57	82.8
82	0.6	82.7	0.50	0.69	0.49	71.2
83	0.6	100.0	0.60	0.69	0.69	100.0
84	0.6	97.4	0.58	0.69	0.66	96.0
85	0.6	71.8	0.43	0.69	0.36	52.7
86	0.6	65.0	0.39	0.69	0.29	42.2
87	0.6	46.0	0.28	0.69	0.13	19.0
88	0.6	66.5	0.40	0.69	0.31	44.3
89	0.6	81.8	0.49	0.69	0.48	69.7
90	0.6	100.0	0.60	0.69	0.69	100.0
91	0.6	60.8	0.36	0.69	0.25	36.0
92	0.6	87.7	0.53	0.69	0.55	79.9
93	0.6	17.2	0.10	0.69	0.02	3.4
94	0.6	70.5	0.42	0.69	0.35	50.7
95	0.6	88.0	0.53	0.69	0.56	80.4
96	0.6	95.0	0.57	0.69	0.64	92.2

97	0.6	96.7	0.58	0.69	0.66	94.8
98	0.6	80.9	0.49	0.69	0.47	68.0
99	0.6	90.8	0.54	0.69	0.59	85.2
100	0.6	45.9	0.28	0.69	0.13	18.9

Simulated Sample 5

Compliance Distribution: Beta(0.5,0.5)

n	Dose Presc.	Compliance (%)	Dose Taken	Response (expected)	Response (Actual)	Response (%)
1	6.0	64.4	3.87	0.84	0.13	15.3
2	6.0	99.7	5.98	0.84	0.84	99.5
3	6.0	84.7	5.08	0.84	0.53	63.3
4	6.0	0.1	0.00	0.84	0.00	0.0
5	6.0	89.3	5.36	0.84	0.64	76.1
6	6.0	54.0	3.24	0.84	0.04	4.6
7	6.0	4.9	0.29	0.84	0.00	0.0
8	6.0	85.6	5.13	0.84	0.55	65.8
9	6.0	9.4	0.56	0.84	0.00	0.0
10	6.0	96.0	5.76	0.84	0.78	92.3
11	6.0	0.1	0.01	0.84	0.00	0.0
12	6.0	32.9	1.98	0.84	0.00	0.2
13	6.0	24.4	1.46	0.84	0.74	87.4
14	6.0	93.8	5.63	0.84	0.74	87.4
15	6.0	39.9	2.40	0.84	0.00	0.5
16	6.0	47.8	2.87	0.84	0.02	2.0
17	6.0	98.9	5.93	0.84	0.82	98.0

18	6.0	45.3	2.72	0.84	0.01	1.3
19	6.0	86.5	5.19	0.84	0.57	68.3
20	6.0	99.8	5.99	0.84	0.84	99.7
21	6.0	16.3	0.98	0.84	0.00	0.0
22	6.0	96.5	5.79	0.84	0.79	93.4
23	6.0	72.4	4.34	0.84	0.26	30.4
24	6.0	57.4	3.44	0.84	0.06	7.1
25	6.0	30.3	1.82	0.84	0.00	0.1
26	6.0	2.4	0.14	0.84	0.00	0.0
27	6.0	99.8	5.99	0.84	0.84	99.6
28	6.0	94.9	5.69	0.84	0.76	89.8
29	6.0	6.9	0.41	0.84	0.00	0.0
30	6.0	86.9	5.21	0.84	0.58	69.5
31	6.0	77.7	4.66	0.84	0.37	43.7
32	6.0	92.9	5.57	0.84	0.72	85.1
33	6.0	10.6	0.63	0.84	0.00	0.0
34	6.0	12.0	0.72	0.84	0.00	0.0
35	6.0	2.4	0.14	0.84	0.00	0.0
36	6.0	47.0	2.82	0.84	0.01	1.7
37	6.0	61.0	3.66	0.84	0.09	10.7
38	6.0	9.1	0.55	0.84	0.00	0.0
39	6.0	31.3	1.88	0.84	0.00	0.1
40	6.0	7.0	0.42	0.84	0.00	0.0
41	6.0	18.1	1.09	0.84	0.00	0.0
42	6.0	41.5	2.49	0.84	0.01	0.7
43	6.0	9.9	0.60	0.84	0.00	0.0

44	6.0	0.1	0.00	0.84	0.00	0.0
45	6.0	28.5	1.71	0.84	0.00	0.1
46	6.0	97.3	5.84	0.84	0.80	94.9
47	6.0	18.4	1.11	0.84	0.00	0.0
48	6.0	38.9	2.33	0.84	0.00	0.5
49	6.0	10.1	0.61	0.84	0.00	0.0
50	6.0	76.6	4.60	0.84	0.34	40.8
51	6.0	49.3	2.96	0.84	0.02	2.4
52	6.0	62.5	3.75	0.84	0.11	12.6
53	6.0	62.0	3.72	0.84	0.10	11.9
54	6.0	0.2	0.01	0.84	0.00	0.0
55	6.0	12.9	0.78	0.84	0.00	0.0
56	6.0	98.5	5.91	0.84	0.82	97.3
57	6.0	46.1	2.76	0.84	0.01	1.5
58	6.0	67.0	4.02	0.84	0.16	19.4
59	6.0	45.2	2.71	0.84	0.01	1.3
60	6.0	44.2	2.65	0.84	0.01	1.1
61	6.0	26.7	1.60	0.84	0.00	0.0
62	6.0	0.5	0.03	0.84	0.00	0.0
63	6.0	40.6	2.44	0.84	0.01	0.6
64	6.0	1.6	0.09	0.84	0.00	0.0
65	6.0	3.3	0.20	0.84	0.00	0.0
66	6.0	100.0	6.00	0.84	0.84	100.0
67	6.0	7.8	0.47	0.84	0.00	0.0
68	6.0	43.5	2.61	0.84	0.01	1.0
69	6.0	16.6	1.00	0.84	0.00	0.0

70	6.0	92.7	5.56	0.84	0.71	84.7
71	6.0	9.6	0.57	0.84	0.00	0.0
72	6.0	7.8	0.47	0.84	0.00	0.0
73	6.0	24.2	1.45	0.84	0.00	0.0
74	6.0	95.0	5.70	0.84	0.76	90.2
75	6.0	17.6	1.06	0.84	0.00	0.0
76	6.0	100.0	6.00	0.84	0.84	100.0
77	6.0	26.9	1.61	0.84	0.00	0.0
78	6.0	71.5	4.29	0.84	0.24	28.4
79	6.0	1.2	0.07	0.84	0.00	0.0
80	6.0	76.5	4.59	0.84	0.34	40.6
81	6.0	44.7	2.68	0.84	0.01	1.2
82	6.0	94.3	5.66	0.84	0.74	88.5
83	6.0	77.5	4.65	0.84	0.36	43.2
84	6.0	99.4	5.96	0.84	0.83	98.9
85	6.0	33.3	2.00	0.84	0.00	0.2
86	6.0	4.4	0.27	0.84	0.00	0.0
87	6.0	80.1	4.81	0.84	0.42	50.4
88	6.0	31.6	1.89	0.84	0.00	0.1
89	6.0	44.0	2.64	0.84	0.01	1.1
90	6.0	19.6	1.18	0.84	0.00	0.0
91	6.0	98.3	5.90	0.84	0.82	97.0
92	6.0	12.5	0.75	0.84	0.00	0.0
93	6.0	35.9	2.15	0.84	0.00	0.3
94	6.0	59.2	3.55	0.84	0.07	8.8
95	6.0	94.9	5.69	0.84	0.76	89.8

96	6.0	1.5	0.09	0.84	0.00	0.0
97	6.0	29.2	1.75	0.84	0.00	0.1
98	6.0	5.8	0.35	0.84	0.00	0.0
99	6.0	44.3	2.66	0.84	0.00	1.1
100	6.0	59.3	3.56	0.84	0.07	8.9

Simulated Sample 6

Compliance Distribution: Beta(1, 1)

n	Dose Presc.	Compliance (%)	Dose taken	Response (expected)	Response (actual)	Response (%)
1	6.0	96.6	5.80	0.84	0.79	93.6
2	6.0	26.1	1.56	0.84	0.00	0.0
3	6.0	76.6	4.60	0.84	0.34	40.8
4	6.0	56.9	3.42	0.84	0.06	6.7
5	6.0	84.5	5.07	0.84	0.53	62.7
6	6.0	4.4	0.27	0.84	0.00	0.0
7	6.0	98.7	5.92	0.84	0.82	97.7
8	6.0	60.1	3.61	0.84	0.08	9.7
9	6.0	89.6	5.38	0.84	0.65	76.9
10	6.0	38.1	2.29	0.84	0.00	0.4
11	6.0	1.6	0.10	0.84	0.00	0.0
12	6.0	58.7	3.52	0.84	0.07	8.3
13	6.0	48.9	2.93	0.84	0.02	2.3
14	6.0	16.9	1.01	0.84	0.00	0.0
15	6.0	21.3	1.28	0.84	0.00	0.0
16	6.0	19.7	1.18	0.84	0.00	0.0

17	6.0	9.0	0.54	0.84	0.00	0.0
18	6.0	39.5	2.37	0.84	0.00	0.5
19	6.0	34.6	2.08	0.84	0.00	0.2
20	6.0	14.2	0.85	0.84	0.00	0.0
21	6.0	56.6	3.40	0.84	0.00	6.5
22	6.0	89.9	5.39	0.84	0.65	77.6
23	6.0	28.9	1.74	0.84	0.00	0.1
24	6.0	89.8	5.39	0.84	0.65	77.5
25	6.0	22.6	1.35	0.84	0.00	0.0
26	6.0	4.6	0.28	0.84	0.00	0.0
27	6.0	71.0	4.26	0.84	0.23	27.2
28	6.0	87.3	5.24	0.84	0.59	70.7
29	6.0	3.3	0.20	0.84	0.00	0.0
30	6.0	88.7	5.32	0.84	0.63	74.5
31	6.0	47.9	2.87	0.84	0.02	2.0
32	6.0	68.3	4.10	0.84	0.18	21.9
33	6.0	65.9	3.96	0.84	0.15	17.6
34	6.0	82.6	4.96	0.84	0.48	57.5
35	6.0	46.1	2.77	0.84	0.01	1.5
36	6.0	81.3	4.88	0.84	0.45	53.6
37	6.0	66.0	3.96	0.84	0.15	17.7
38	6.0	16.9	1.02	0.84	0.00	0.0
39	6.0	50.3	3.02	0.84	0.02	2.8
40	6.0	61.6	3.70	0.84	0.10	11.5
41	6.0	68.0	4.08	0.84	0.18	21.2
42	6.0	71.1	4.26	0.84	0.23	27.4

43	6.0	48.5	2.91	0.84	0.02	2.2
44	6.0	5.1	0.31	0.84	0.00	0.0
45	6.0	52.9	3.17	0.84	0.03	4.0
46	6.0	58.1	3.49	0.84	0.07	7.7
47	6.0	72.7	4.36	0.84	0.26	31.2
48	6.0	28.8	1.73	0.84	0.00	0.1
49	6.0	95.4	5.73	0.84	0.77	91.1
50	6.0	4.3	0.26	0.84	0.00	0.0
51	6.0	14.6	0.87	0.84	0.00	0.0
52	6.0	33.1	1.98	0.84	0.00	0.2
53	6.0	91.8	5.51	0.84	0.69	82.6
54	6.0	17.4	1.04	0.84	0.00	0.0
55	6.0	77.7	4.66	0.84	0.37	43.6
56	6.0	47.9	2.88	0.84	0.02	2.0
57	6.0	97.7	5.86	0.84	0.80	95.7
58	6.0	95.2	5.71	0.84	0.76	90.6
59	6.0	10.5	0.63	0.84	0.00	0.0
60	6.0	9.0	0.54	0.84	0.00	0.0
61	6.0	75.7	4.54	0.84	0.32	38.4
62	6.0	88.3	5.30	0.84	0.62	73.4
63	6.0	85.7	5.14	0.84	0.56	66.1
64	6.0	85.0	5.10	0.84	0.54	64.1
65	6.0	87.5	5.25	0.84	0.60	71.2
66	6.0	88.0	5.28	0.84	0.61	72.4
67	6.0	40.2	2.41	0.84	0.00	0.6
68	6.0	61.1	3.67	0.84	0.09	10.8

69	6.0	13.1	0.79	0.84	0.00	0.0
70	6.0	84.0	5.04	0.84	0.51	61.2
71	6.0	79.6	4.77	0.84	0.41	48.8
72	6.0	3.7	0.22	0.84	0.00	0.0
73	6.0	68.8	4.13	0.84	0.19	22.7
74	6.0	16.0	0.96	0.84	0.00	0.0
75	6.0	2.4	0.14	0.84	0.00	0.0
76	6.0	8.8	0.53	0.84	0.00	0.0
77	6.0	56.2	3.37	0.84	0.05	6.2
78	6.0	21.8	1.31	0.84	0.00	0.0
79	6.0	26.6	1.60	0.84	0.00	0.0
80	6.0	14.3	0.86	0.84	0.00	0.0
81	6.0	84.0	5.04	0.84	0.52	61.4
82	6.0	23.3	1.40	0.84	0.00	0.0
83	6.0	97.9	5.87	0.84	0.81	96.1
84	6.0	62.6	3.76	0.84	0.11	12.7
85	6.0	18.6	1.12	0.84	0.00	0.0
86	6.0	54.2	3.25	0.84	0.04	4.8
87	6.0	7.0	0.42	0.84	0.00	0.0
88	6.0	18.9	1.13	0.84	0.00	0.0
89	6.0	7.1	0.43	0.84	0.00	0.0
90	6.0	46.0	2.76	0.84	0.01	1.5
91	6.0	54.0	3.24	0.84	0.04	4.7
92	6.0	57.4	3.45	0.84	0.06	7.1
93	6.0	28.9	1.74	0.84	0.00	0.1
94	6.0	23.1	1.39	0.84	0.00	0.0

95	6.0	11.0	0.66	0.84	0.00	0.0
96	6.0	34.5	2.07	0.84	0.00	0.2
97	6.0	25.6	1.53	0.84	0.00	0.0
98	6.0	37.9	2.27	0.84	0.00	0.4
99	6.0	10.2	0.61	0.84	0.00	0.0
100	6.0	37.3	2.24	0.84	0.00	0.3

Simulated Sample 7

Compliance Distribution: Beta(2, 2)

n	Dose Presc.	Compliance (%)	Dose taken	Response (expected)	Response (actual)	Response (%)
1	6.0	78.5	4.71	0.84	0.39	45.8
2	6.0	52.2	3.13	0.84	0.03	3.7
3	6.0	69.0	4.14	0.84	0.20	23.2
4	6.0	29.4	1.76	0.84	0.00	0.1
5	6.0	19.7	1.18	0.84	0.00	0.0
6	6.0	94.9	5.70	0.84	0.76	90.0
7	6.0	44.9	2.69	0.84	0.01	1.3
8	6.0	44.4	2.66	0.84	0.01	1.2
9	6.0	40.6	2.44	0.84	0.01	0.6
10	6.0	58.5	3.51	0.84	0.07	8.1
11	6.0	80.8	4.85	0.84	0.44	52.3
12	6.0	85.5	5.13	0.84	0.55	65.7
13	6.0	79.1	4.74	0.84	0.40	47.4
14	6.0	64.4	3.86	0.84	0.13	15.2
15	6.0	52.1	3.13	0.84	0.03	3.6

16	6.0	16.5	0.99	0.84	0.00	0.0
17	6.0	58.7	3.52	0.84	0.07	8.3
18	6.0	74.0	4.44	0.84	0.29	34.1
19	6.0	30.6	1.83	0.84	0.00	0.1
20	6.0	42.0	2.52	0.84	0.01	0.8
21	6.0	51.9	3.11	0.84	0.03	3.5
22	6.0	58.0	3.48	0.84	0.06	7.6
23	6.0	4.4	0.26	0.84	0.00	0.0
24	6.0	60.9	3.66	0.84	0.09	10.6
25	6.0	61.7	3.70	0.84	0.10	11.5
26	6.0	27.1	1.63	0.84	0.00	0.0
27	6.0	9.5	0.57	0.84	0.00	0.0
28	6.0	23.0	1.38	0.84	0.00	0.0
29	6.0	78.7	4.72	0.84	0.39	46.5
30	6.0	17.3	1.04	0.84	0.00	0.0
31	6.0	19.0	1.14	0.84	0.00	0.0
32	6.0	18.7	1.12	0.84	0.00	0.0
33	6.0	40.2	2.41	0.84	0.00	0.6
34	6.0	85.9	5.15	0.84	0.56	66.6
35	6.0	93.0	5.58	0.84	0.72	85.5
36	6.0	38.9	2.33	0.84	0.00	0.5
37	6.0	34.2	2.05	0.84	0.00	0.2
38	6.0	33.2	1.99	0.84	0.00	0.2
39	6.0	57.9	3.48	0.84	0.06	7.6
40	6.0	41.4	2.49	0.84	0.01	0.7
41	6.0	20.2	1.21	0.84	0.00	0.0

42	6.0	9.9	0.59	0.84	0.00	0.0
43	6.0	73.9	4.44	0.84	0.29	34.0
44	6.0	70.3	4.22	0.84	0.22	25.9
45	6.0	45.4	2.72	0.84	0.01	1.4
46	6.0	17.4	1.04	0.84	0.00	0.0
47	6.0	55.5	3.33	0.84	0.05	5.6
48	6.0	84.8	5.09	0.84	0.54	63.7
49	6.0	77.0	4.62	0.84	0.35	41.9
50	6.0	84.1	5.05	0.84	0.52	61.6
51	6.0	91.7	5.50	0.84	0.69	82.2
52	6.0	49.1	2.95	0.84	0.02	2.4
53	6.0	83.8	5.03	0.84	0.51	60.8
54	6.0	45.3	2.72	0.84	0.01	1.3
55	6.0	24.5	1.47	0.84	0.00	0.0
56	6.0	50.8	3.05	0.84	0.03	3.0
57	6.0	24.5	1.47	0.84	0.00	0.0
58	6.0	33.0	1.98	0.84	0.00	0.2
59	6.0	59.9	3.59	0.84	0.08	9.5
60	6.0	31.1	1.87	0.84	0.00	0.1
61	6.0	46.0	2.76	0.84	0.01	1.5
62	6.0	38.5	2.31	0.84	0.00	0.4
63	6.0	58.6	3.52	0.84	0.07	8.2
64	6.0	89.7	5.38	0.84	0.65	77.2
65	6.0	18.9	1.14	0.84	0.00	0.0
66	6.0	51.1	3.07	0.84	0.03	3.1
67	6.0	33.3	2.00	0.84	0.00	0.2

68	6.0	66.3	3.98	0.84	0.15	18.3
69	6.0	10.0	0.60	0.84	0.00	0.0
70	6.0	85.7	5.14	0.84	0.56	66.2
71	6.0	58.7	3.52	0.84	0.07	8.3
72	6.0	73.0	4.38	0.84	0.27	31.7
73	6.0	52.8	3.17	0.84	0.03	4.0
74	6.0	87.5	5.25	0.84	0.60	71.2
75	6.0	4.5	0.27	0.84	0.00	0.0
76	6.0	68.5	4.11	0.84	0.19	22.2
77	6.0	32.0	1.92	0.84	0.00	0.1
78	6.0	86.9	5.21	0.84	0.58	69.5
79	6.0	43.5	2.61	0.84	0.01	1.0
80	6.0	29.8	1.79	0.84	0.00	0.1
81	6.0	86.3	5.18	0.84	0.57	67.8
82	6.0	59.9	3.60	0.84	0.08	9.5
83	6.0	28.9	1.74	0.84	0.00	0.1
84	6.0	24.8	1.49	0.84	0.00	0.0
85	6.0	38.4	2.30	0.84	0.00	0.4
86	6.0	79.8	4.79	0.84	0.42	49.4
87	6.0	57.0	3.42	0.84	0.06	6.8
88	6.0	44.5	2.67	0.84	0.01	1.2
89	6.0	39.9	2.39	0.84	0.00	0.5
90	6.0	54.0	3.24	0.84	0.04	4.7
91	6.0	52.5	3.15	0.84	0.03	3.8
92	6.0	92.4	5.54	0.84	0.71	83.9
93	6.0	97.5	5.85	0.84	0.80	95.4

94	6.0	53.5	3.21	0.84	0.04	4.4
95	6.0	22.2	1.33	0.84	0.00	0.0
96	6.0	5.7	0.34	0.84	0.00	0.0
97	6.0	82.3	4.94	0.84	0.48	56.5
98	6.0	56.0	3.36	0.84	0.05	6.0
99	6.0	53.4	3.20	0.84	0.04	4.3
100	6.0	46.2	2.77	0.84	0.01	1.5

Simulated Sample 8

Compliance Distribution: Beta(2, 0.5)

n	Dose Presc.	Compliance (%)	Dose taken	Response (expected)	Response (actual)	Response (%)
1	6.0	22.1	1.32	0.84	0.00	0.0
2	6.0	58.0	3.48	0.84	0.06	7.7
3	6.0	47.3	2.84	0.84	0.02	1.8
4	6.0	38.6	2.32	0.84	0.00	0.4
5	6.0	100.0	6.00	0.84	0.84	100.0
6	6.0	84.5	5.07	0.84	0.53	62.8
7	6.0	97.1	5.82	0.84	0.79	94.5
8	6.0	99.5	5.97	0.84	0.83	99.1
9	6.0	92.2	5.53	0.84	0.70	83.6
10	6.0	79.1	4.74	0.84	0.40	47.4
11	6.0	94.6	5.67	0.84	0.75	89.1
12	6.0	96.7	5.80	0.84	0.79	93.7
13	6.0	99.9	6.00	0.84	0.84	99.9
14	6.0	85.1	5.11	0.84	0.54	64.6

15	6.0	86.2	5.17	0.84	0.57	67.6
16	6.0	70.0	4.20	0.84	0.21	25.2
17	6.0	83.6	5.02	0.84	0.51	60.3
18	6.0	67.9	4.07	0.84	0.18	21.1
19	6.0	84.8	5.09	0.84	0.53	63.5
20	6.0	81.9	4.91	0.84	0.47	55.3
21	6.0	62.7	3.76	0.84	0.11	12.8
22	6.0	25.6	1.54	0.84	0.00	0.0
23	6.0	98.6	5.92	0.84	0.82	97.5
24	6.0	34.3	2.06	0.84	0.00	0.2
25	6.0	56.7	3.40	0.84	0.06	6.6
26	6.0	99.3	5.96	0.84	0.83	98.8
27	6.0	89.5	5.37	0.84	0.64	76.6
28	6.0	98.9	5.93	0.84	0.82	98.0
29	6.0	54.2	3.25	0.84	0.04	4.8
30	6.0	67.0	4.02	0.84	0.16	19.5
31	6.0	100.0	6.00	0.84	0.84	100.0
32	6.0	79.4	4.76	0.84	0.41	48.4
33	6.0	95.4	5.72	0.84	0.77	91.0
34	6.0	47.9	2.88	0.84	0.02	2.0
35	6.0	97.8	5.87	0.84	0.81	95.9
36	6.0	99.7	5.98	0.84	0.84	99.4
37	6.0	99.7	5.98	0.84	0.84	99.4
38	6.0	81.1	4.87	0.84	0.45	53.1
39	6.0	94.6	5.67	0.84	0.75	89.1
40	6.0	99.2	5.95	0.84	0.83	98.6

41	6.0	95.8	5.75	0.84	0.77	91.8
42	6.0	99.3	5.96	0.84	0.83	98.8
43	6.0	90.8	5.45	0.84	0.67	79.9
44	6.0	75.5	4.53	0.84	0.32	38.0
45	6.0	78.3	4.70	0.84	0.38	45.4
46	6.0	95.7	5.74	0.84	0.77	91.6
47	6.0	100.0	6.00	0.84	0.84	100.0
48	6.0	88.6	5.32	0.84	0.62	74.2
49	6.0	27.2	1.63	0.84	0.00	0.0
50	6.0	89.9	5.40	0.84	0.65	77.7
51	6.0	93.3	5.60	0.84	0.72	86.2
52	6.0	99.7	5.98	0.84	0.84	99.5
53	6.0	43.9	2.63	0.84	0.01	1.1
54	6.0	97.2	5.83	0.84	0.80	94.9
55	6.0	82.1	4.92	0.84	0.47	55.9
56	6.0	94.2	5.65	0.84	0.74	88.3
57	6.0	99.9	5.99	0.84	0.84	99.8
58	6.0	98.8	5.93	0.84	0.82	97.9
59	6.0	38.4	2.31	0.84	0.00	0.4
60	6.0	71.6	4.30	0.84	0.24	28.7
61	6.0	57.6	3.45	0.84	0.06	7.3
62	6.0	90.4	5.42	0.84	0.66	78.9
63	6.0	75.2	4.51	0.84	0.31	37.2
64	6.0	83.6	5.02	0.84	0.51	60.2
65	6.0	99.7	5.98	0.84	0.84	99.4
66	6.0	79.6	4.78	0.84	0.41	49.0

67	6.0	99.1	5.95	0.84	0.83	98.5
68	6.0	99.5	5.97	0.84	0.83	99.1
69	6.0	42.4	2.54	0.84	0.01	0.8
70	6.0	98.7	5.92	0.84	0.82	97.6
71	6.0	85.1	5.10	0.84	0.54	64.4
72	6.0	94.4	5.66	0.84	0.75	88.7
73	6.0	65.4	3.92	0.84	0.14	16.8
74	6.0	97.3	5.84	0.84	0.80	95.1
75	6.0	95.4	5.72	0.84	0.77	90.9
76	6.0	87.7	5.26	0.84	0.60	71.8
77	6.0	59.3	3.56	0.84	0.07	8.9
78	6.0	72.7	4.36	0.84	0.26	31.0
79	6.0	98.0	5.88	0.84	0.81	96.4
80	6.0	20.3	1.22	0.84	0.00	0.0
81	6.0	89.5	5.37	0.84	0.64	76.5
82	6.0	82.7	4.96	0.84	0.49	57.6
83	6.0	100.0	6.00	0.84	0.84	100.0
84	6.0	97.4	5.85	0.84	0.80	95.2
85	6.0	71.8	4.31	0.84	0.24	29.0
86	6.0	65.0	3.90	0.84	0.14	16.2
87	6.0	46.0	2.76	0.84	0.01	1.5
88	6.0	66.5	3.99	0.84	0.16	18.5
89	6.0	81.8	4.91	0.84	0.46	55.2
90	6.0	100.0	6.00	0.84	0.84	100.0
91	6.0	60.8	3.65	0.84	0.09	10.4
92	6.0	87.7	5.26	0.84	0.60	71.8

93	6.0	17.2	1.03	0.84	0.00	0.0
94	6.0	70.5	4.23	0.84	0.22	26.3
95	6.0	88.0	5.28	0.84	0.61	72.5
96	6.0	95.0	5.70	0.84	0.76	90.2
97	6.0	96.7	5.80	0.84	0.79	93.7
98	6.0	80.9	4.85	0.84	0.44	52.4
99	6.0	90.8	5.45	0.84	0.67	80.0
100	6.0	45.9	2.75	0.84	0.01	1.5

Stem-Leaf plot 1

d	stem	leaves
3	0	0, 5, 9
3	1	
3	2	
3	3	
3	4	
4	5	4
5	6	4
(0)	7	
5	8	5, 6, 9
2	9	6
1	10	0

Stem-Leaf Plot 2

d	stem	leaves
1	0	4
1	1	
2	2	6
3	3	8
3	4	
4	5	7
5	6	0
5	7	7
4	8	4
3	9	0, 7, 9

Stem-Leaf Plot 3

d	stem	leaves
2	2	0, 9
2	3	
5	4	1, 4, 5
5	5	2, 8
3	6	9
2	7	8
1	8	
1	9	5

Stem-Leaf Plot 4

d	stem	leaves
1	2	2
2	3	9
3	4	7
4	5	8
4	6	
5	7	9
4	8	5
4	9	2, 7, 9
1	10	0

Stem-Leaf Plot 5

d	stem	leaves
10	0	0, 0, 0, 2, 2, 5, 7, 7, 9, 9
16	1	0, 0, 2, 6, 8, 8
18	2	4, 8
23	3	0, 1, 3, 9, 9
(5)	4	0, 1, 5, 7, 8
22	5	4, 7
20	6	1, 4
18	7	2, 7, 8
15	8	5, 6, 6, 7, 9
10	9	3, 4, 5, 6, 7, 7, 9
3	10	0, 0, 0

Stem-Leaf Plot 6

d	stem	leaves
7	0	2, 3, 4, 4, 5, 5, 9
10	1	4, 7, 7
16	2	0, 1, 3, 6, 9, 9
19	3	5, 8, 9
23	4	6, 8, 9, 9
(6)	5	0, 3, 7, 7, 8, 9
21	6	0, 2, 6, 6, 8, 8
15	7	1, 1, 3, 7
11	8	1, 3, 4, 7, 9
6	9	0, 0, 0, 5, 7, 9

Stem-Leaf Plot 7

d	stem	leaves
2	0	4, 9
8	1	0, 7, 7, 7, 9, 9
13	2	0, 0, 3, 7, 9
17	3	1, 3, 4, 9
24	4	0, 1, 1, 2, 4, 5, 5
(8)	5	2, 2, 2, 5, 8, 8, 8, 9
18	6	1, 2, 4, 9
14	7	0, 4, 4, 7, 8, 9, 9
7	8	1, 4, 5, 6, 6
2	9	3, 5

Stem-Leaf Plot 8

d	stem	leaves
	LO	22,
3	2	6, 7
4	3*	4
5	3.	9
5	4*	
7	4.	7, 8
8	5*	4
10	5.	7, 8
11	6*	3
13	6.	7, 8

14	7*	0
18	7.	6, 8, 9, 9
21	8*	1, 2, 4
(5)	8.	5, 5, 5, 6, 9
24	9*	0, 0, 1, 2
20	9.	5, 5, 5, 6, 6, 7, 7, 8, 9, 9, 9, 9, 9, 9
6	10*	0, 0, 0, 0, 0, 0

Stem-Leaf Plot 9

d	stem	leaves
20	0	0, 0, 0, 0, 1, 1, 1, 2, 2, 2, 3, 4, 5, 6, 7, 7, 8, 8, 9, 9
32	1	0, 0, 0, 1, 2, 3, 3, 6, 7, 8, 8, 8
39	2	0, 4, 4, 7, 7, 8, 9
46	3	0, 1, 2, 3, 3, 6, 9
(14)	4	0, 1, 1, 4, 4, 4, 4, 5, 5, 5, 6, 7, 8, 9
40	5	4, 7, 9, 9
36	6	1, 2, 3, 4, 7
31	7	1, 2, 7, 7, 8, 8
25	8	0, 5, 6, 6, 7, 9
19	9	3, 3, 4, 4, 5, 5, 5, 6, 7, 7, 8, 9, 9, 9
5	10	0, 0, 0, 0, 0

Stem-Leaf Plot 10

d	stem	leaves
6	+0*	2, 2, 3, 4, 4, 4
13	+0.	5, 5, 7, 7, 9, 9, 9

19	1*	0, 0, 1, 3, 4, 4
26	1.	5, 6, 7, 7, 7, 9, 9
32	2*	0, 1, 2, 3, 3, 3
38	2.	6, 6, 7, 9, 9, 9
39	3*	3
45	3.	5, 5, 7, 8, 8, 9
46	4*	0
(6)	4.	6, 6, 8, 8, 9, 9
48	5*	0, 3, 4, 4
44	5.	6, 7, 7, 7, 8, 9
38	6*	0, 1, 2, 3
34	6.	6, 6, 8, 8, 9
29	7*	1, 1, 3
26	7.	6, 7, 8
23	8*	0, 1, 3, 4, 4, 4
17	8.	5, 6, 7, 8, 8, 8, 9
10	9*	0, 0, 0, 2
6	9.	5, 5, 7, 8, 8, 9

Stem-Leaf Plot 11

d	stem	leaves
1	+0*	4
4	+0.	5, 6, 9
6	1*	0, 0
12	1.	7, 7, 7, 9, 9, 9
16	2*	0, 0, 2, 3

22	2.	5, 5, 5, 7, 9, 9
30	3*	0, 1, 1, 2, 3, 3, 3, 4
33	3.	8, 8, 9
41	4*	0, 0, 1, 1, 2, 4, 4, 4
47	4.	5, 5, 5, 6, 6, 9
(10)	5*	1, 1, 2, 2, 2, 3, 3, 3, 4, 4
43	5.	5, 6, 7, 8, 8, 8, 9, 9, 9
34	6*	0, 0, 1, 2, 4
29	6.	6, 9, 9
26	7*	0, 3, 4, 4
22	7.	7, 8, 9, 9
18	8*	0, 1, 2, 4, 4
13	8.	5, 6, 6, 6, 6, 7, 8
6	9*	0, 2, 2, 3
2	9.	5, 8

Stem-Leaf Plot 12

d	stem	leaves
	Lo	17,20
5	2.	6,7
6	3*	4
8	3.	8,9
10	4*	2,4
14	4.	6,6,7,8
15	5*	4
19	5.	7,8,8,9

21	6*	1,3
26	6.	5,5,6,7,8
31	7*	0,1,2,2,3
36	7.	5,6,8,9,9
45	8*	0,1,1,2,2,2,3,4,4
(10)	8.	5,5,5,5,6,8,8,8,9,9
45	9*	0,0,0,1,1,2,3,4,4
36	9.	5,5,5,5,5,6,6,7,7,7,7,7,7,8,8,9,9,9,9,9,9,9,9,9,9
11	10*	0,0,0,0,0,0,0,0,0,0,0

APPENDIX B

FIGURES

FOR

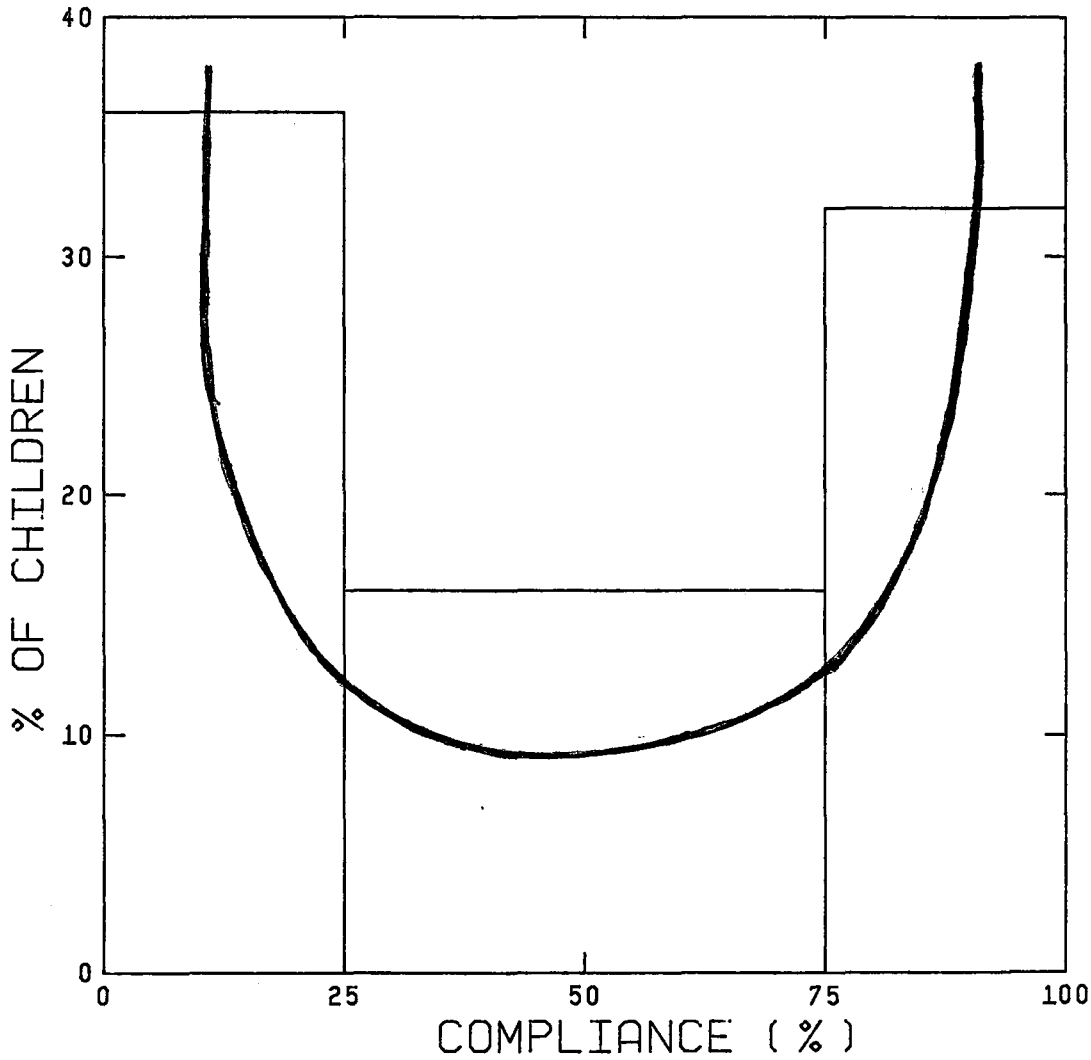
DOSE - RESPONSE CURVES(3.1 - 3.6)

AND

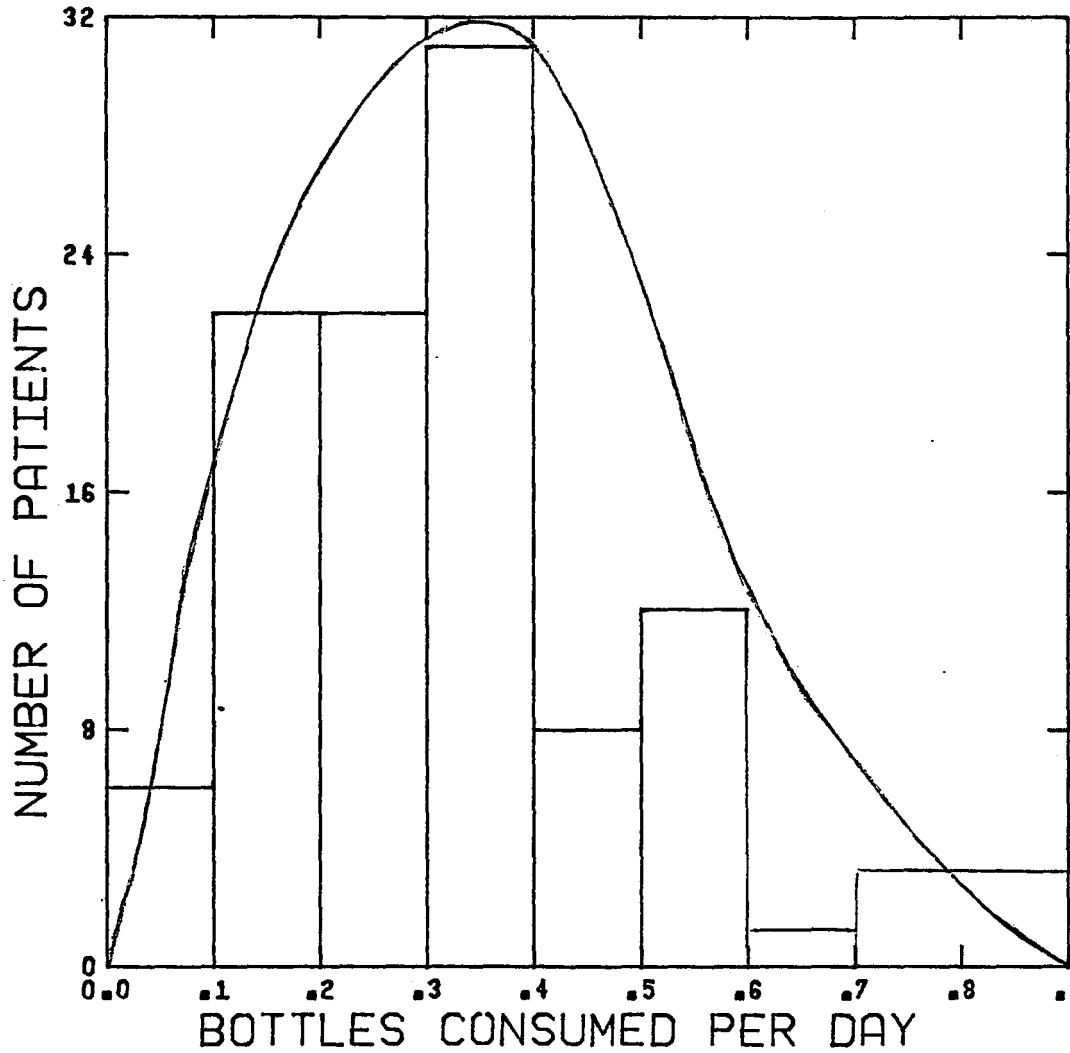
COMPLIANCE-DOSE-RESPONSE CURVES(3.7 - 3.30)

AND

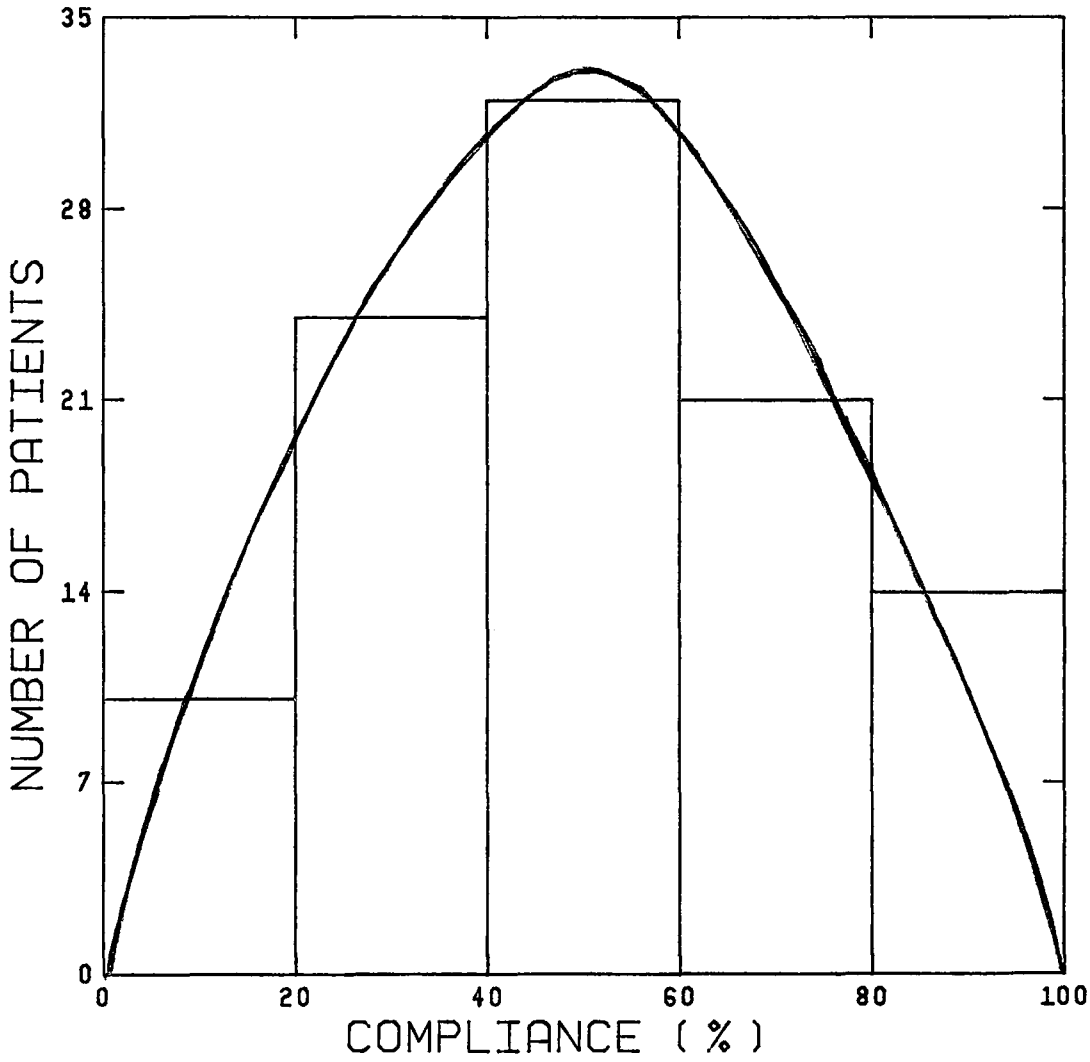
COMPLIANCE - RESPONSE CURVES(3.31 - 3.34)



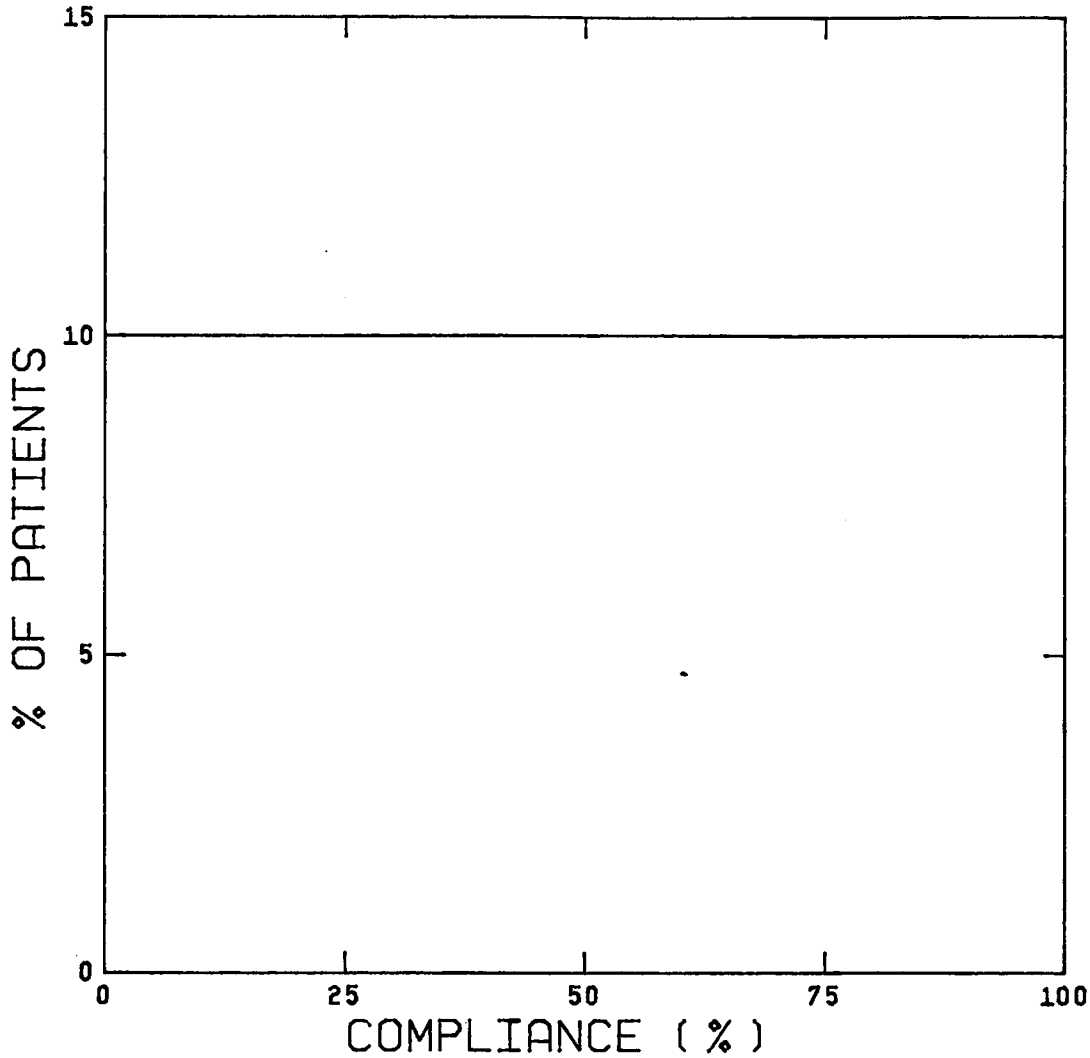
U - SHAPED DISTRIBUTION
FIGURE 2.1



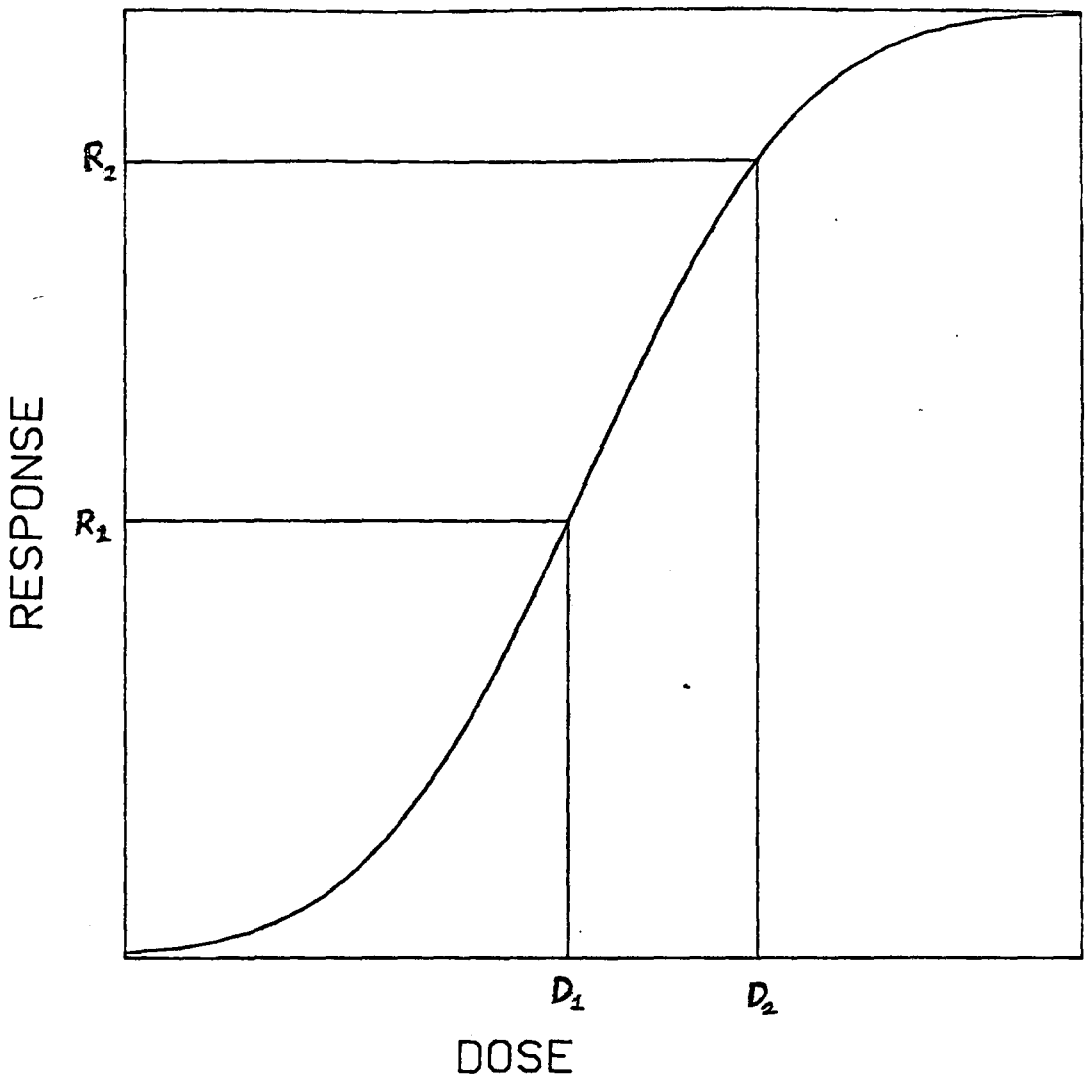
BELL - SHAPED DISTRIBUTION
FIGURE 2.2



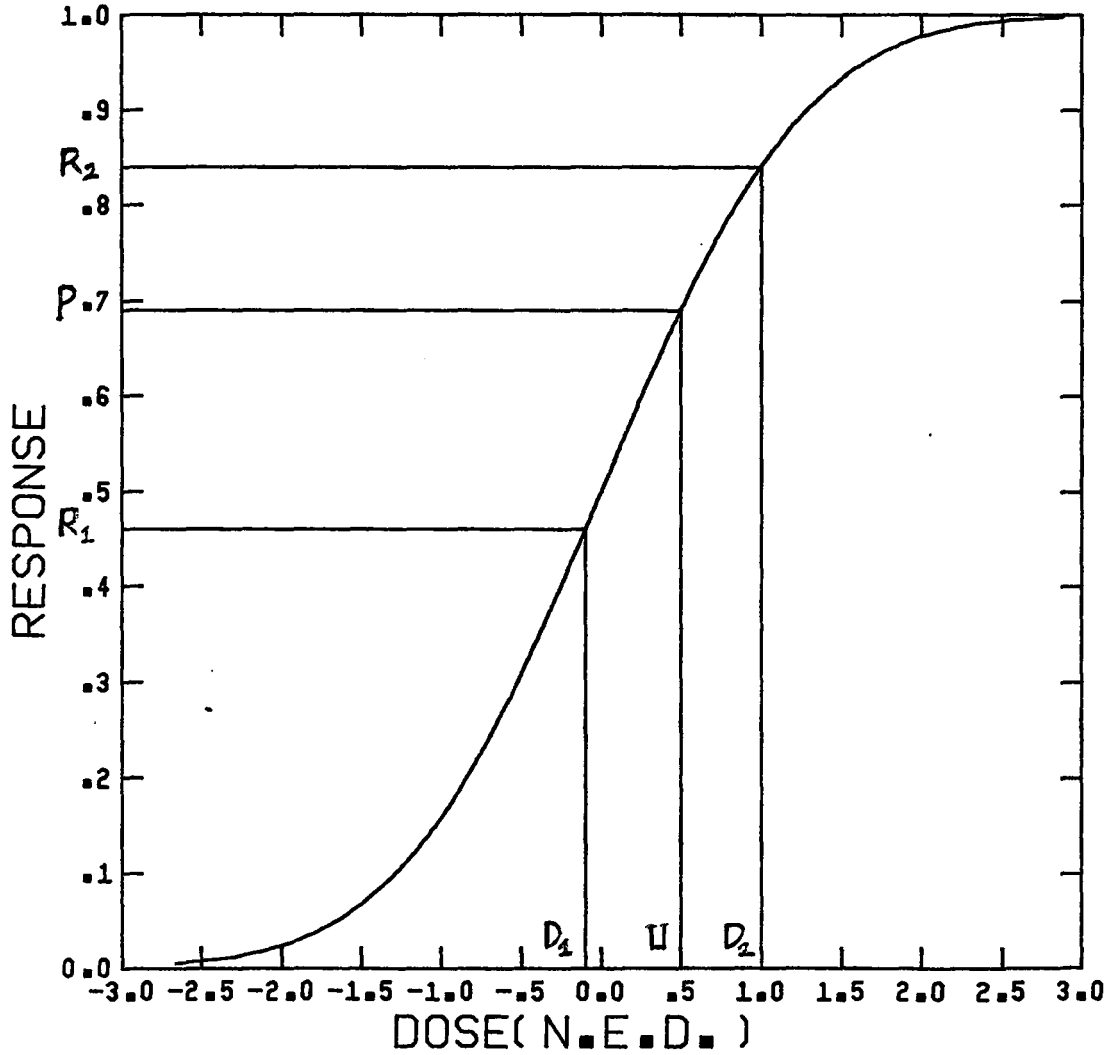
BELL - SHAPED DISTRIBUTION
FIGURE 2.3



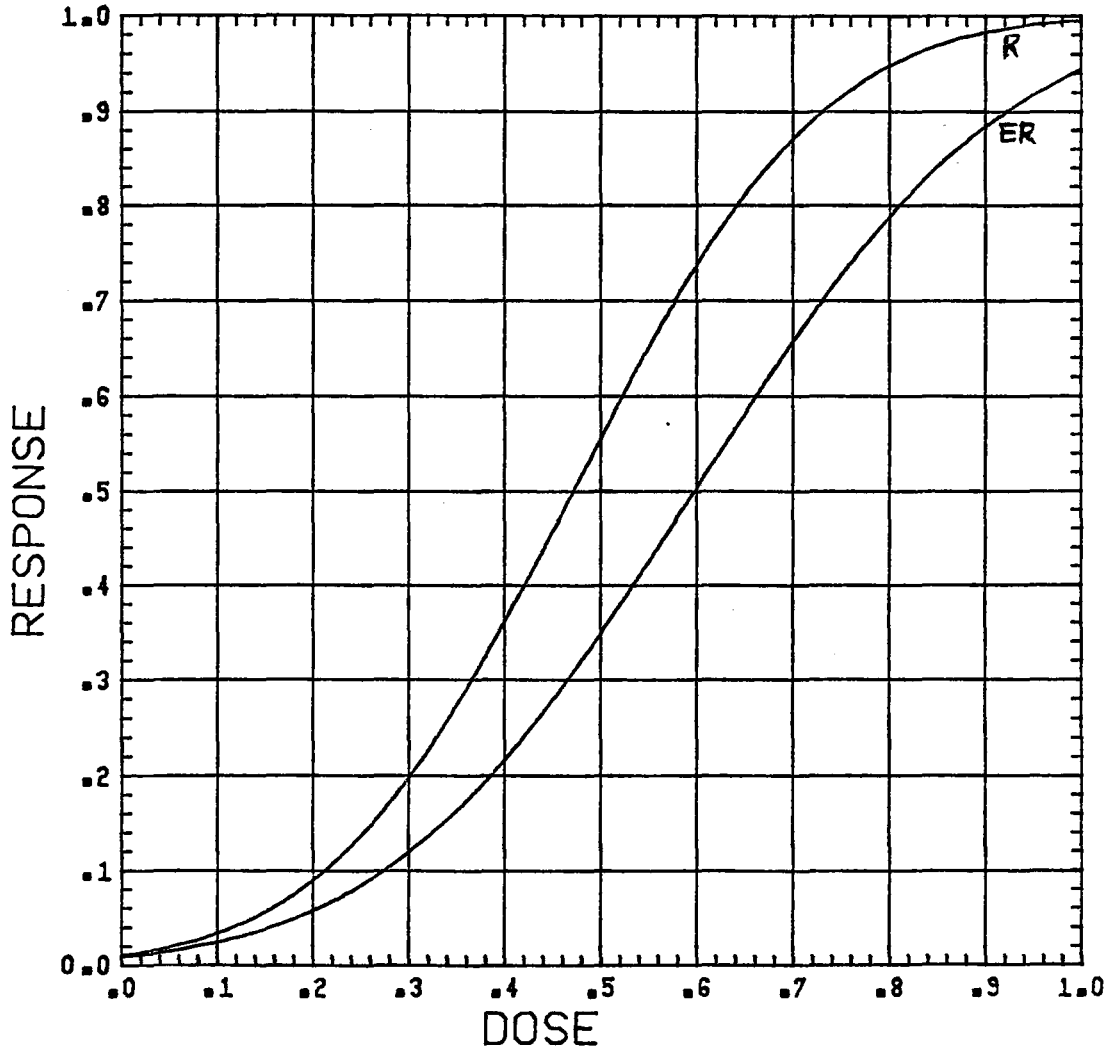
UNIFORM DISTRIBUTION
FIGURE 2.4



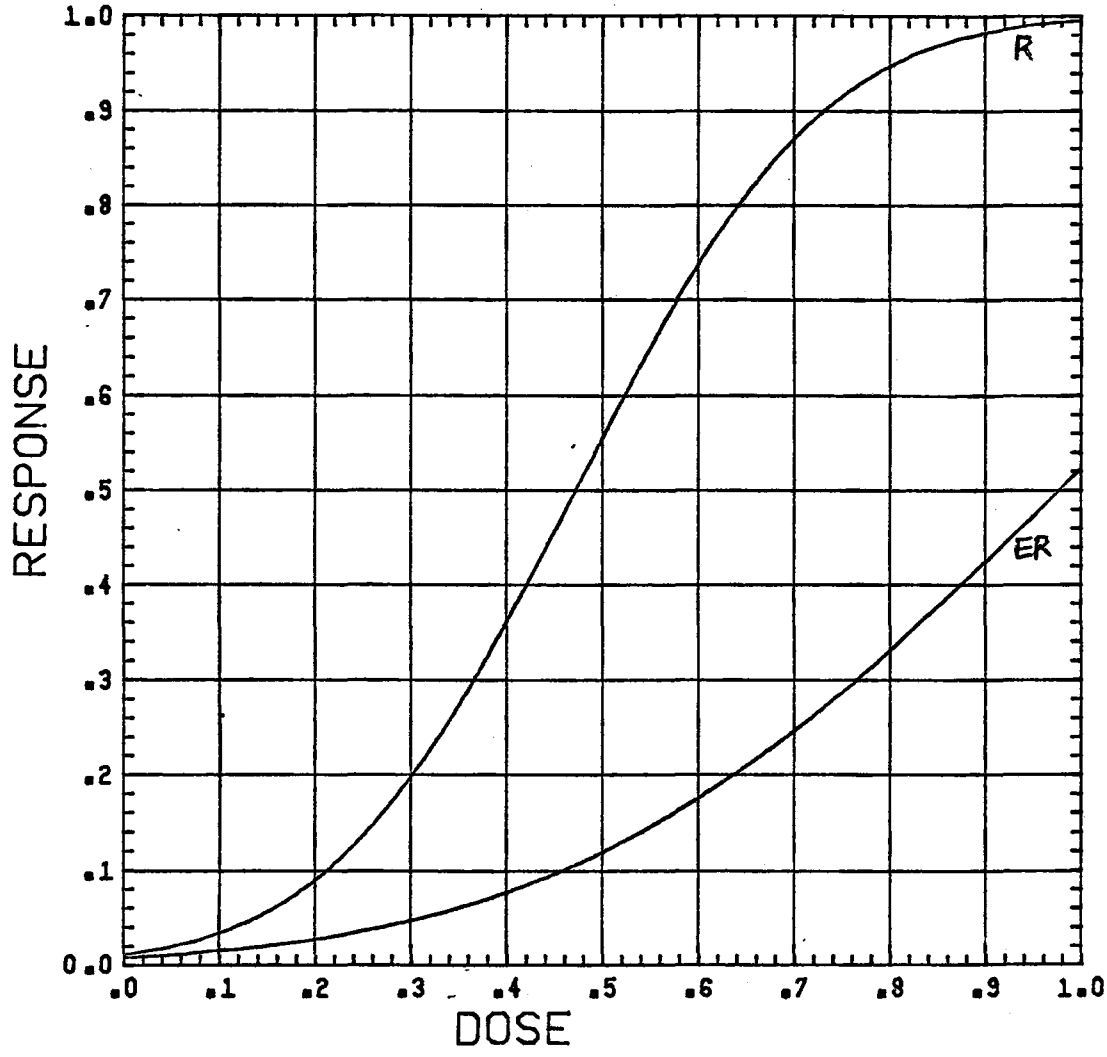
DOSE - RESPONSE CURVE
IN THERAPEUTIC TRIALS
FIGURE 3.1



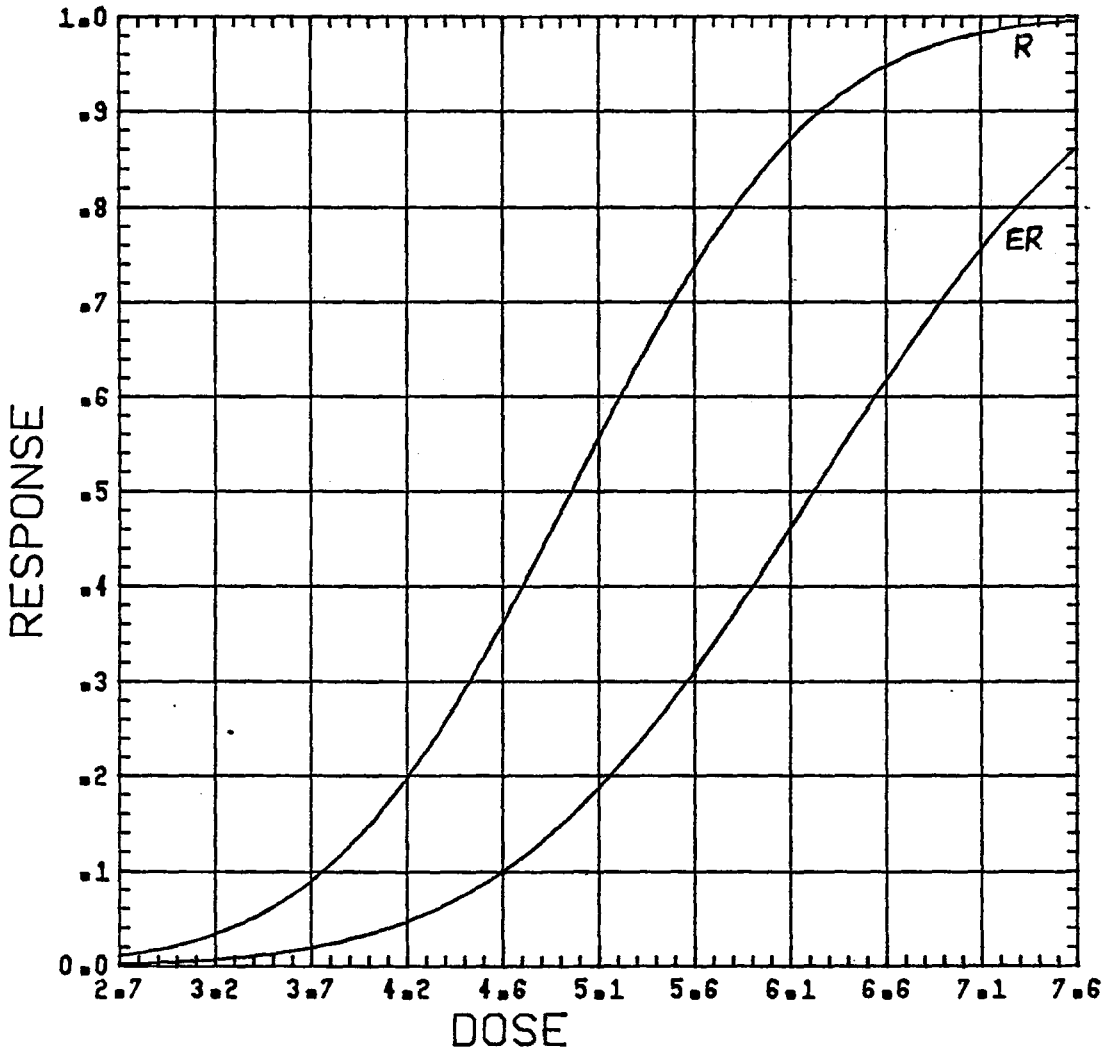
DOSE - RESPONSE CURVE
IN THERAPEUTIC TRIALS
FIGURE 3.2



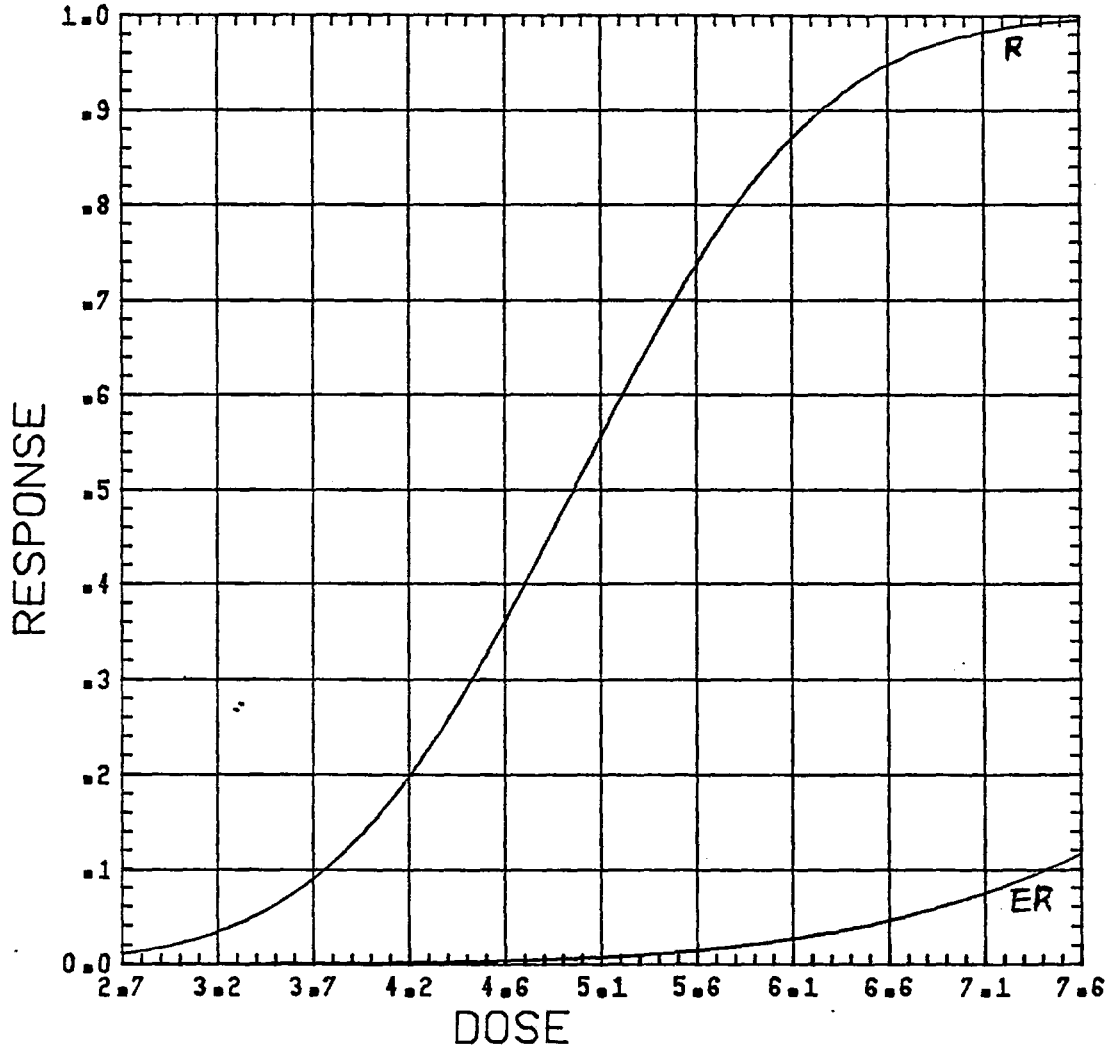
DOSE - RESPONSE CURVE
CASE 1.1
80% COMPLIANCE: (ER)
FIGURE 3.3



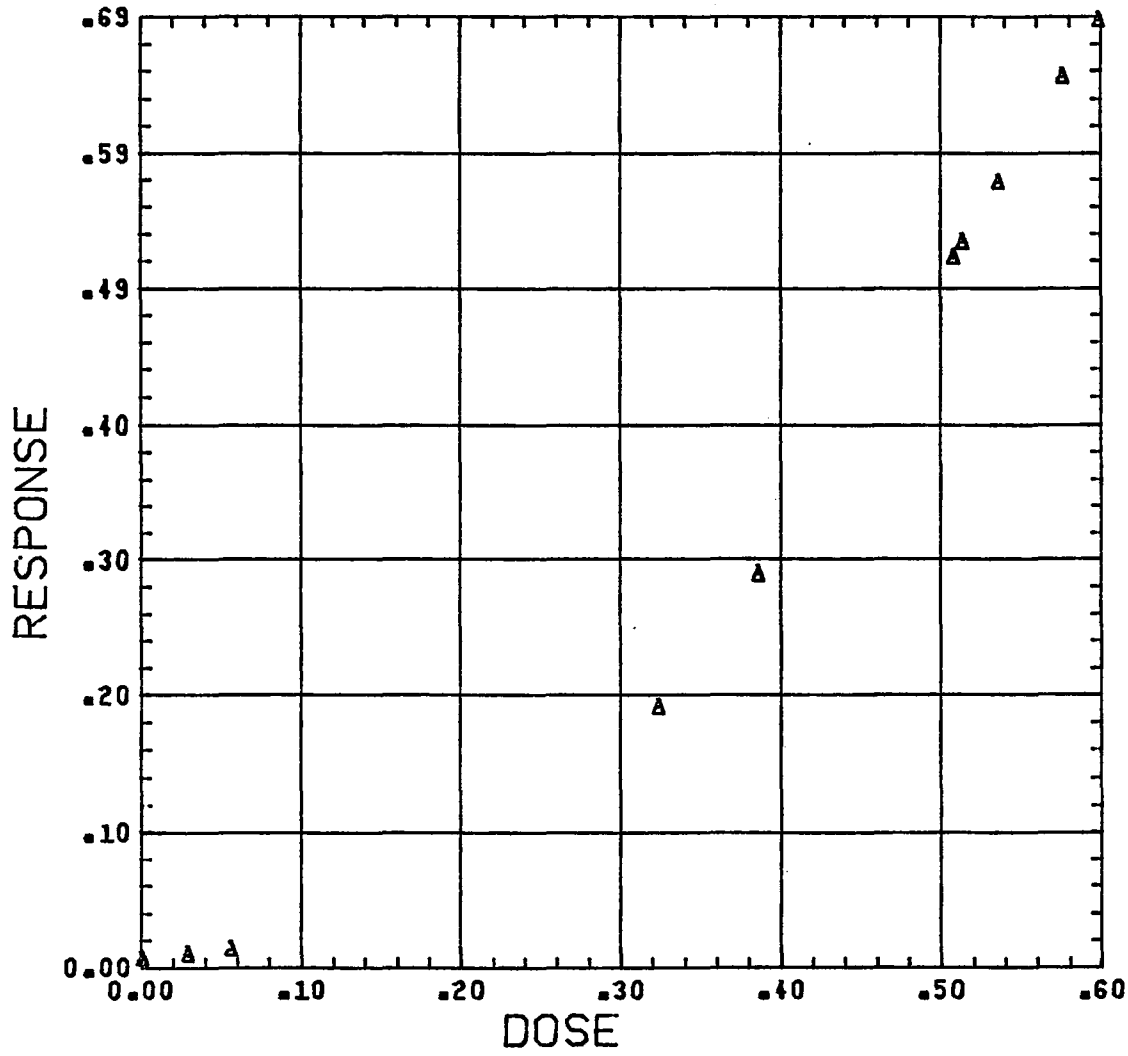
DOSE - RESPONSE CURVE
CASE 1.2
50% COMPLIANCE: (ER)
FIGURE 3.4



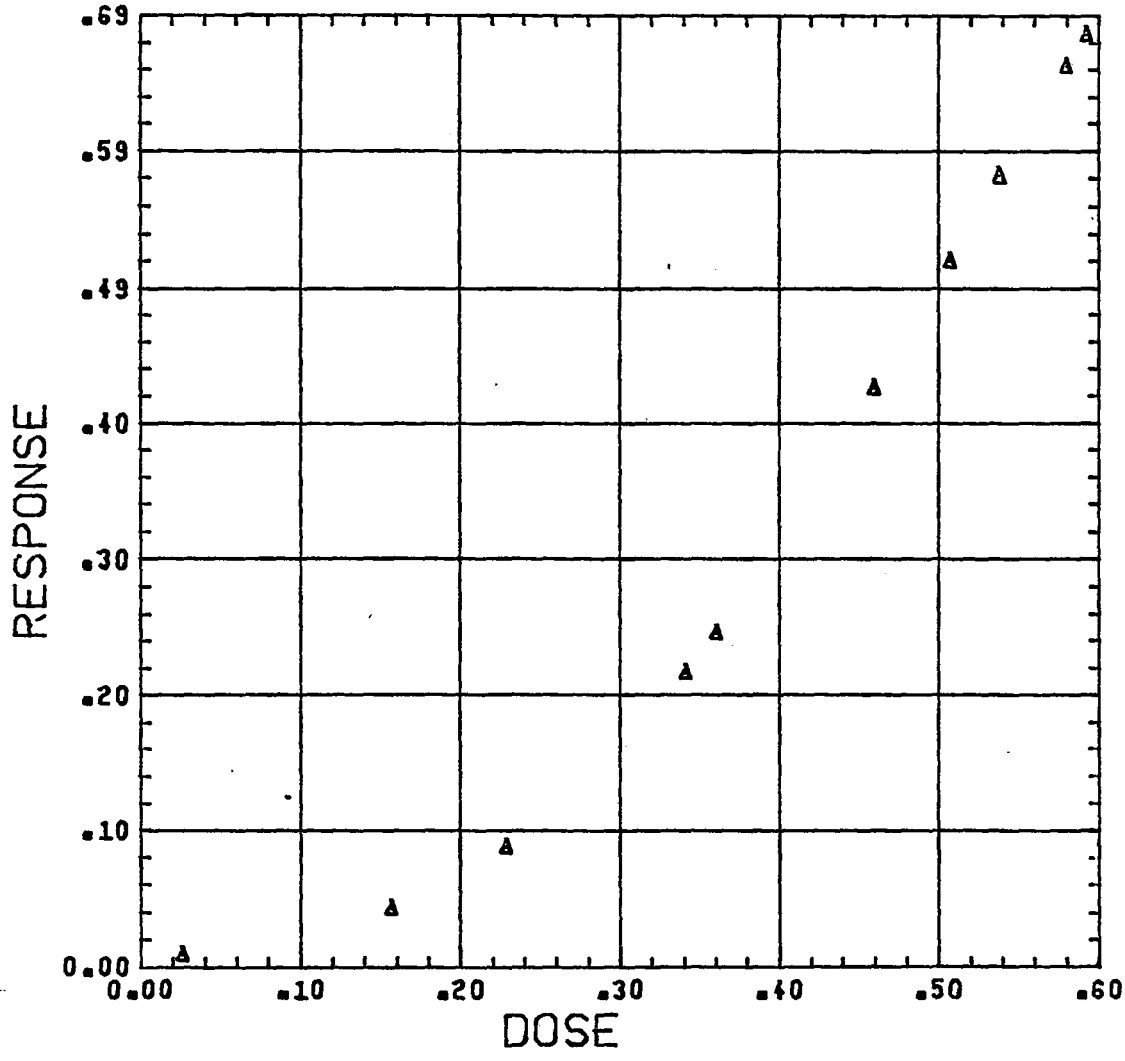
DOSE - RESPONSE CURVE
CASE 2.1
80% COMPLIANCE: (ER)
FIGURE 3.5



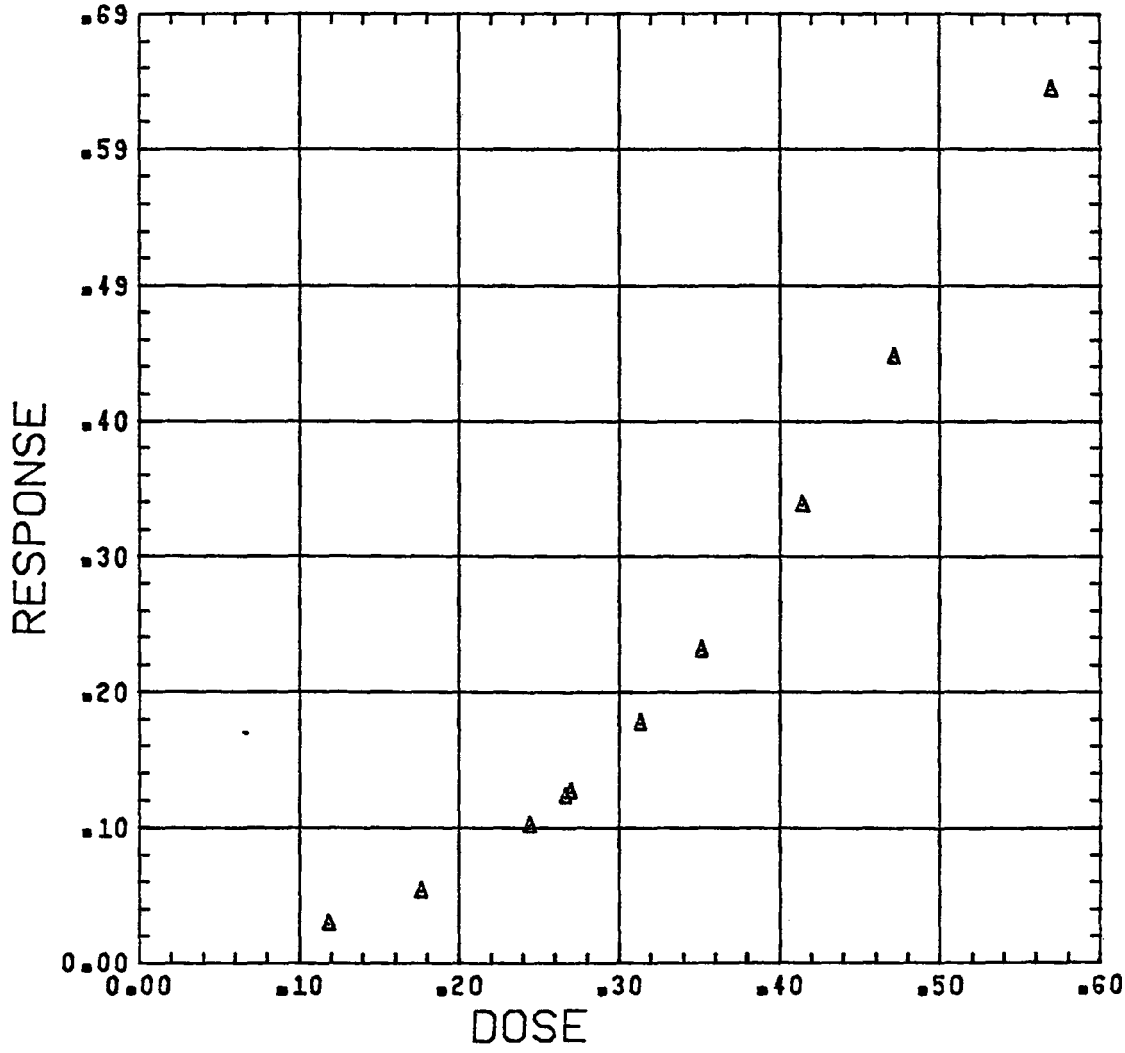
DOSE - RESPONSE CURVE
CASE 2.2
50% COMPLIANCE: (ER)
FIGURE 3.6



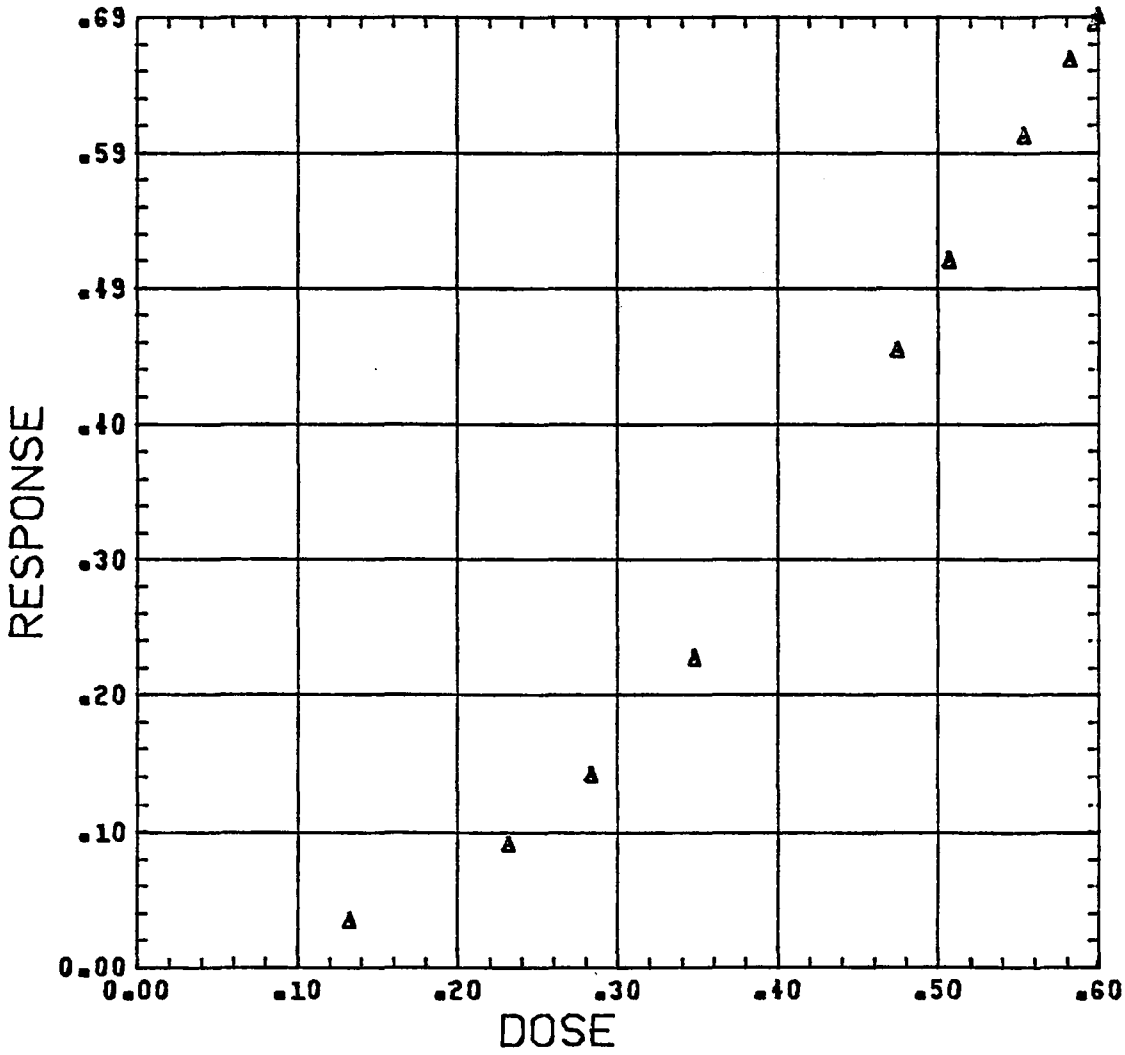
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 10
COMPLIANCE VARIABLES: B(0.5,0.5)
FIGURE 3.7



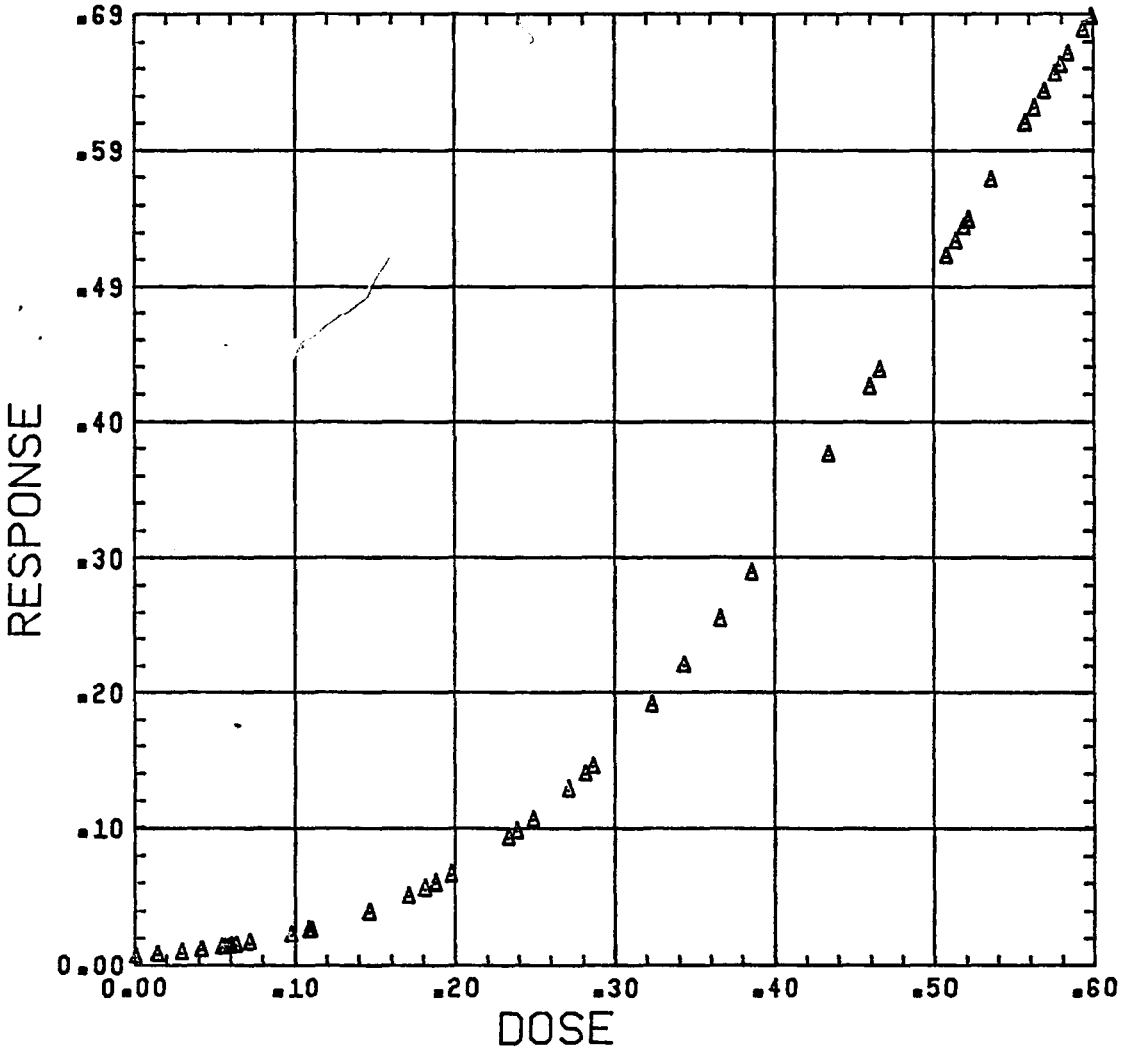
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 10
COMPLIANCE VARIABLES: B(1, 1)
FIGURE 3.8



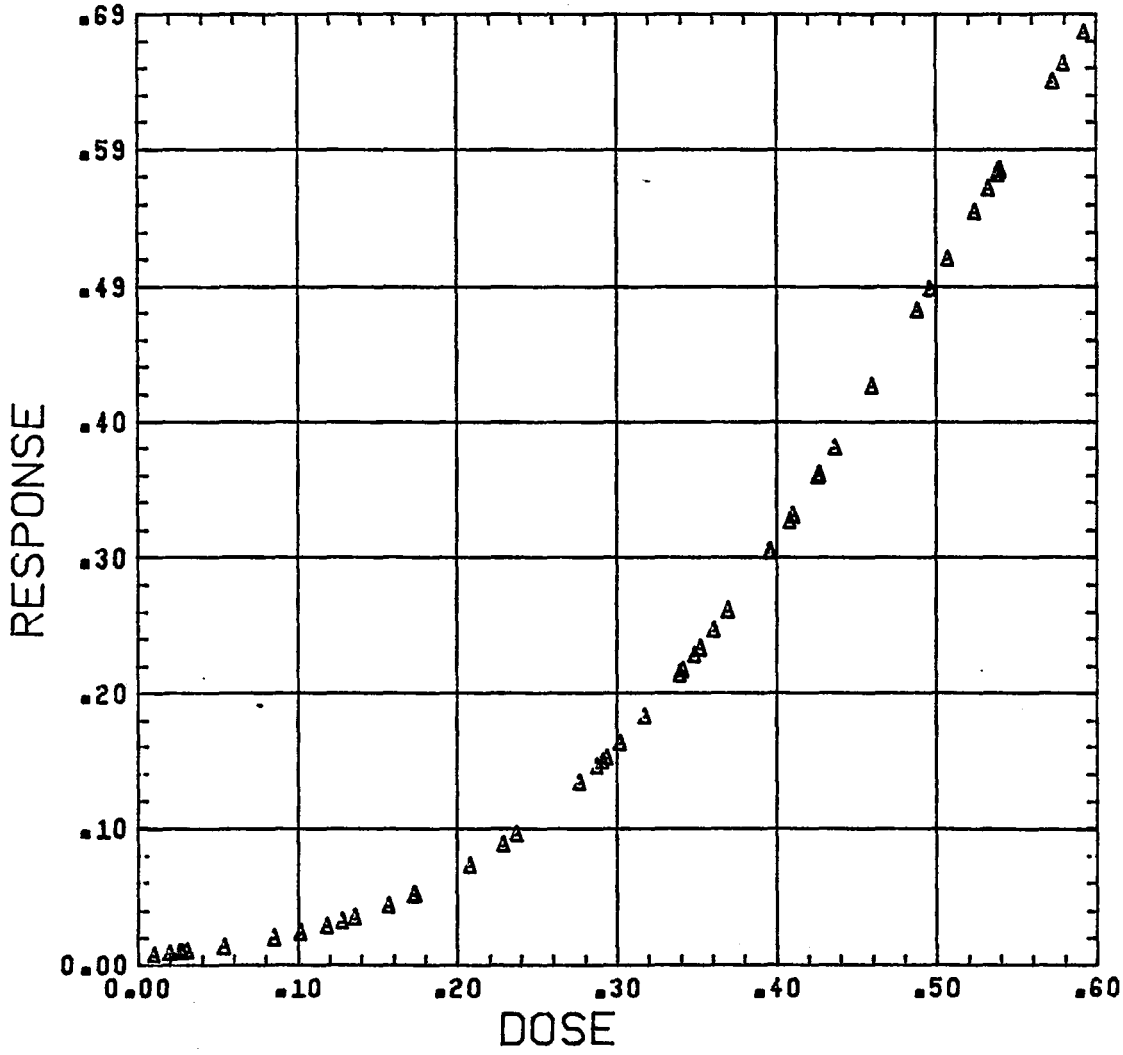
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 10
COMPLIANCE VARIABLES: B(2, 2)
FIGURE 3.9



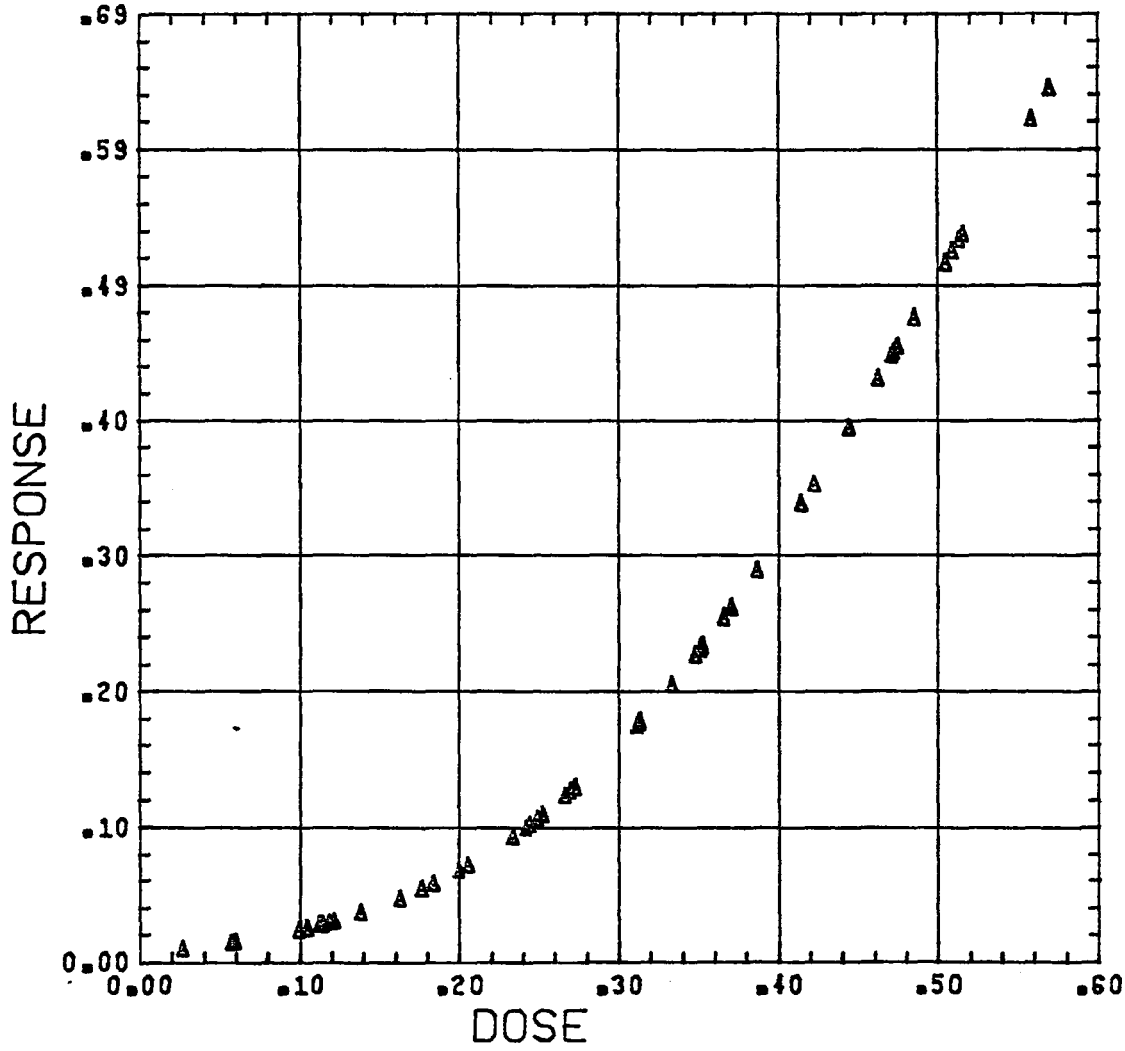
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 10
COMPLIANCE VARIABLES: B(2, 0.5)
FIGURE 3.10



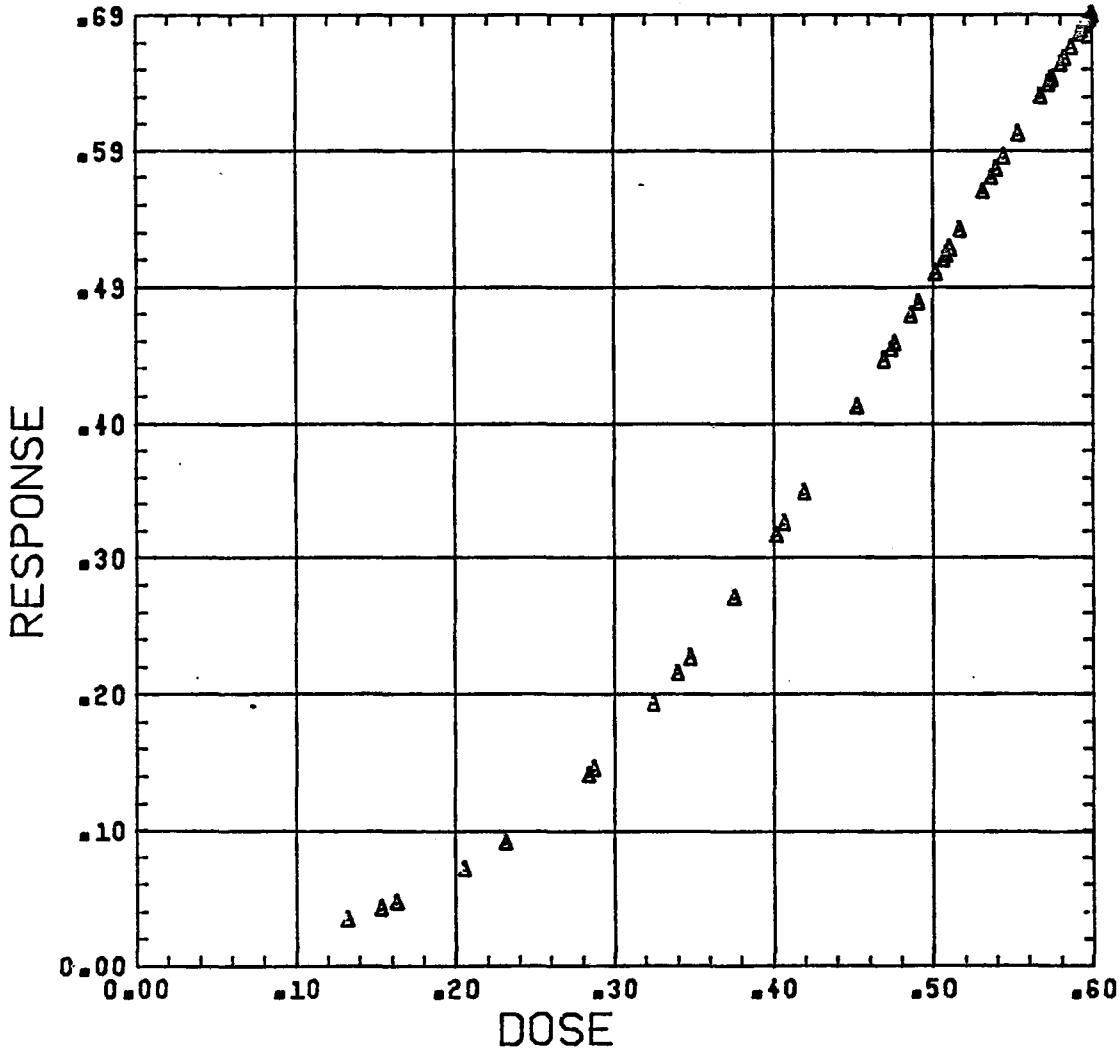
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 50
COMPLIANCE VARIABLES: B(0.5, 0.5)
FIGURE 3.11



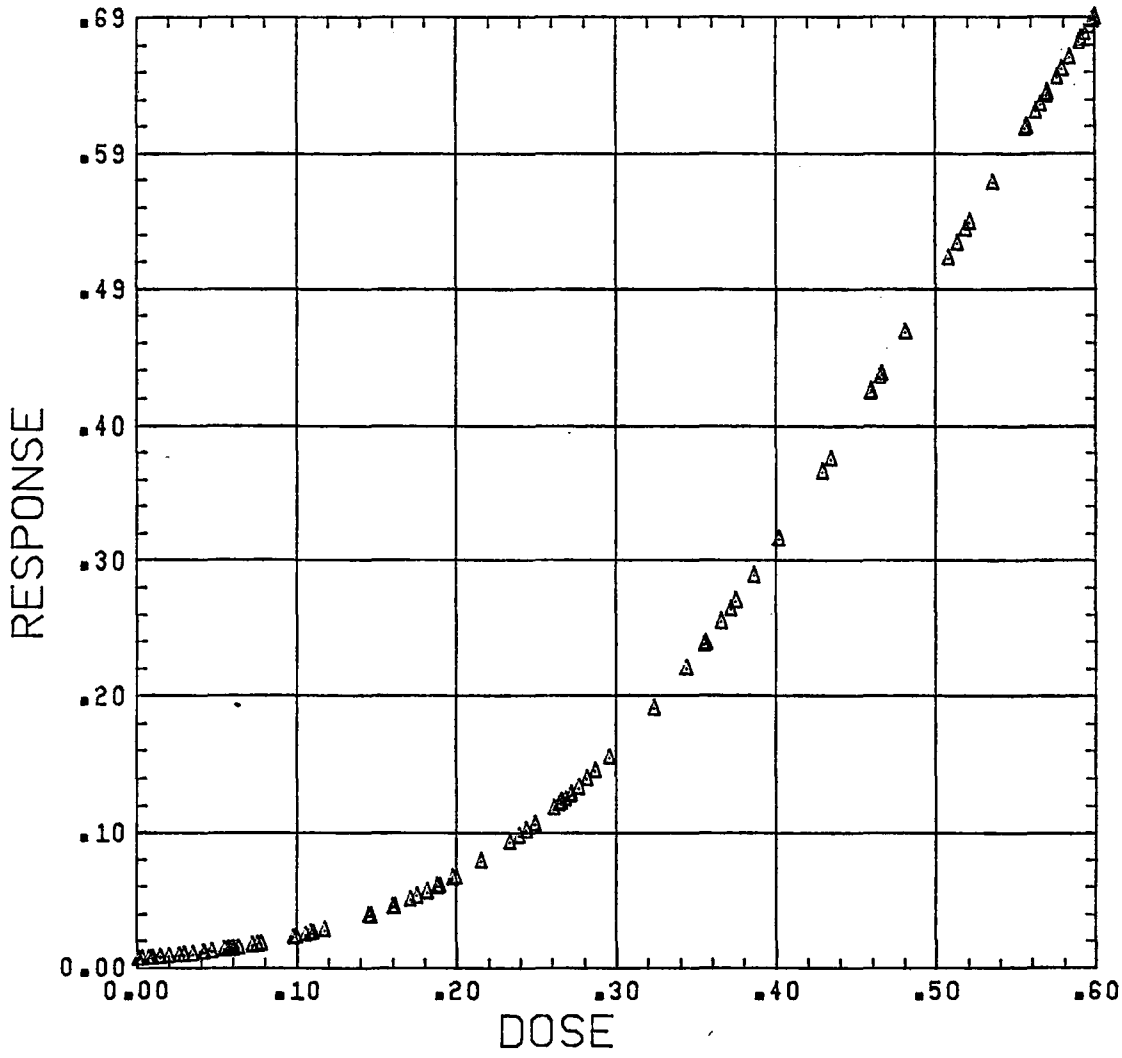
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 50
COMPLIANCE VARIABLES: B(1, 1)
FIGURE 3.12



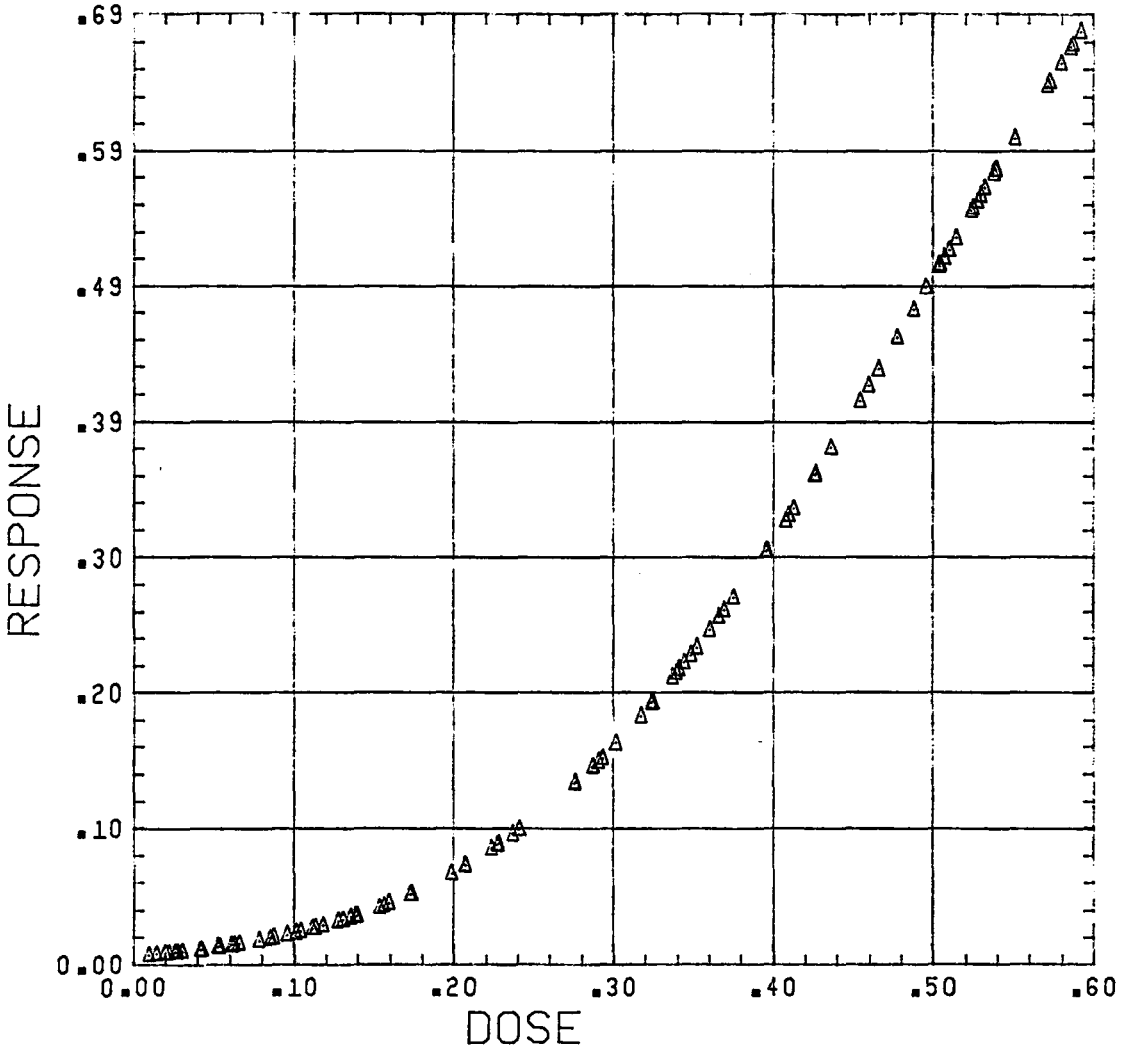
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 50
COMPLIANCE VARIABLES: B(2, 2)
FIGURE 3.13



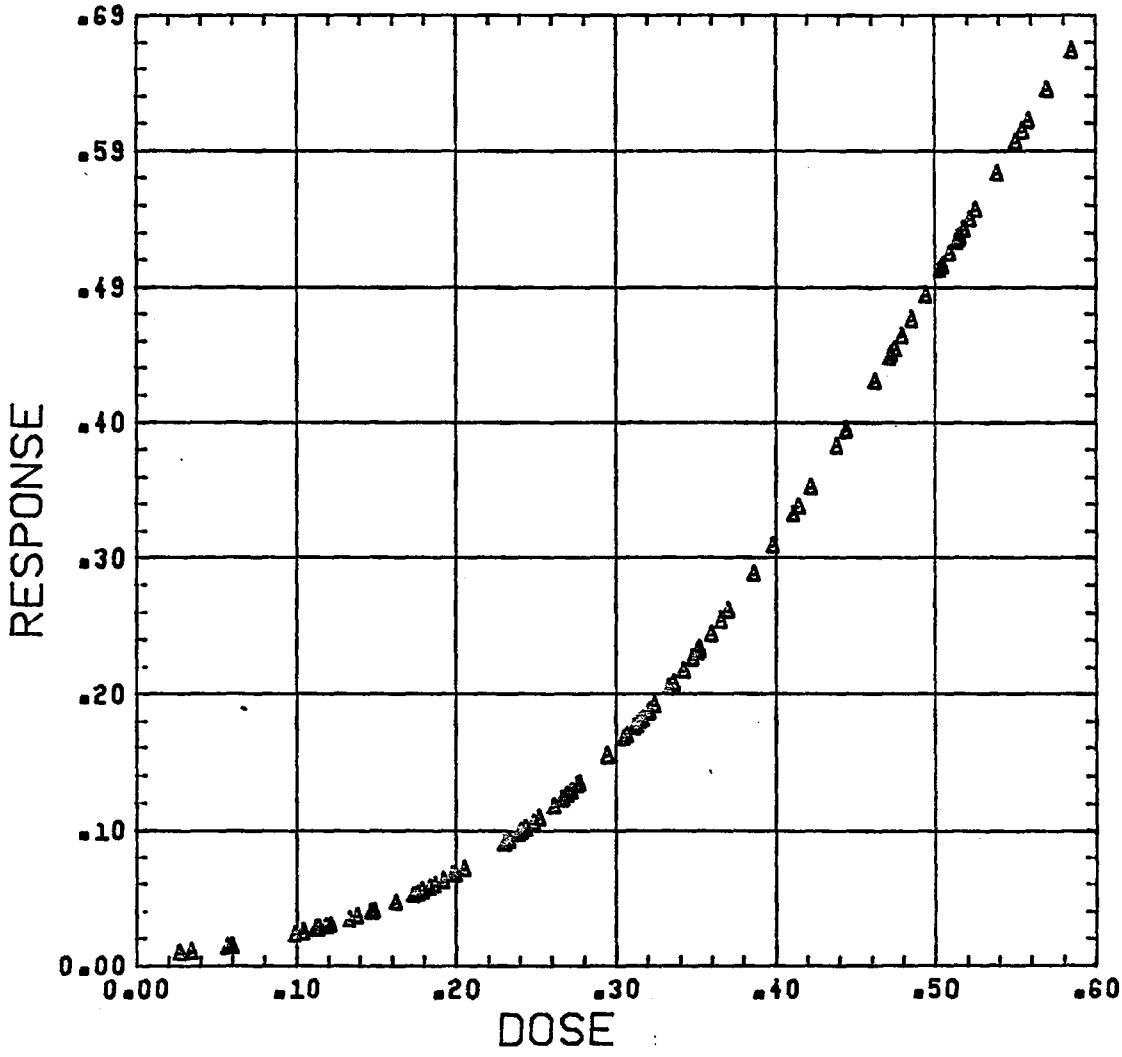
COMPLIANCE/DOSE--RESPONSE CURVE
SAMPLE SIZE: N = 50
COMPLIANCE VARIABLES: B(2, 0.5)
FIGURE 3.14



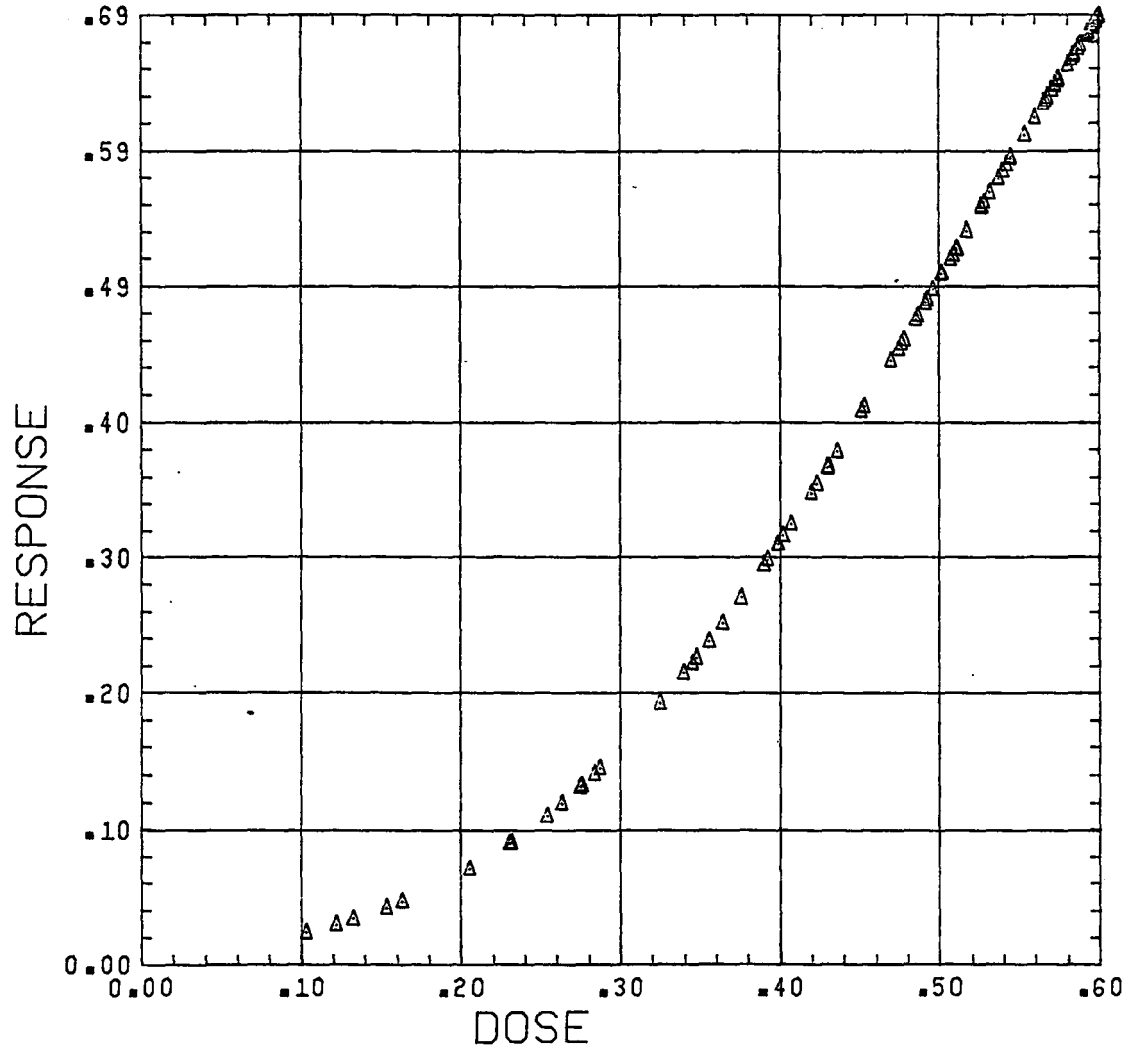
COMPLIANCE/DOSE RESPONSE CURVE
SAMPLE SIZE: N = 100
COMPLIANCE VARIABLES: B(0.5, 0.5)
FIGURE 3.15



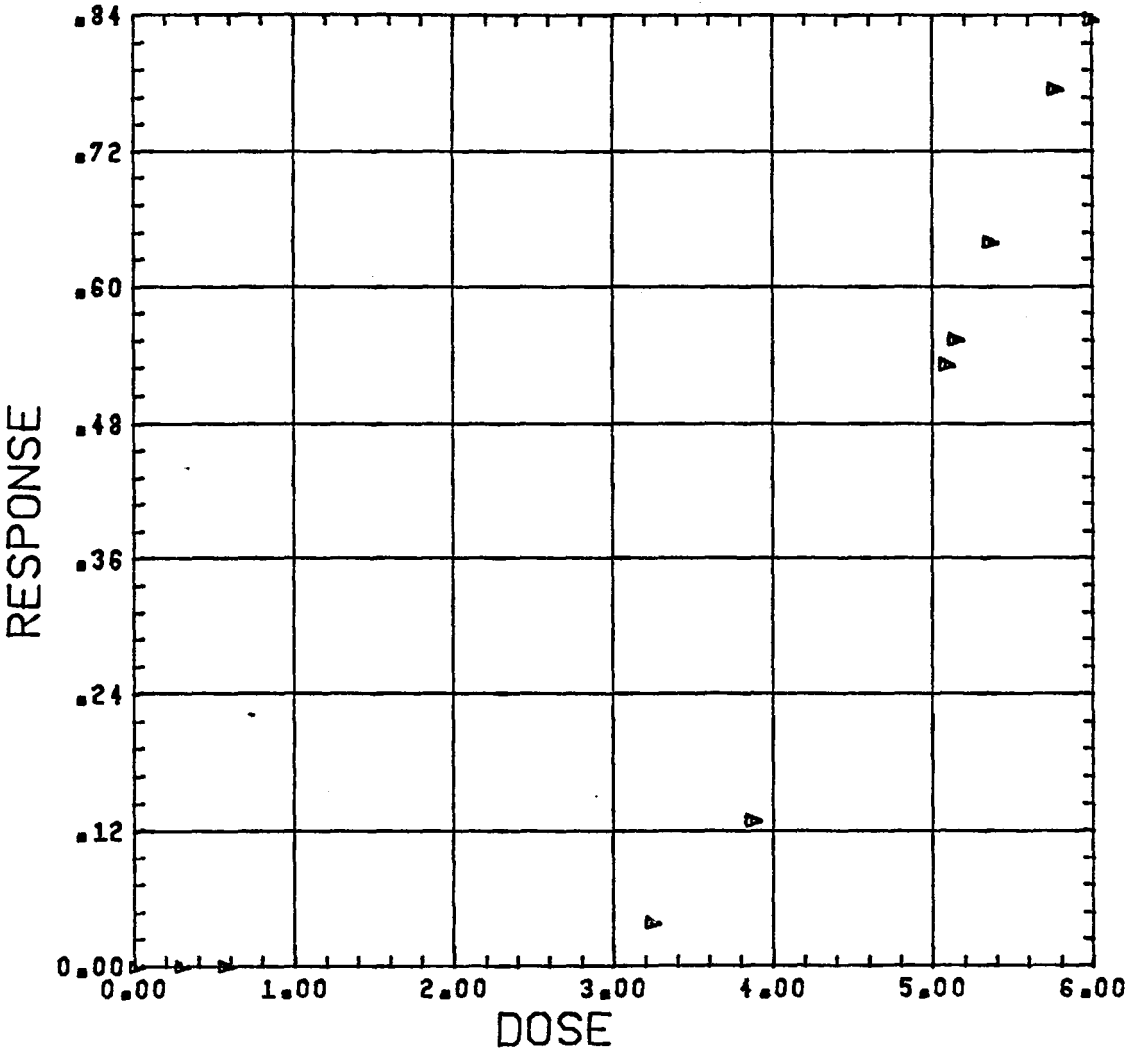
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 100
COMPLIANCE VARIABLES: B(1, 1)
FIGURE 3.16



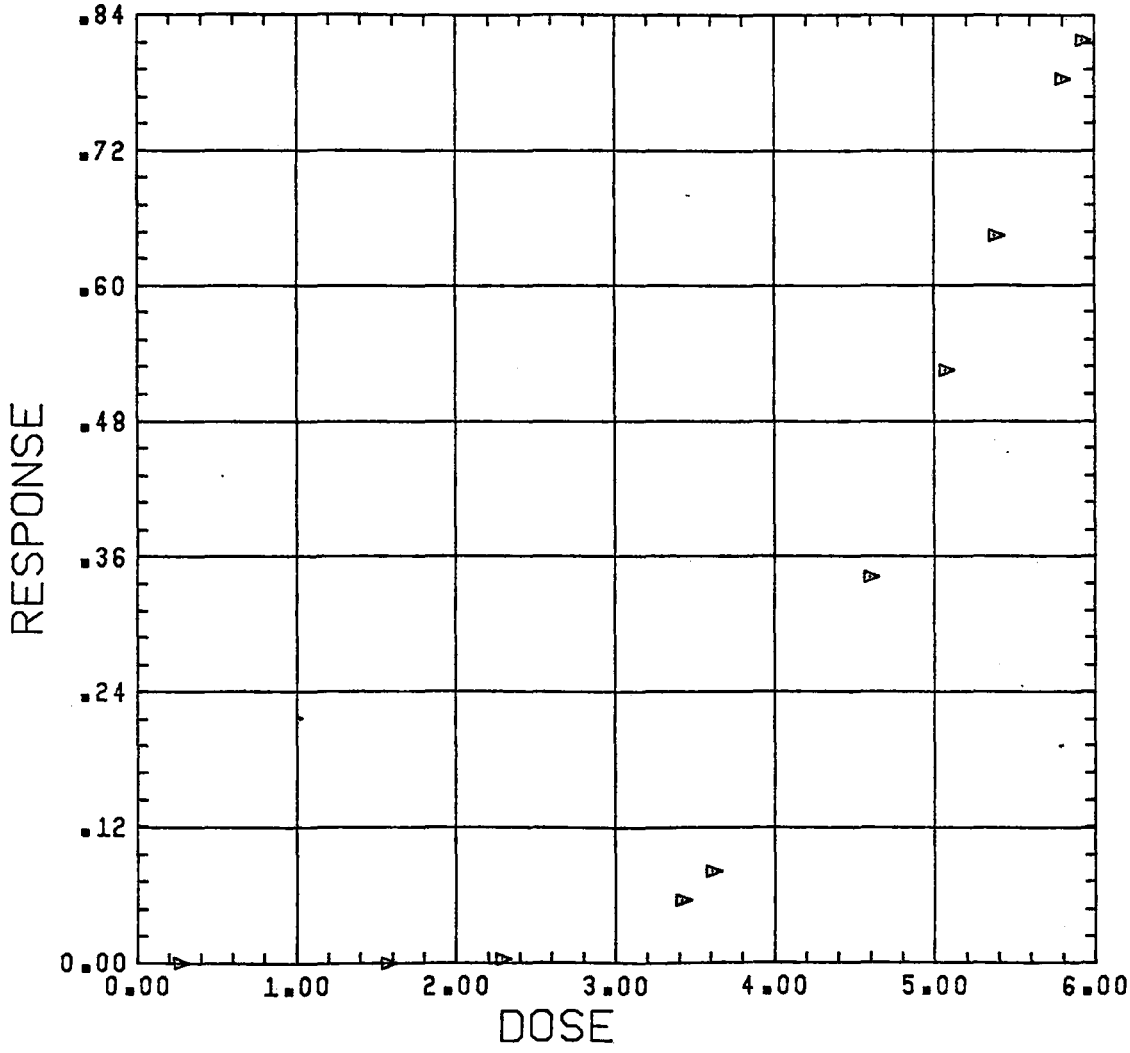
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 100
COMPLIANCE VARIABLES: B(2, 2)
FIGURE 3.17



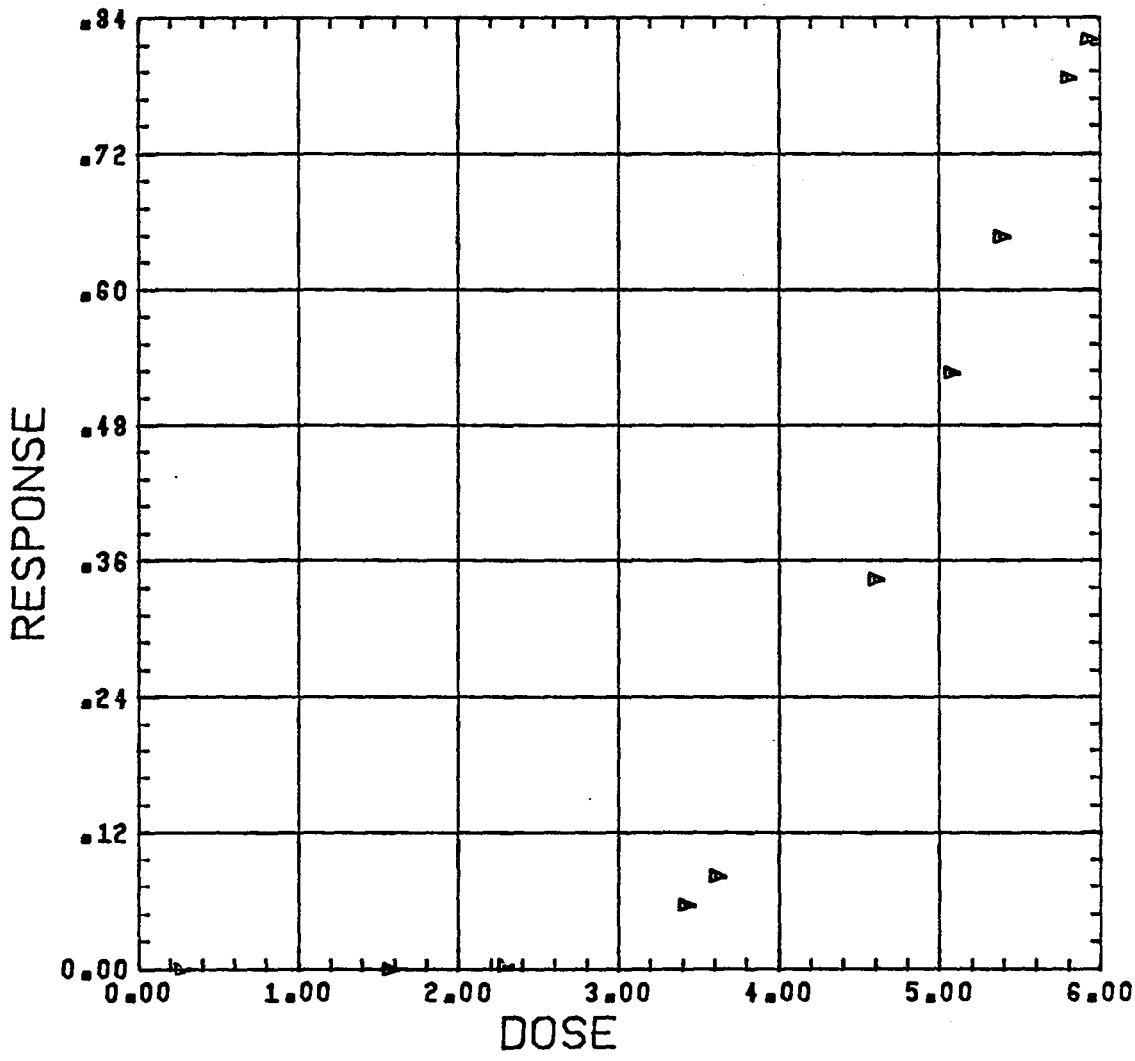
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 100
COMPLIANCE VARIABLES: B(2,0.5)
FIGURE 3.18



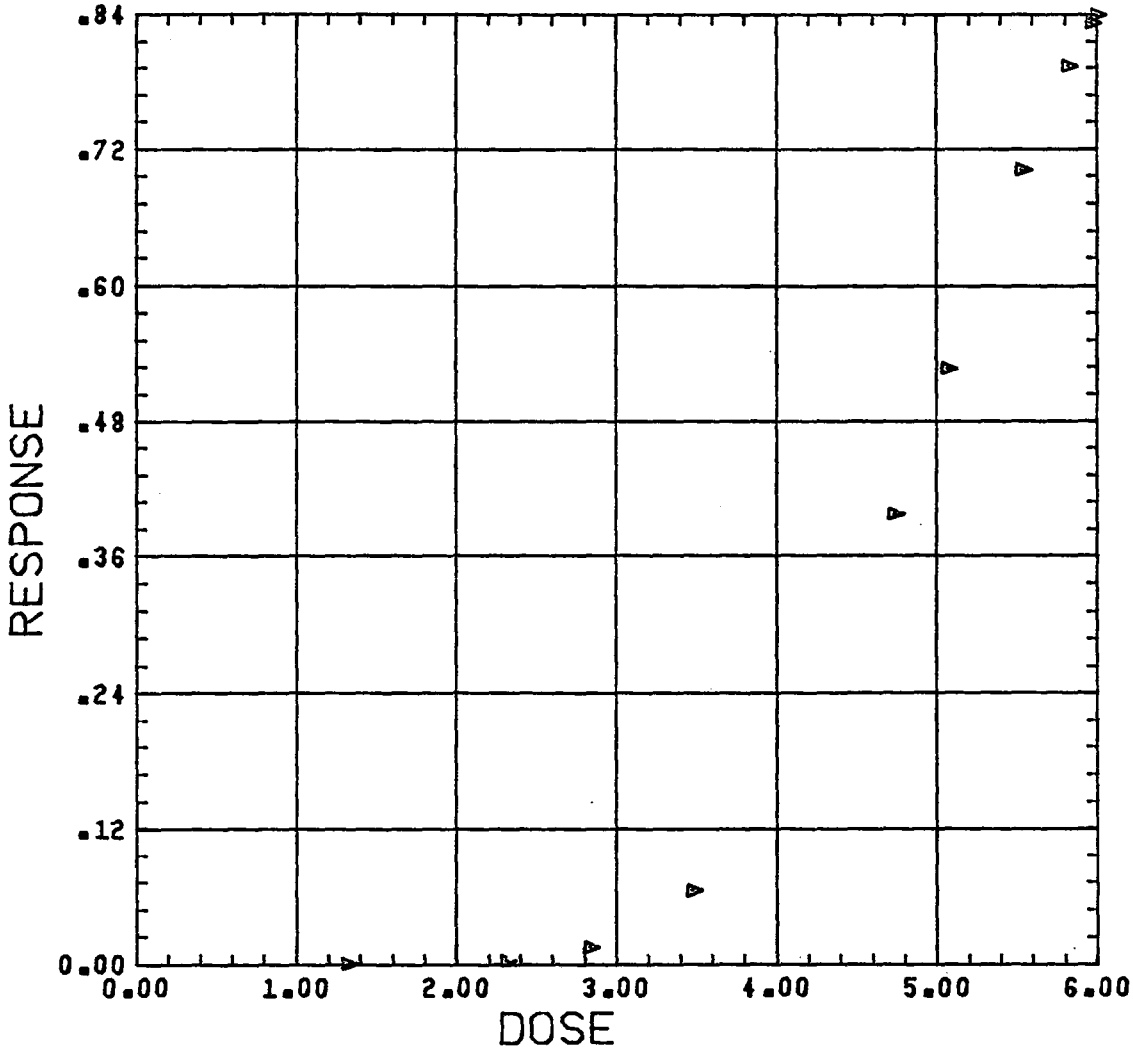
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 10
COMPLIANCE VARIABLES: B(0.5,0.5)
FIGURE 3.19



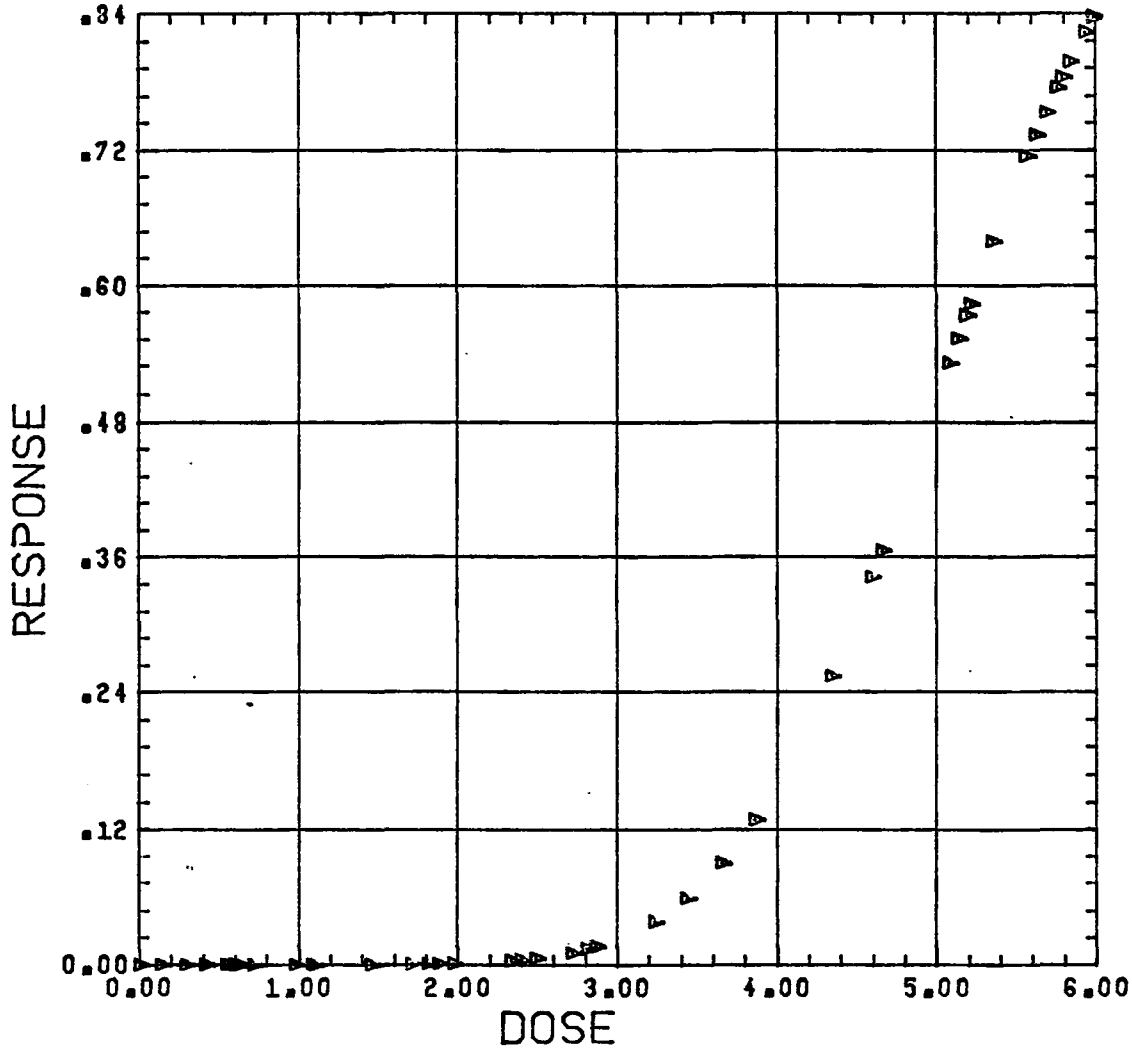
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 10
COMPLIANCE VARIABLES: B(1, 1)
FIGURE 3.20



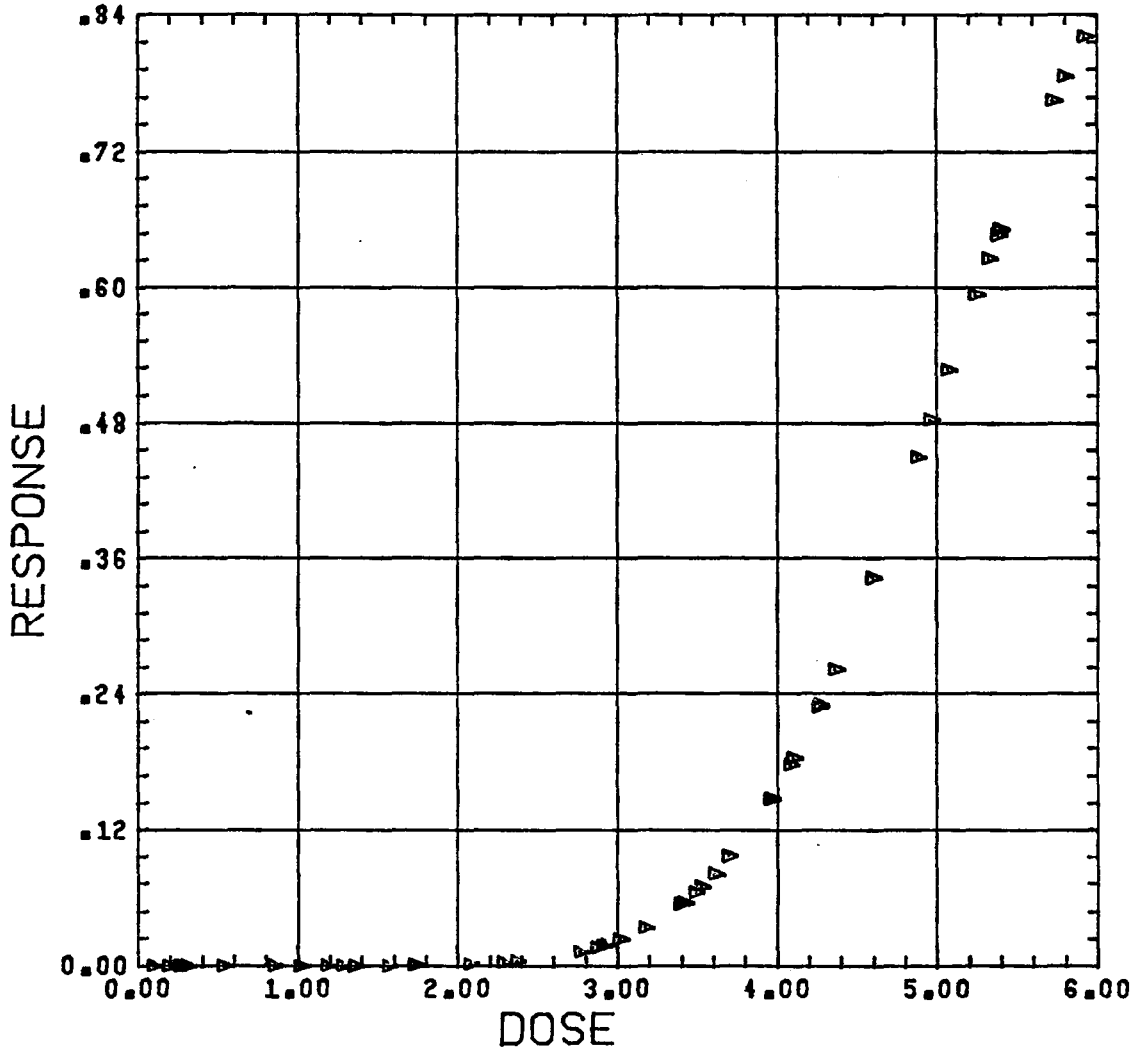
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 10
COMPLIANCE VARIABLES: B(2, 2)
FIGURE 3.21



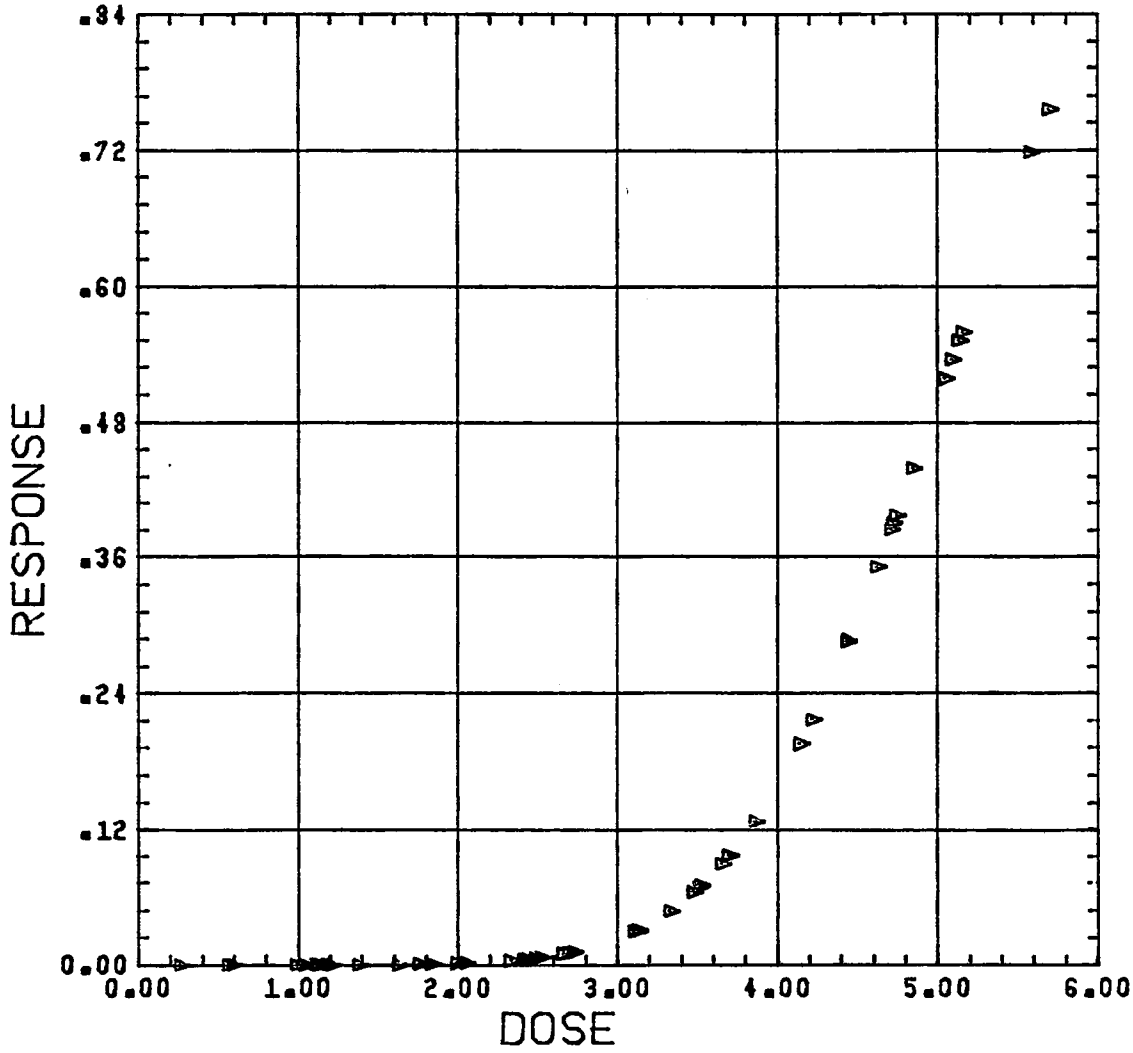
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 10
COMPLIANCE VARIABLES: B(2, 0.5)
FIGURE 3.22



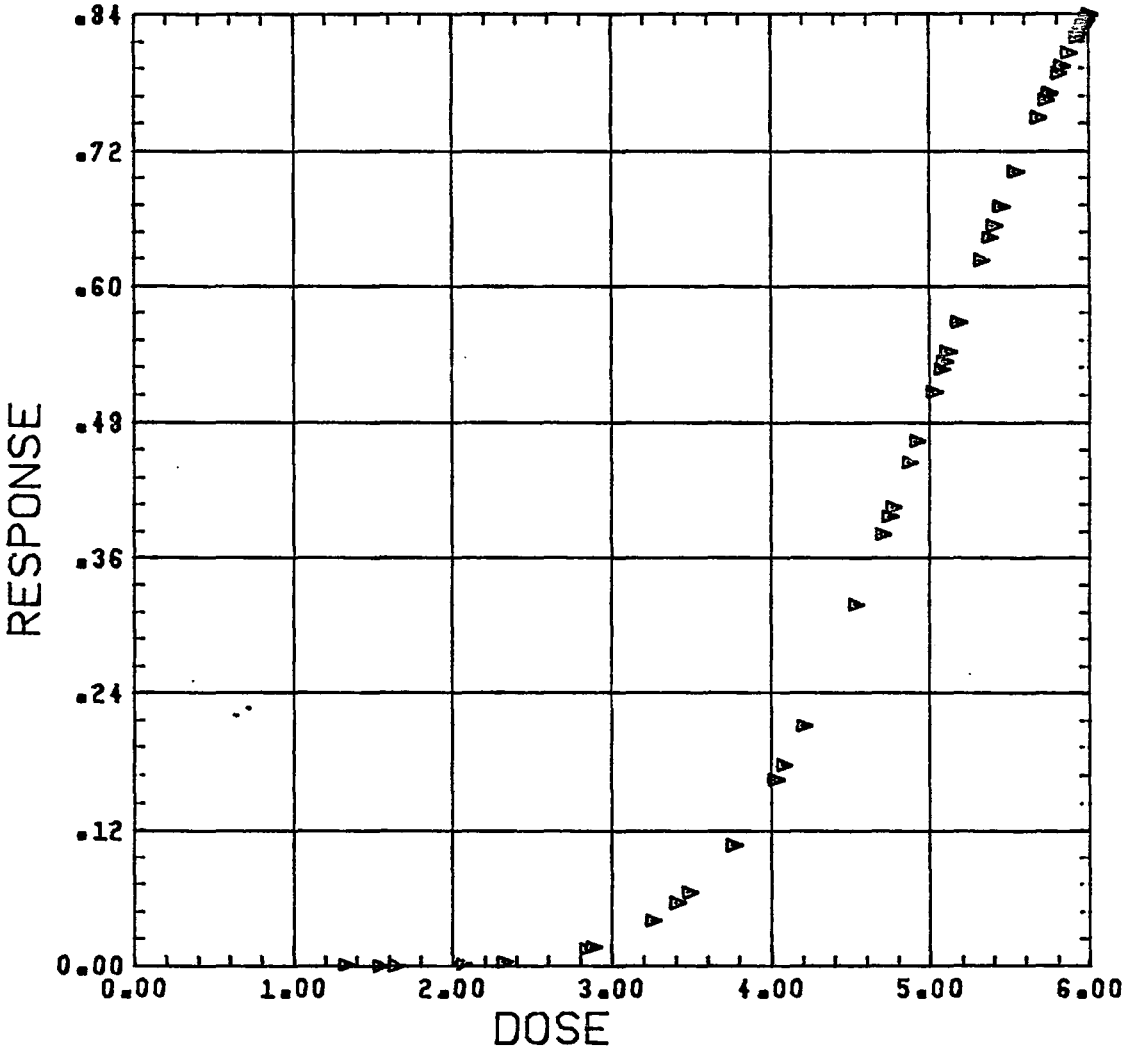
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 50
COMPLIANCE VARIABLES: B(0.5 , 0.5)
FIGURE 3.23



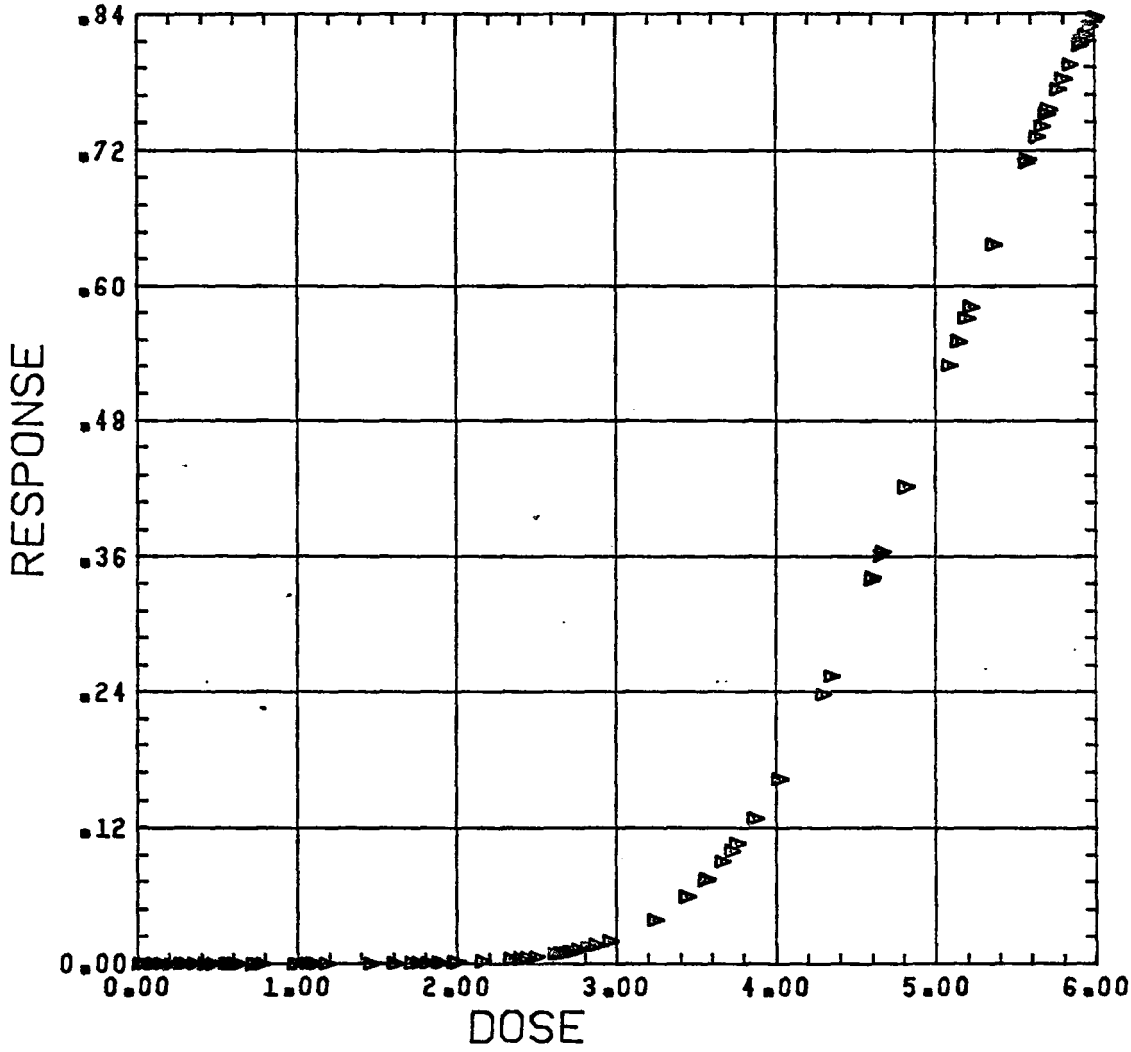
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 50
COMPLIANCE VARIABLES: B(1, 1)
FIGURE 3.24



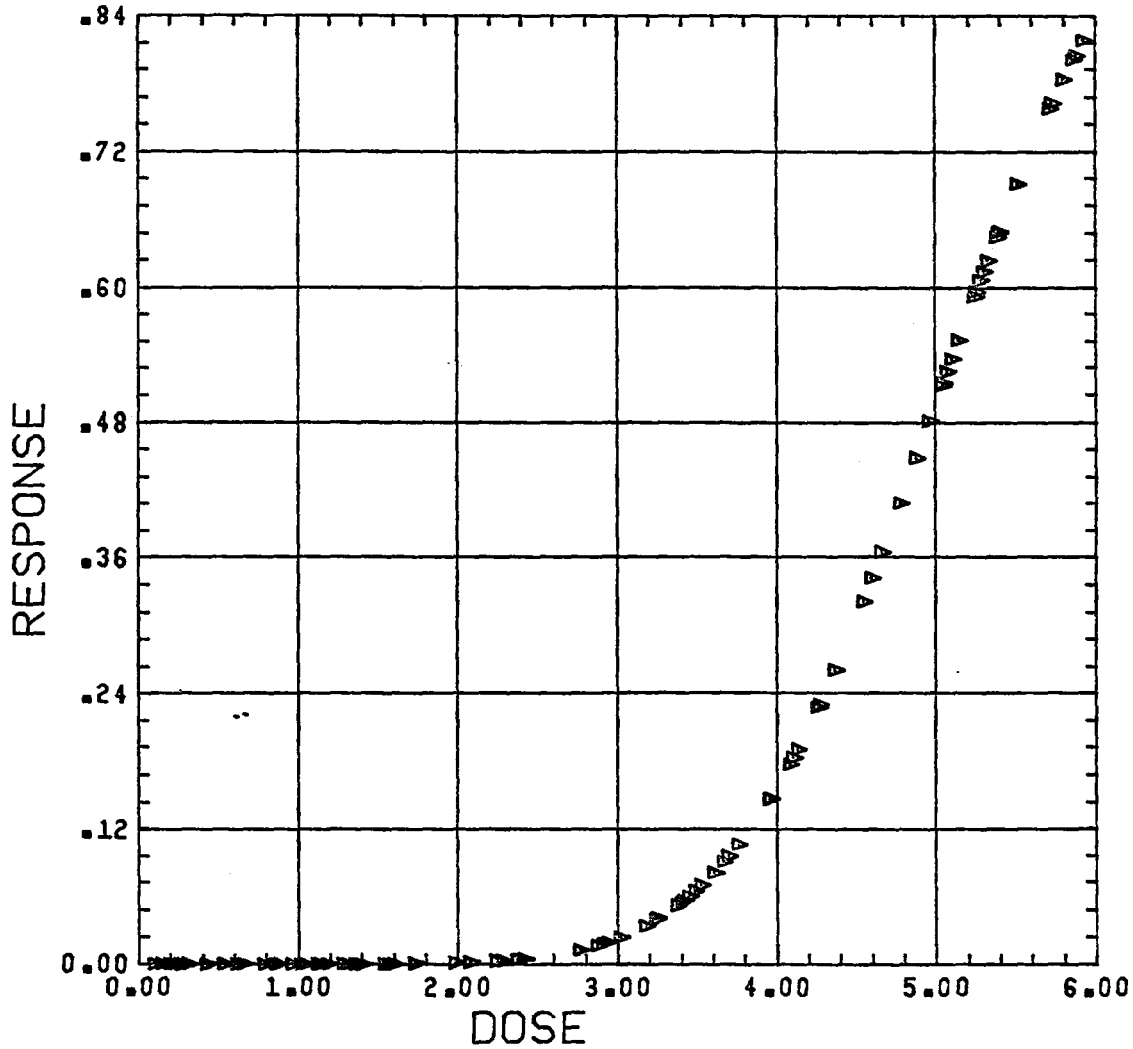
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 50
COMPLIANCE VARIABLES: B(2, 2)
FIGURE 3.25



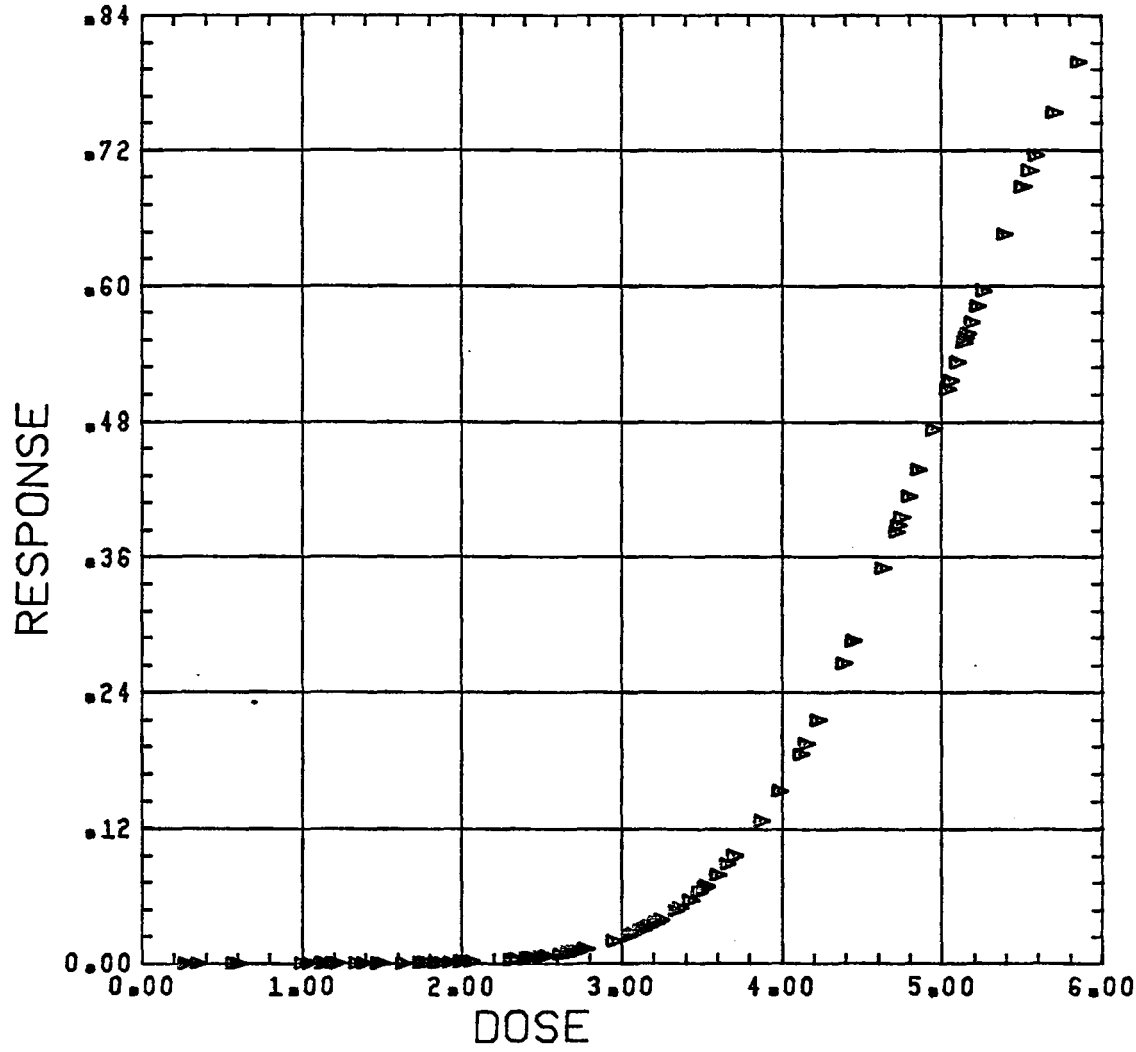
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 50
COMPLIANCE VARIABLES: B(2, 0.5)
FIGURE 3.26



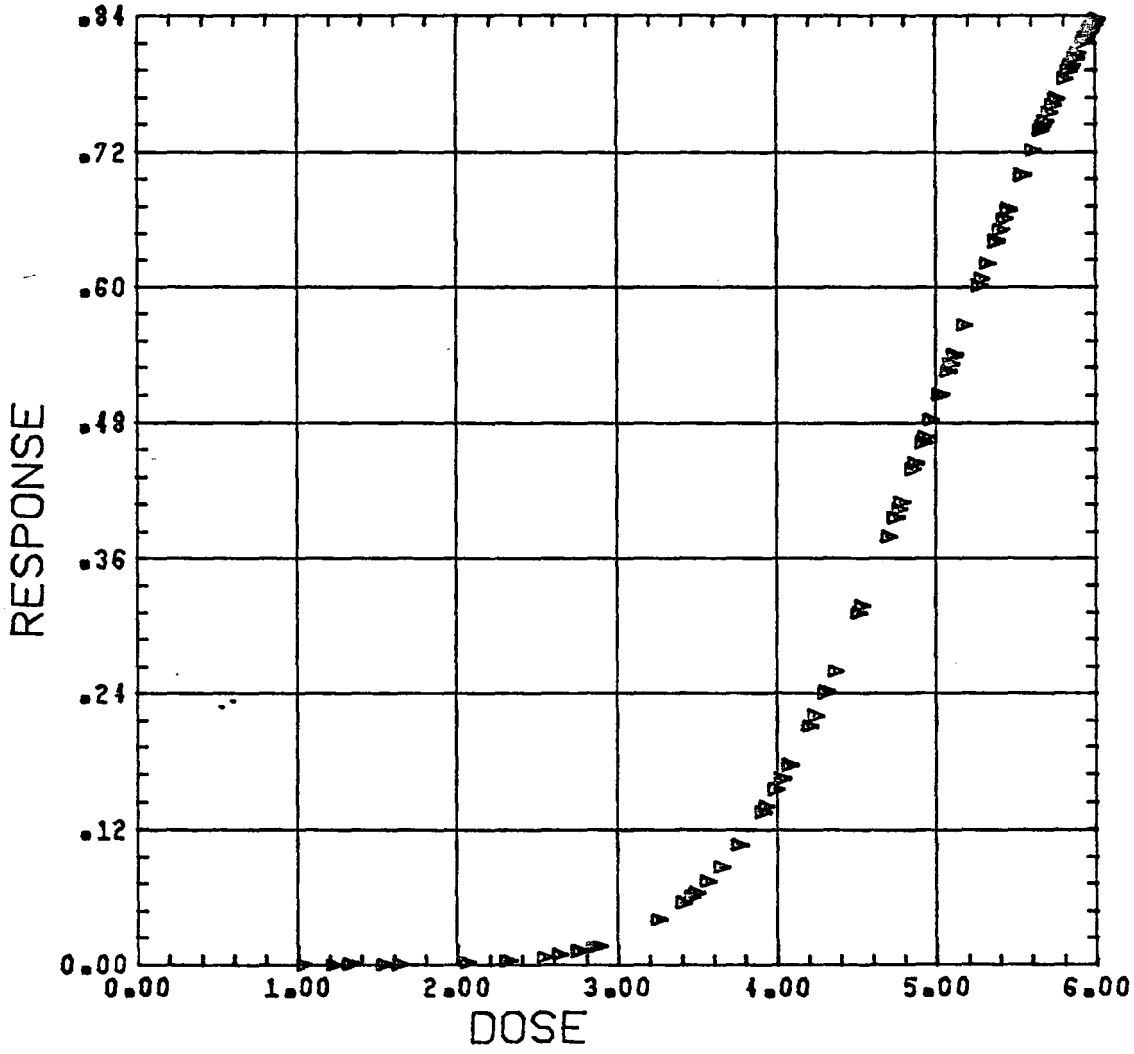
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 100
COMPLIANCE VARIABLES: B(0.5,0.5)
FIGURE 3.27



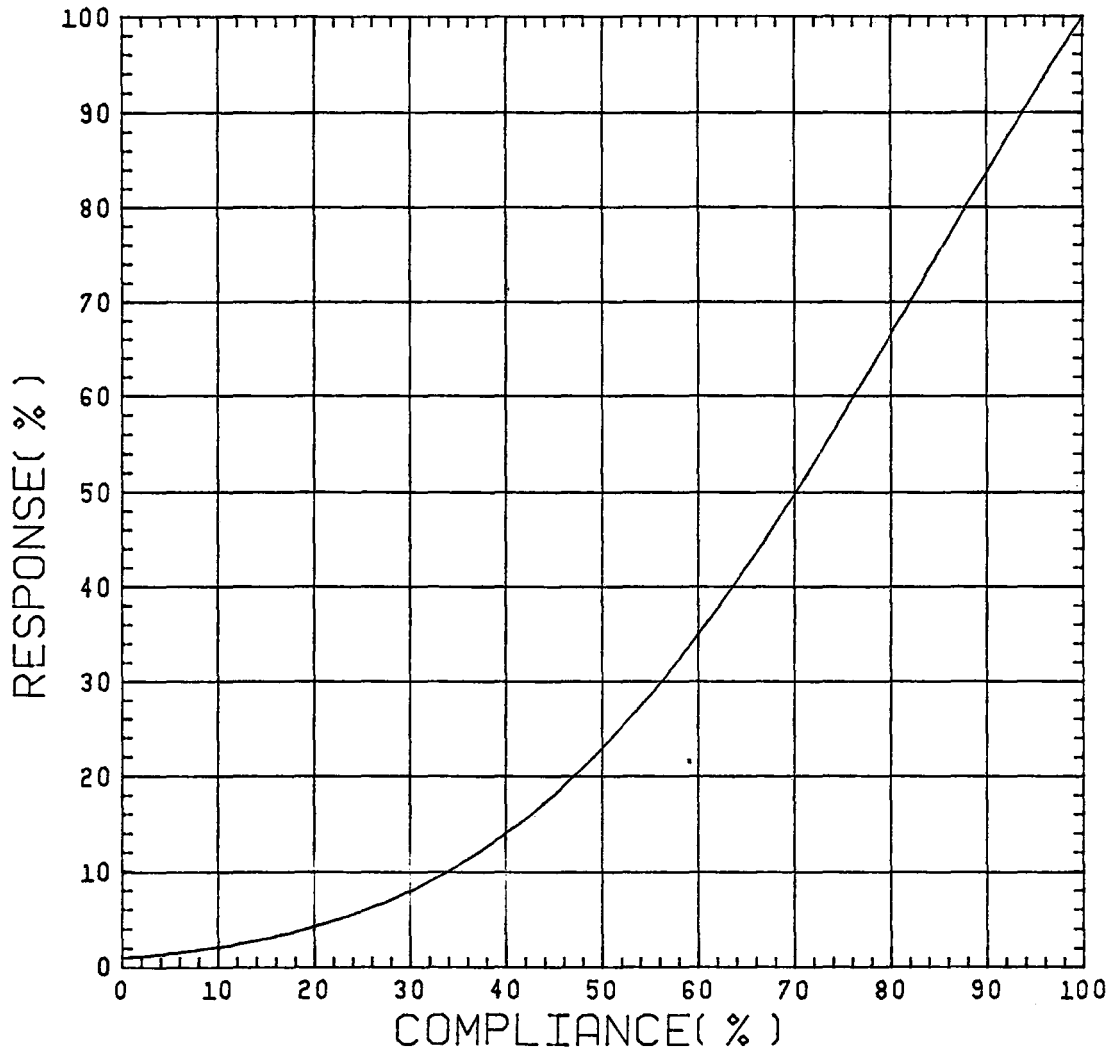
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 100
COMPLIANCE VARIABLES: B(1, 1)
FIGURE 3.28



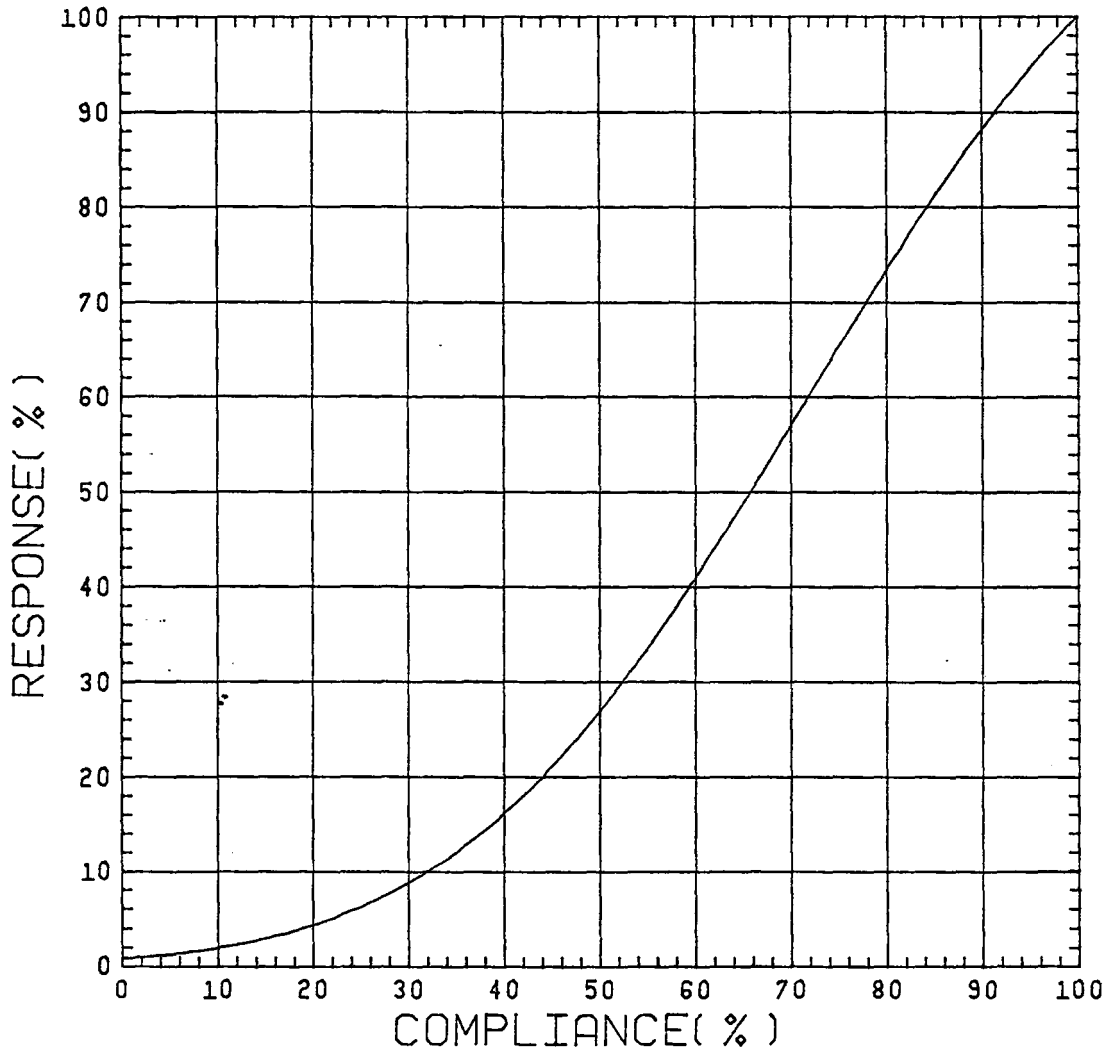
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 100
COMPLIANCE VARIABLES: B(2, 2)
FIGURE 3.29



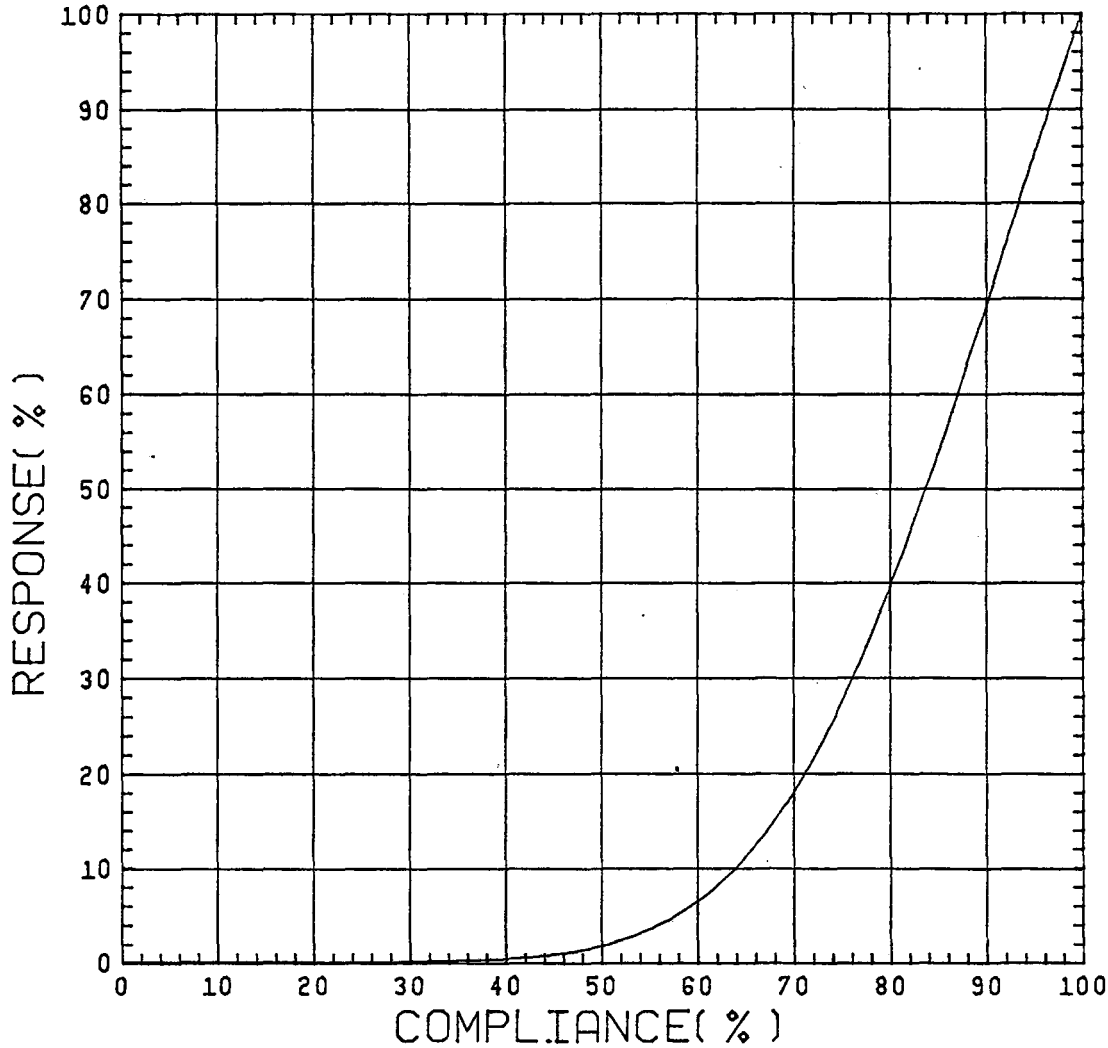
COMPLIANCE/DOSE-RESPONSE CURVE
SAMPLE SIZE: N = 100
COMPLIANCE VARIABLES: B(2, 0.5)
FIGURE 3.30



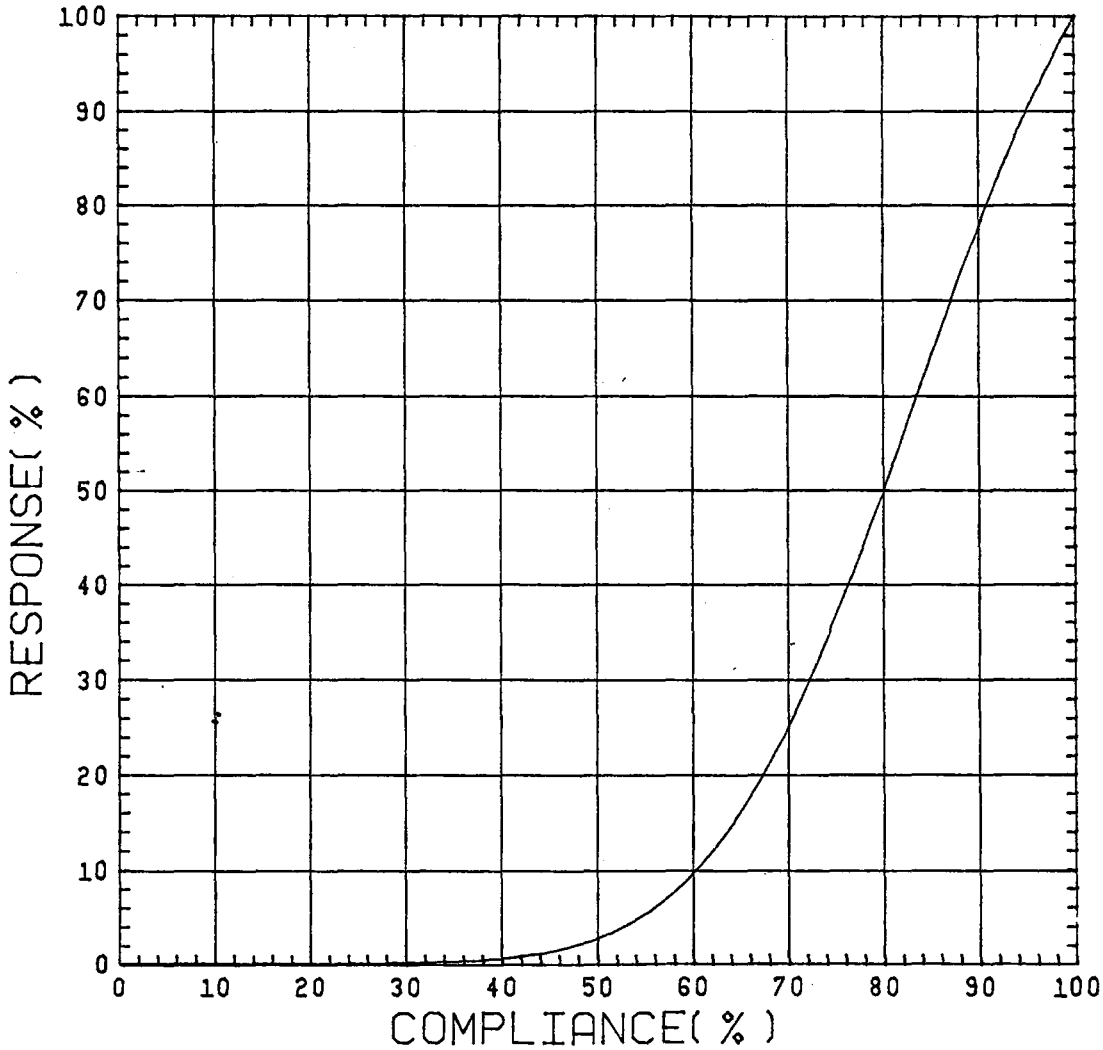
COMPLIANCE - RESPONSE CURVE
CASE 1.1
FIGURE 3.31



COMPLIANCE - RESPONSE CURVE
CASE 1.2
FIGURE 3.32



COMPLIANCE - RESPONSE CURVE
CASE 2.1
FIGURE 3.33



COMPLIANCE - RESPONSE CURVE
CASE 2.2
FIGURE 3.34

APPENDIX C

COMPUTER PROGRAMS

```
100  * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
110     PROGRAM DR
120     *THIS PROGRAM GIVES THE DATA FILE FOR THE MODEL OF
130     *DOSE-RESPONSE CURVE AS STANDARDIZED NORMAL
140     *CUMULATIVE DISTRIBUTION FUNCTION.
150  * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
160     INTEGER N,M
170     *N IS A SAMPLE SIZE.
180     REAL U(600),P(600),E,F,X(600),C,Z(600),O(600),Q(600)
190     REAL D1(2),S1(2),D2(1),S2(2),D3(2),S3(2),D4(2),S4(2)
200     REAL D5(2),S5(2),D6(2),S6(2)
210     DOUBLE PRECISION DSEED
220     N=600
230     DSEED=123457.D0
240     OPEN(1,FILE='Q1')
250     OPEN(2,FILE='Q2')
260     OPEN(3,FILE='Q3')
270     OPEN(4,FILE='Q4')
280     OPEN(5,FILE='Q5')
290     OPEN(6,FILE='Q6')
300     OPEN(7,FILE='Q7')
310     OPEN(8,FILE='Q8')
320     REWIND 1
330     REWIND 2
340     REWIND 3
350     REWIND 4
```

```
360     REWIND 5
370     REWIND 6
380     REWIND 7
390     REWIND 8
400     CALL GGNML(DSEED,N,U)
410     *GGNML IS IMSL ROUTINE WHICH GENERATES PSEUDO-RANDOM
420     *DEVIATES, U'S, WITH SAMPLE SIZE N.
430     DO 10,N=1,600
440     CALL MDNOR(U(N),P(N))
450     CALL VSRTA(U,N)
460     CALL VSRTA(P,N)
470     10 CONTINUE
480     *MDNOR IS IMSL ROUTINE WHICH GIVES THE NORMAL DENSITY, P(N),
490     *AT EACH POINT, U(N).
500     *VSRTA IS IMSL ROUTINE WHICH SORTS OUT THE DATA, U'S,
510     *WITH SAMPLE SIZE N.
520     DO 20,N=1,600
530     WRITE(1,*)U(N),P(N)
540     20 CONTINUE
550     READ *,E,F
560     READ *,C
570     *E AND F ARE THE MEAN DOSE AND STANDARD DEVIATION,
580     *RESPECTIVELY(THEY WILL GIVEN AS 0.5 AND 0.2, OR, 5.0 AND 1.0).
590     *C IS A COMPLIANCE MEASURE(IT WILL GIVEN 0.8 OR 0.5).
600     DO 30,N=1,600
610     X(N)=E+(F*U(N))
```

```
620     Z(N)=C*X(N)
630     O(N)=(Z(N)-E)|f
640     CALL VSRTA(Q,N)
650     30 CONTINUE
660     DO 40,N=1,600
670     WRITE(2,*)U(N),Q(N)
680     40 CONTINUE
690     D1(1)=-0.1
700     S1(1)=0.0
710     D1(2)=-0.1
720     S1(2)=0.46
730     D2(1)=-0.1
740     S2(1)=0.46
750     D2(2)=-3.0
760     S2(2)=0.46
770     D3(1)=1.0
780     S3(1)=0.0
790     D3(2)=1.0
800     S3(2)=0.84
810     D4(1)=1.0
820     S4(1)=0.84
830     D4(2)=-3.0
840     S4(2)=0.84
850     D5(1)=0.5
860     S5(1)=0.0
870     D5(2)=0.5
```

```
880     S5(2)=0.69
890     D6(1)=-3.0
900     S6(1)=0.69
910     D6(2)=0.5
920     S6(2)=0.69
930     DO 50,M=1,2
940     WRITE(3,*)D1(M),S1(M)
950     WRITE(4,*)D2(M),S2(M)
960     WRITE(5,*)D3(M),S3(M)
970     WRITE(6,*)D4(M),S4(M)
980     WRITE(7,*)D5(M),S5(M)
990     WRITE(8,*)D6(M),S6(M)
1000    50 CONTINUE
1100    *S1(M)-S6(M) ARE FROM MDNOR AT THE GIVEN POINTS, D1(M)-D6(M).
1200    *IN ORDER TO GIVE THE THERAPEUTIC INTERVAL(FOR FIGURES 3.1-3.2)
1300    *Q1-Q2 ARE PACKED AS ONE DATA FILE(FOR FIGURES 3.3-3.6).
1400    WRITE(1,*)999999.,999999.
1500    WRITE(2,*)999999.,999999.
1600    WRITE(3,*)999999.,999999.
1700    WRITE(4,*)999999.,999999.
1800    WRITE(5,*)999999.,999999.
1900    WRITE(6,*)999999.,999999.
2000    WRITE(7,*)999999.,999999.
2100    WRITE(8,*)999999.,999999.
2200    *IPLOT FETCHES DATA FILE AFTER COPYING ANG PACKING Q1-Q8
2300    *UP AS ONE DATA FILE.
2400    END
```

```
100 * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
110       PROGRAM SIM
120       *THIS PROGRAM GENERATES THE DATA FILE FOR
130       *COMPLIANCE-DOSE-RESPONSE CURVES.
140 * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *
150       INTEGER N,M
160       *N IS A SAMPLE SIZE(HERE WE TAKE 10, 50, 100 IN TURN.).
170       *M IS A DUMMY VARIABLE FOR N.
180       REAL A,B,E,F,X0,C(100),Z(100),U,O(100),P,Q(100)
190       REAL D(100),R(100)
200       DOUBLE PRECISION DSEED
210       OPEN(1,FILE='DR')
220       REWIND 1
230       READ *,N
240       READ *,A,B
250       *A AND B ARE THE BETA DISTRIBUTION PARAMETERS.
260       READ *,X0
270       *X0 IS THE FIXED DOSE PRESCRIBED BY PHYSICIAN OR CLINICIAN.
280       READ *,E,F
290       *E AND F REFER TO THE MEAN DOSE AND THE STANDARA DEVIATION,
300        RESPECTIVELLY.
310       DSEED=123457.D0
320       U = (X0 - E)|F
330       *U IS THE STANDARDIZED FORM OF X0.
340       CALL MDNOR(U, P)
350       *IMSL ROUTINE MDNOR GIVES THE CUMULATIVE NORMAL DENSITY
```

```
360     *VALUE, P, AT GIVEN X0.
370     CALL GGBTR(DSEED,A,B,N,C)
380     *IMSL ROUTINE GGBTR GENERATES THE PSEUDO-RANDOM DEVIATES, C'S,
390     *FROM THE UNDERLYING DISTRIBUTIONS, WHICH ARE THE BETA
400     *DISTRIBUTIONS WITH PARAMETERS A AND B, WITH THE SAMPLE
410     *SIZES, N = 10,50,100, TAKING THE VALUES BETWEEN 0 AND 1.
420     DO 10,M=1,N
430     Z(N) = X0*C(N)
440     *Z(N) ARE DOSE TAKEN(= DOSE PRESCRIBED*COMPLIANCE MEASURE).
450     W(N) = (Z(N) - E)|F
460     *W(N) ARE THE STANDARDIZED FORM OF Z(N).
470     CALL MDNOR(O(N), Q(N))
480     *IMSL ROUTINE GGNML GIVES THE CUMULATIVE NORMAL DENSITY
490     *VALUES, Q(N), AT GIVEN POINTS, O(N).
500     WRITE(1,*)O(N),P(N)
510     10 CONTINUE
520     DO 20,M=1,N
530     D(M)=100*C(M)
540     *D(N) ARE THE PERCENTAGES OF COMPLIANCE(POSITIVE SCALE).
550     R(M)=100*(Q(M)|P)
560     *R(M) ARE THE PERCENTAGES OF RESPONSE(N.E.D. SCALE).
570     PRINT 177,X0,D(M),Z(M),P,Q(M),Q(M),R(M)
580     20 CONTINUE
590     177 FORMAT(10X,F3.1,5X,F5.1,5X,F4.2,5X,F4.2,5X,F5.1)
600     WRITE(1,*)999999.,999999.
610     *IPLOT FETCHES DATA FILE DR.
620     END
```