federal register

Wednesday
November 9, 1994

Part VI

Department of Health and Human Services

Food and Drug Administration

International Conference on Harmonisation; Dose-Response Information to Support Drug Registration; Guideline; Availability; Notice

SUN EXHIBIT 1049, IPR2024-00107, PAGE 1

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 93D–0194]

International Conference on Harmonisation; Dose-Response Information to Support Drug Registration; Guideline; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is publishing a final guideline entitled "Dose-Response Information To Support Drug Registration." The guideline is applicable to both drugs and biological products. This guideline was prepared by the Efficacy Expert Working Group of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The guideline describes why dose-response information is useful and how it should be obtained in the course of drug development. This information can help identify an appropriate starting dose as well as how to adjust dosage to the needs of a particular patient. It can also identify the maximum dosage beyond which any added benefits to the patient would be unlikely or would produce unacceptable side effects. This guideline is intended to help ensure that dose response information to support drug registration is generated according to sound scientific principles.

EFFECTIVE DATE: November 9, 1994.

ADDRESSES: Submit written comments on the guideline to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Copies of the guideline are available from the CDER Executive Secretariat Staff (HFD–8), Center for Drug Evaluation and Research, Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855.

FOR FURTHER INFORMATION CONTACT:

Regarding the guideline: Robert Temple, Center for Drug Evaluation and Research (HFD–100), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4330.

Regarding ICH: Janet Showalter, Office of Health Affairs (HFY–1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–1382.

SUPPLEMENTARY INFORMATION: In recent years, many important initiatives have been undertaken by regulatory authorities and industry associations to promote international harmonization of regulatory requirements. FDA has participated in many meetings designed to enhance harmonization and is committed to seeking scientifically based harmonized technical procedures for pharmaceutical development. One of the goals of harmonization is to identify and then reduce differences in technical requirements for drug development.

ICH was organized to provide an opportunity for harmonization initiatives to be developed with input from both regulatory and industry representatives. FDA also seeks input from consumer representatives and others. ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States. The six ICH sponsors are the European Commission, the European Federation of Pharmaceutical Industry Associations, the Japanese Ministry of Health and Welfare, the Japanese Pharmaceutical Manufacturers Association, FDA, and the U.S. Pharmaceutical Research and Manufacturers of America. The ICH Secretariat, which coordinates the preparation of documentation, is provided by the International Federation of Pharmaceutical Manufacturers Associations (IFPMA).

The ICH Steering Committee includes representatives from each of the ICH sponsors and IFPMA, as well as observers from the World Health Organization, the Canadian Health Protection Branch, and the European Free Trade Area.

At a meeting held on March 8, 9, and 10, 1993, the ICH Steering Committee agreed that the draft tripartite guideline entitled "Dose-Response Information To Support Drug Registration" should be made available for comment. (The document is the product of the Efficacy Export Working Group of ICH.) Subsequently, the draft guideline was made available for comment by the European Union and Japan, as well as by FDA (see 58 FR 37402, July 9, 1993), in accordance with their consultation procedures. The comments were analyzed and the guideline was revised as necessary. At a meeting held on March 10, 1994, the ICH Steering Committee agreed that this final guideline should be published.

With this notice, FDA is publishing a final guideline entitled "Dose-Response Information To Support Drug Registration." It is applicable to both drugs and biological products. This guideline has been endorsed by all ICH sponsors. The guideline describes the value and uses of dose-response information and the kinds of studies that can obtain such information, and gives specific guidance to manufacturers on the kinds of information they should obtain.

In the past, guidelines have generally been issued under § 10.90(b) (21 CFR 10.90(b)), which provides for the use of guidelines to state procedures or standards of general applicability that are not legal requirements but that are acceptable to FDA. The agency is now in the process of revising § 10.90(b). Therefore, the guideline is not being issued under the authority of current § 10.90(b), and it does not create or confer any rights, privileges, or benefits for or on any person, nor does it operate to bind FDA in any way.

As with all of FDA's guidelines, the public is encouraged to submit written comments with new data or other new information pertinent to this guideline. The comments in the docket will be periodically reviewed, and where appropriate, the guideline will be amended. The public will be notified of any such amendments through a notice in the **Federal Register**.

Interested persons may, at any time, submit written comments on the guideline to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except the individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. The guideline and received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

The text of the final guideline follows:

Dose-Response Information to Support Drug Registration

I. Introduction

Purpose of Dose-Response Information

Knowledge of the relationships among dose, drug concentration in blood, and clinical response (effectiveness and undesirable effects) is important for the safe and effective use of drugs in individual patients. This information can help identify an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose beyond which increases would be unlikely to provide added benefit or would produce unacceptable side effects. Dose-concentration, concentration- and/or dose-response information is used to prepare dosage and administration instructions in product labeling. In addition, knowledge of dose-response may provide an economical approach to global drug development, by enabling multiple regulatory agencies to make approval decisions from a common database.

Historically, drugs have often been initially marketed at what were later recognized as excessive doses (i.e., doses well onto the plateau of the dose-response curve for the desired effect), sometimes with adverse consequences (e.g., hypokalemia and other metabolic disturbances with thiazide-type diuretics in hypertension). This situation has been improved by attempts to find the smallest dose with a discernible useful effect or a maximum dose beyond which no further beneficial effect is seen, but practical study designs do not exist to allow for precise determination of these doses. Further, expanding knowledge indicates that the concepts of minimum effective dose and maximum useful dose do not adequately account for individual differences and do not allow a comparison, at various doses, of both beneficial and undesirable effects. Any given dose provides a mixture of desirable and undesirable effects, with no single dose necessarily optimal for all patients.

Use of Dose-Response Information in Choosing Doses

What is most helpful in choosing the starting dose of a drug is knowing the shape and location of the population (group) average dose-response curve for both desirable and undesirable effects. Selection of dose is best based on that information, together with a judgment about the relative importance of desirable and undesirable effects. For example, a relatively high starting dose (on or near the plateau of the effectiveness dose-response curve) might be recommended for a drug with a large demonstrated separation between its useful and undesirable dose ranges or where a rapidly evolving disease process demands rapid effective intervention. A high starting dose, however, might be a poor choice for a drug with a small demonstrated separation between its useful and undesirable dose ranges. In these cases, the recommended starting dose might best be a low dose exhibiting a clinically important effect in even a fraction of the patient population, with the intent to titrate the dose upwards as long as the drug is well tolerated. Choice of a starting dose might also be affected by potential intersubject variability in pharmacodynamic response to a given blood concentration level, or by anticipated intersubject pharmacokinetic differences, such as could arise from nonlinear kinetics, metabolic polymorphism, or a high potential for pharmacokinetic drug-drug interactions. In these cases, a lower starting dose would protect patients who obtain higher blood concentrations. It is entirely possible that different physicians and even different regulatory authorities, looking at the same data, would make different choices as to the appropriate starting doses, dose-titration steps, and maximum recommended dose, based on different perceptions of risk/benefit relationships. Valid dose response data allow the use of such judgment.

In adjusting the dose in an individual patient after observing the response to an initial dose, what would be most helpful is knowledge of the shape of individual dose-response curves, which is usually not the same as the population (group) average dose-response curve. Study designs that allow estimation of individual dose-response curves could therefore be useful in guiding titration, although experience with such designs and their analysis is very limited.

In utilizing dose-response information, it is important to identify, to the extent possible, factors that lead to differences in pharmacokinetics of drugs among individuals, including demographic factors (e.g., age, gender, race), other diseases (e.g., renal or hepatic failure), diet, concurrent therapies, or individual characteristics (e.g., weight, body habitus, other drugs, metabolic differences).

Uses of Concentration-Response Data

Where a drug can be safely and effectively given only with blood concentration monitoring, the value of concentration-response information is obvious. In other cases, an established concentration-response relationship is often not needed, but may be useful: (1) For ascertaining the magnitude of the clinical consequences of pharmacokinetic differences, such as those due to drug-disease (e.g, renal failure) or drug-drug interactions; or (2) for assessing the effects of the altered pharmacokinetics of new dosage forms (e.g., controlled release formulation) or new dosage regimens without need for additional clinical trial data, where such assessment is permitted by regional regulations. Prospective randomized concentration-response studies are obviously critical to defining concentration monitoring therapeutic "windows," but are also useful when pharmacokinetic variability among patients is great; in that case, a concentration-response relationship may in principle be discerned in a prospective study with a smaller number of subjects than could the dose-response relationship in a standard dose-response study. Note that collection of concentration-response information does not imply that therapeutic blood level monitoring will be needed to administer the drug properly. Concentration-response relationships can be translated into dose-response information. Concentration-response information can also allow selection of doses (based on the range of concentrations they will achieve) most likely to lead to a satisfactory response. Alternatively, if the relationships between concentration and observed effects (e.g., an undesirable or desirable pharmacologic effect) are defined, the drug can be titrated according to patient response without the need for further blood level monitoring.

Problems With Titration Designs

A study design widely used to demonstrate effectiveness utilizes dose titration to some effectiveness or safety endpoint. Such titration designs, without careful analysis, are usually not informative about dose-response relationships. In many studies, there is a tendency to spontaneous improvement over time that is not easily distinguishable from an increased response to higher doses or cumulative drug exposure. This leads to a tendency to choose, as a recommended dose, the highest dose used in such studies that was reasonably well tolerated. Historically, this approach has often led to a dose that was well in excess of what was really necessary, resulting in increased undesirable effects, e.g., to high-dose diuretics used for hypertension. In some cases, notably where an early answer is essential, the titration-to-highest-tolerable-dose approach is acceptable, because it often requires a minimum number of patients. For example, the first marketing of zidovudine (AZT) for treatment of people with acquired immune deficiency syndrome (AIDS) was based on studies at a high dose; later studies showed that lower doses were as effective and far better tolerated. The urgent need for the first effective anti-HIV (human immunodeficiency virus) treatment made the absence of dose-response information at the time of approval reasonable (with the condition that more data were to be obtained after marketing), but in less urgent cases this approach is discouraged.

Interactions Between Dose-Response and Time

The choice of the size of an individual dose is often intertwined with the frequency of dosing. In general, when the dose interval is long compared to the half-life of the drug, attention should be directed to the pharmacodynamic basis for the chosen dosing interval. For example, there might be a comparison of the long dose interval regimen with the same dose in a more divided regimen, looking, where this is feasible, for persistence of desired effect throughout the dose interval and for adverse effects associated with blood level peaks. Within a single dose interval, the dose-response relationships at peak and trough blood levels may differ and the relationship could depend on the dose interval chosen.

Dose-response studies should take time into account in a variety of other ways. The study period at a given dose should be long enough for the full effect to be realized, whether delay is the result of pharmacokinetic or pharmacodynamic factors. The dose-response may also be different for morning versus evening dosing. Similarly, the dose-response relationship during early dosing may not be the same as in the subsequent maintenance dosing period. Responses could also be related to cumulative dose, rather than daily dose, to duration of exposure (e.g., tachyphylaxis, tolerance, or hysteresis) or to the relationships of dosing to meals.

II. Obtaining Dose-Response Information

Dose-Response Assessment Should Be an Integral Part of Drug Development

Assessment of dose-response should be an integral component of drug development with studies designed to assess dose-response an inherent part of establishing the safety and effectiveness of the drug. If development of dose-response information is built into the development process it can usually be accomplished with no loss of time and minimal extra effort compared to development plans that ignore dose-response.

Studies in Life-Threatening Diseases

In particular therapeutic areas, different therapeutic and investigational behaviors

have evolved; these affect the kinds of studies typically carried out. Parallel dose-response study designs with placebo, or placebo-controlled titration study designs (very effective designs, typically used in studies of angina, depression, hypertension, etc.) would not be acceptable in the study of some conditions, such as life-threatening infections or potentially curable tumors, at least if there were effective treatments known. Moreover, because in those therapeutic areas considerable toxicity could be accepted, relatively high doses of drugs are usually chosen to achieve the greatest possible beneficial effect rapidly. This approach may lead to recommended doses that deprive some patients of the potential benefit of a drug by inducing toxicity that leads to cessation of therapy. On the other hand, use of low, possibly subeffective, doses, or of titration to desired effect may be unacceptable, as an initial failure in these cases may represent an opportunity for cure forever lost.

Nonetheless, even for life-threatening diseases, drug developers should always be weighing the gains and disadvantages of varying regimens and considering how best to choose dose, dose-interval and dose-escalation steps. Even in indications involving life-threatening diseases, the highest tolerated dose, or the dose with the largest effect on a surrogate marker will not always be the optimal dose. Where only a single dose is studied, blood concentration data, which will almost always show considerable individual variability due to pharmacokinetic differences, may retrospectively give clues to possible concentration-response relationships.

Use of just a single dose has been typical of large-scale intervention studies (e.g., post-myocardial infarction studies) because of the large sample sizes needed. In planning an intervention study, the potential advantages of studying more than a single dose should be considered. In some cases, it may be possible to simplify the study by collecting less information on each patient, allowing study of a larger population treated with several doses without significant increase in costs.

Regulatory Considerations When Dose-Response Data Are Imperfect

Even well-laid plans are not invariably successful. An otherwise well-designed dose-response study may have utilized doses that were too high, or too close together, so that all appear equivalent (albeit superior to placebo). In that case, there is the possibility that the lowest dose studied is still greater than needed to exert the drug's maximum effect. Nonetheless, an acceptable balance of observed undesired effects and beneficial effects might make marketing at one of the doses studied reasonable. This decision would be easiest, of course, if the drug had special value, but even if it did not, in light of the studies that partly defined the proper dose range, further dose-finding might be pursued in the postmarketing period. Similarly, although seeking dose response data should be a goal of every development program, approval based on data from studies using a fixed single dose or a defined dose range (but without valid dose response information) might be appropriate where benefit from a new therapy in treating or preventing a serious disease is clear.

Examining the Entire Database for Dose-Response Information

In addition to seeking dose-response information from studies specifically designed to provide it, the entire database should be examined intensively for possible dose-response effects. The limitations imposed by certain study design features should, of course, be appreciated. For example, many studies titrate the dose upward for safety reasons. As most side effects of drugs occur early and may disappear with continued treatment, this can result in a spuriously higher rate of undesirable effects at the lower doses. Similarly, in studies where patients are titrated to a desired response, those patients relatively unresponsive to the drug are more likely to receive the higher dose, giving an apparent, but misleading, inverted "U-shaped" dose-response curve. Despite such limitations, clinical data from all sources should be analyzed for dose-related effects using multivariate or other approaches, even if the analyses can yield principally hypotheses, not definitive conclusions. For example, an inverse relation of effect to weight or creatinine clearance could reflect a dose-related covariate relationship. If pharmacokinetic screening (obtaining a small number of steady-state blood concentration measurements in most Phase 2 and Phase 3 study patients) is carried out, or if other approaches to obtaining drug concentrations during trials are used, a relation of effects (desirable or undesirable) to blood concentrations may be discerned. The relationship may by itself be a persuasive description of concentration-response or may suggest further study.

III. Study Designs for Assessing Dose Response

General

The choice of study design and study population in dose-response trials will depend on the phase of development, the therapeutic indication under investigation, and the severity of the disease in the patient population of interest. For example, the lack of appropriate salvage therapy for life-threatening or serious conditions with irreversible outcomes may ethically preclude conduct of studies at doses below the maximum tolerated dose. A homogeneous patient population will generally allow achievement of study objectives with small numbers of subjects given each treatment. On the other hand, larger, more diverse populations allow detection of potentially important covariate effects.

In general, useful dose-response information is best obtained from trials specifically designed to compare several doses. A comparison of results from two or more controlled trials with single fixed doses might sometimes be informative, e.g., if control groups were similar, although even in that case, the many across-study differences that occur in separate trials usually make this approach unsatisfactory. It is also possible in some cases to derive, retrospectively, blood concentration-response relationships from the variable concentrations attained in a fixed-dose trial. While these analyses are potentially confounded by disease severity or other patient factors, the information can be useful and can guide subsequent studies. Conducting dose-response studies at an early stage of clinical development may reduce the number of failed Phase 3 trials, speeding the drug development process and conserving development resources.

Pharmacokinetic information can be used to choose doses that ensure adequate spread of attained concentration-response values and diminish or eliminate overlap between attained concentrations in dose-response trials. For drugs with high pharmacokinetic variability, a greater spread of doses could be chosen. Alternatively, the dosing groups could be individualized by adjusting for pharmacokinetic covariates (e.g., correction for weight, lean body mass, or renal function) or a concentration-controlled study could be carried out.

As a practical matter, valid dose-response data can be obtained more readily when the response is measured by a continuous or categorical variable, is relatively rapidly obtained after therapy is started, and is rapidly dissipated after therapy is stopped (e.g., blood pressure, analgesia, bronchodilation). In this case, a wider range of study designs can be used and relatively small, simple studies can give useful information. Placebo-controlled individual subject titration designs typical of many early drug development studies, for example, properly conducted and analyzed (quantitative analysis that models and estimates the population and individual dose-response relationships), can give guidance for more definitive parallel, fixed-dose, dose-response studies or may be definitive on their own.

In contrast, when the study endpoint or adverse effect is delayed, persistent, or irreversible (e.g., stroke or heart attack prevention, asthma prophylaxis, arthritis treatments with late onset response, survival in cancer, treatment of depression), titration and simultaneous assessment of response is usually not possible, and the parallel dose-response study is usually needed. The parallel dose-response study also offers protection against missing an effective dose because of an inverted "U-shaped" (umbrella or bell-shaped) dose-response curve, where higher doses are less effective than lower doses, a response that can occur, for example, with mixed agonist-antagonists.

Trials intended to evaluate dose- or concentration-response should be well-controlled, using randomization and blinding (unless blinding is unnecessary or impossible) to assure comparability of treatment groups and to minimize potential patient, investigator, and analyst bias, and should be of adequate size.

It is important to choose as wide a range of doses as is compatible with practicality and patient safety to discern clinically meaningful differences. This is especially important where there are no pharmacologic or plausible surrogate endpoints to give initial guidance as to dose.

Specific Trial Designs

A number of specific study designs can be used to assess dose-response. The same approaches can also be used to measure concentration-response relationships. Although not intended to be an exhaustive list, the following approaches have been shown to be useful ways of deriving valid dose-response information. Some designs outlined in this guidance are better established than others, but all are worthy of consideration. These designs can be applied to the study of established clinical endpoints or surrogate endpoints.

1. Parallel Dose-Response

Randomization to several fixed-dose groups (the randomized parallel dose-response study) is simple in concept and is a design that has had extensive use and considerable success. The fixed dose is the final or maintenance dose; patients may be placed immediately on that dose or titrated gradually (in a scheduled "forced" titration) to it if that seems safer. In either case, the final dose should be maintained for a time adequate to allow the dose-response comparison. Although including a placebo group in dose-response studies is desirable, it is not theoretically necessary in all cases; a positive slope, even without a placebo group, provides evidence of a drug effect. To measure the absolute size of the drug effect, however, a placebo or comparator with very limited effect on the endpoint of interest is usually needed. Moreover, because a difference between drug groups and placebo unequivocally shows effectiveness, inclusion of a placebo group can salvage, in part, a study that used doses that were all too high and, therefore, showed no dose-response slope, by showing that all doses were superior to placebo. In principle, being able to detect a statistically significant difference in pair-wise comparisons between doses is not necessary if a statistically significant trend (upward slope) across doses can be established using all the data. It should be demonstrated, however, that the lowest dose(s) tested, if it is to be recommended, has a statistically significant and clinically meaningful effect.

The parallel dose-response study gives group mean (population-average) dose-response, not the distribution or shape of individual dose-response curves.

It is all too common to discover, at the end of a parallel dose-response study, that all doses were too high (on the plateau of the dose-response curve), or that doses did not go high enough. A formally planned interim analysis (or other multi-stage design) might detect such a problem and allow study of the proper dose range.

As with any placebo-controlled trial, it may also be useful to include one or more doses of an active drug control. Inclusion of both placebo and active control groups allows assessment of "assay sensitivity," permitting a distinction between an ineffective drug and an "ineffective" (null, no test) study. Comparison of dose-response curves for test and control drugs, not yet a common design, may also represent a more valid and informative comparative effectiveness/safety study than comparison of single doses of the two agents.

The factorial trial is a special case of the parallel dose-response study to be considered when combination therapy is being evaluated. It is particularly useful when both agents are intended to affect the same response variable (a diuretic and another anti-hypertensive, for example), or when one drug is intended to mitigate the side effects of the other. These studies can show effectiveness (a contribution of each component of the combination) and, in addition, provide dosing information for the drugs used alone and together.

A factorial trial employs a parallel fixed-dose design with a range of doses of each separate drug and some or all combinations of these doses. The sample size need not be large enough to distinguish single cells from each other in pair-wise comparisons because all of the data can be used to derive dose-response relationships for the single agents and combinations, i.e., a dose-response surface. These trials, therefore, can be of moderate size. The doses and combinations that could be approved for marketing might not be limited to the actual doses studied but might include doses and combinations in between those studied. There may be some exceptions to the ability to rely entirely on the response surface analysis in choosing dose(s). At the low end of the dose range, if the doses used are lower than the recognized effective doses of the single agents, it would ordinarily be important to have adequate evidence that these can be distinguished from placebo in a pair-wise comparison. One way to do this in the factorial study is to have the lowest dose combination and placebo groups be somewhat larger than other groups; another is to have a separate study of the low-dose combination. Also, at the high end of the dose range, it may be necessary to confirm the contribution of each component to the overall effect.

2. Cross-over Dose-Response

A randomized multiple cross-over study of different doses can be successful if drug effect develops rapidly and patients return to baseline conditions quickly after cessation of therapy, if responses are not irreversible (cure, death), and if patients have reasonably stable disease. This design suffers, however, from the potential problems of all cross-over studies: It can have analytic problems if there are many treatment withdrawals; it can be quite long in duration for an individual patient; and there is often uncertainty about carry-over effects (longer treatment periods may minimize this problem), baseline comparability after the first period, and period-by-treatment interactions. The length of the trial can be reduced by approaches that do not require all patients to receive each dose, such as balanced incomplete block designs.

The advantages of the design are that each individual receives several different doses so that the distribution of individual dose-response curves may be estimated, as well as the population average curve, and that, compared to a parallel design, fewer patients may be needed. Also, in contrast to titration designs, dose and time are not confounded and carry-over effects are better assessed.

3. Forced Titration

A forced titration study, where all patients move through a series of rising doses, is similar in concept and limitations to a randomized multiple cross-over dose-response study, except that assignment to dose levels is ordered, not random. If most patients complete all doses, and if the study is controlled with a parallel placebo group, the forced titration study allows a series of comparisons of an entire randomized group given several doses of drug with a concurrent placebo, just as the parallel fixed-dose trial does. A critical disadvantage is that, by itself, this study design cannot distinguish response to increased dose from response to increased time on drug therapy or a cumulative drug dosage effect. It is therefore an unsatisfactory design when response is delayed, unless treatment at each dose is prolonged. Even where the time until development of effect is known to be short (from other data), this design gives poor information on adverse effects, many of which have time-dependent characteristics. A tendency toward spontaneous improvement, a very common circumstance, will be revealed by the placebo group, but is nonetheless a problem for this design, as over time, the higher doses may find little room to show an increased effect. This design can give a reasonable first approximation of both population-average dose response and the distribution of individual dose-response relationships if the cumulative (time-dependent) drug effect is minimal and the number of treatment withdrawals is not excessive. Compared to a parallel dose-response study, this design may use fewer patients, and by extending the study duration, can be used to investigate a wide range of doses, again making it a reasonable first study. With a concurrent placebo group this design can provide clear evidence of effectiveness, and may be especially valuable in helping choose doses for a parallel dose-response study.

4. Optional Titration (Placebo-Controlled Titration to Endpoint)

In this design, patients are titrated until they reach a well-characterized favorable or unfavorable response, defined by dosing rules expressed in the protocol. This approach is most applicable to conditions where the response is reasonably prompt and is not an irreversible event, such as stroke or death. A crude analysis of such studies, e.g., comparing the effects in the subgroups of patients titrated to various dosages, often gives a misleading inverted "U-shaped" curve, as only poor responders are titrated to the highest dose. However, more sophisticated statistical analytical approaches that correct for this occurrence, by modeling and estimating the population and individual dose-response relationships, appear to allow calculation of valid dose-response information. Experience in deriving valid dose-response information in this fashion is still limited. It is important, in this design, to maintain a concurrent placebo group to correct for spontaneous changes, investigator expectations, etc. Like other designs that use several doses in the same patient, this design may use fewer patients than a parallel fixed-dose study of similar

statistical power and can provide both population average and individual dose-response information. The design does, however, risk confounding of time and dose effects and would be expected to have particular problems in finding dose-response relationships for adverse effects. Like the forced titration design, it can be used to study a wide dose range and, with a concurrent placebo group, can provide clear evidence of effectiveness. It too may be especially valuable as an early study to identify doses for a definitive parallel study.

IV. Guidance and Advice

1. Dose response data are desirable for almost all new chemical entities entering the market. These data should be derived from study designs that are sound and scientifically based; a variety of different designs can give valid information. The studies should be well-controlled, using accepted approaches to minimize bias. In addition to carrying out formal dose-response studies, sponsors should examine the entire database for possible dose-response information.

2. The information obtained through targeted studies and analyses of the entire database should be used by the sponsor to:

a. Identify a reasonable starting dose, ideally with specific adjustments (or a firm basis for believing none is needed) for patient size, gender, age, concomitant illness, and concomitant therapy, reflecting an integration of what is known about pharmacokinetic and pharmacodynamic variability. Depending on circumstances (the disease, the drug's toxicity), the starting dose may range from a low dose with some useful effect to a dose that is at or near the full-effect dose.

b. Identify reasonable, response-guided titration steps, and the interval at which they should be taken, again with appropriate adjustments for patient characteristics. These steps would be based either on the shape of the typical individual's dose-effect curves (for both desirable and undesirable effects), if individual dose-response data were available, or if not, on the shape of the population (group)-average dose-response, and the time needed to detect a change in these effects. It should be noted that methodology for finding the population (group)-average dose-response, at present, is better established than is methodology for finding individual dose-response relationships.

c. Identify a dose, or a response (desirable or undesirable), beyond which titration should not ordinarily be attempted because of a lack of further benefit or an unacceptable increase in undesirable effects.

3. It is prudent to carry out dose-ranging or concentration-response studies early in development as well as in later stages in order to avoid failed Phase 3 studies or accumulation of a database that consists largely of exposures at ineffective or excessive doses. The endpoints of studies may vary at different stages of drug development. For example, in studying a drug for heart failure, a pharmacodynamic endpoint might be used early (e.g., cardiac output, pulmonary capillary wedge pressure), an intermediate endpoint might be used later (e.g., exercise tolerance, symptoms) and a mortality or irreversible morbidity endpoint might be the final assessment (survival, new infarction). It should be anticipated that the dose response for these endpoints may be different. Of course, the choice of endpoints that must be studied for marketing approval will depend on the specific situation.

4. A widely used, successful, and acceptable design, but not the only study design for obtaining population average dose-response data, is the randomized parallel, dose-response study with three or more dosage levels, one of which may be zero (placebo). From such a trial, if dose levels are well chosen, the relationship of drug dosage, or drug concentration, to clinical beneficial or undesirable effects can be defined.

Several dose levels are needed, at least two in addition to placebo, but in general, study of more than the minimum number of doses is desirable. A single dose level of drug versus placebo allows a test of the null hypothesis of no difference between drug and placebo, but cannot define the dose-response relationship. Similarly, although a linear relationship can be derived from the response to two active doses (without placebo), this approximation is usually not sufficiently informative. Study designs usually should emphasize elucidation of the dose-response function, not individual pair-wise comparisons. If a particular point on the curve, e.g., whether a certain low dose is useful, becomes an issue, it should be studied separately.

5. Dose-response data for both beneficial and undesirable effects may provide information that allows approval of a range of doses that encompass an appropriate benefit-to-risk ratio. A well-controlled dose-response study is also a study that can serve as primary evidence of effectiveness.

6. Regulatory agencies and drug developers should be open to new approaches and to the concept of reasoned and well-documented exploratory data analysis of existing or future databases in search of dose-response data. Agencies should also be open to the use of various statistical and pharmacometric techniques such as Bayesian and population methods, modeling, and pharmacokinetic-pharmacodynamic approaches. However, these approaches should not subvert the requirement for dose-response data from prospective, randomized, multi-dose-level clinical trials. Post-hoc exploratory data analysis in search of dose-response information from databases generated to meet other objectives will often generate new hypotheses, but will only occasionally provide definitive assessment of dose-response relationships.

A variety of data analytical techniques, including increased use of retrospective population-type analyses, and novel designs (e.g., sequential designs) may help define the dose-response relationship. For example, fixed-dose designs can be reanalyzed as a continuum of dose levels if doses are refigured on a milligram per kilogram (mg/kg) basis, or adjusted for renal function, lean body mass, etc. Similarly, blood levels taken during a dose-response study may allow estimates of concentration-response relationships. Adjustment of drug exposure levels might be made on the basis of reliable information on drug-taking compliance. In all of these cases, one should always be conscious of confounding, i.e., the presence of a factor that alters both the refigured dose and response or that alters both blood level and response, compliance and response, etc.

7. Dose-response data should be explored for possible differences in subsets based on demographic characteristics, such as age, gender, or race. To do this, it is important to know whether there are pharmacokinetic differences among these groups, e.g., due to metabolic differences, differences in body habitus, or composition, etc.

8. Approval decisions are based on a consideration of the totality of information on a drug. Although dose-response information should be available, depending on the kind and degree of effectiveness shown, imperfections in the database may be acceptable with the expectation that further studies will be carried out after approval. Thus, informative dose-response data, like information on responses in special populations, on long-term use, on potential drug-drug and drug-disease interactions, is expected, but might, in the face of a major therapeutic benefit or urgent need, or very low levels of observed toxicity, become a deferred requirement.

Dated: October 25, 1994.

William K. Hubbard,

Interim Deputy Commissioner for Policy.

[FR Doc. 94–27723; Filed 11–8–94; 8:45 am]

BILLING CODE 4160–01–F