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Notices

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

Action: Notice.

Agency

DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) > Public Health Service (PHS) > Food and Drug Administration (FDA)

Identifier: [Docket No. 93D-0194]

Synopsis

[*55972] 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.

Text

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. **[*55973]**

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 **[*55974]** 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

DOCKET ALARM

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