Guidance for Industry

Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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I. INTRODUCTION

This document provides recommendations for sponsors of investigational new drugs (INDs) and applicants submitting new drug applications (NDAs) or biologics license applications (BLAs) on the use of exposure-response information in the development of drugs, including therapeutic biologics. It can be considered along with the International Conference on Harmonisation (ICH) E4 guidance on *Dose-Response Information to Support Drug Registration* and other pertinent guidances (see Appendix A).

This guidance describes (1) the uses of exposure-response studies in regulatory decision-making, (2) the important considerations in exposure-response study designs to ensure valid information, (3) the strategy for prospective planning and data analyses in the exposure-response modeling process, (4) the integration of assessment of exposure-response relationships into all phases of drug development, and (5) the format and content for reports of exposure-response studies.

This guidance is not intended to be a comprehensive listing of all of the situations where exposure-response relationships can play an important role, but it does provide a range of examples of where such information may be of value.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

[1] This guidance has been prepared by the Exposure-Response Working Group under the Medical Policy Coordinating Committee, Center for Drug Evaluation and Research (CDER), in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

II. BACKGROUND

Exposure-response information is at the heart of any determination of the safety and effectiveness of drugs. That is, a drug can be determined to be safe and effective only when the relationship of beneficial and adverse effects to a defined exposure is known. There are some situations, generally involving a very well-tolerated drug with little dose-related toxicity, in which the drug can be used effectively and safely at a single dose well onto the plateau part of its exposure-response curve, with little adjustment for pharmacokinetic (PK) or other influences in individuals. In most situations, however, for more toxic drugs, clinical use is based on weighing the favorable and unfavorable effects at a particular dose. Sometimes with such drugs, the doses can be titrated to effect or tolerability. In most cases, however, it is important to develop information on population exposure-response relationships for favorable and unfavorable effects, and information on how, and whether, exposure can be adjusted for various subsets of the population.

Historically, drug developers have been relatively successful at establishing the relationship of dose to blood concentrations in various populations, thus providing a basis for adjustment of dosage for PK differences among demographic subgroups or subgroups with impaired elimination (e.g., hepatic or renal disease), assuming systemic concentration-response relationships are unaltered. Far less attention has been paid to establishing the relationship between blood concentrations and pharmacodynamic (PD) responses and possible differences among population subsets in these concentration-response (often called PK-PD) relationships. These can be critical, as illustrated by the different responses to angiotensin-converting enzyme (ACE) inhibitors in both effectiveness and safety between Black and Caucasian populations.

For the purposes of this guidance, we are using the broad term *exposure* to refer to dose (drug input to the body) and various measures of acute or integrated drug concentrations in plasma and other biological fluid (e.g., Cmax, Cmin, Css, AUC). Similarly, *response* refers to a direct measure of the pharmacologic effect of the drug. Response includes a broad range of endpoints or biomarkers ranging from the clinically remote biomarkers (e.g., receptor occupancy) to a presumed mechanistic effect (e.g., ACE inhibition), to a potential or accepted *surrogate* (e.g., effects on blood pressure, lipids, or cardiac output), and to the full range of short-term or long-term clinical effects related to either efficacy or safety. This exposure-response guidance focuses on human studies, but exposure-response information in animal pharmacology/toxicology studies is also a highly useful component of planning the drug development process (Peck 1994; Lesko 2000).

III. DRUG DEVELOPMENT AND REGULATORY APPLICATIONS

This section describes the potential uses of exposure-response relationships in drug development and regulatory decision-making. The examples are not intended to be all-inclusive, but rather to illustrate the value of a better understanding of exposure-response relationships. We recommend that sponsors refer to other ICH and FDA guidances for a discussion of the uses of exposure-response relationships (see Appendix A).

A. Information to Support the Drug Discovery and Development Processes

Many drugs thought to be of potential value in treating human disease are introduced into development based on knowledge of in vitro receptor binding properties and identified pharmacodynamic effects in animals. Apart from describing the tolerability and PK of a drug in humans, Phase 1 and 2 studies can be used to explore the relationship of exposure (whether dose or concentration) to a response (e.g., nonclinical biomarkers, potentially valid surrogate endpoints, or short-term clinical effects) to (1) link animal and human findings, (2) provide evidence that the hypothesized mechanism is affected by the drug (proof of concept), (3) provide evidence that the effect on the mechanism leads to a desired short-term clinical outcome (more proof of concept), or (4) provide guidance for designing initial clinical endpoint trials that use a plausibly useful dose range. Both the magnitude of an effect and the time course of effect are important to choosing dose, dosing interval, and monitoring procedures, and even to deciding what dosage form (e.g., controlled-release dosage form) to develop. Exposure-response and PK data can also define the changes in dose and dosing regimens that account for intrinsic and extrinsic patient factors.

B. Information to Support a Determination of Safety and Efficacy

Apart from their role in helping design the well-controlled studies that will establish the effectiveness of a drug, exposure-response studies, depending on study design and endpoints, can:

- Represent a well-controlled clinical study, in some cases a particularly persuasive one, contributing to substantial evidence of effectiveness (where clinical endpoints or accepted surrogates are studied)

- Add to the weight of evidence supporting efficacy where mechanism of action is well understood (e.g., when an effect on a reasonably well-established biomarker/surrogate is used as an endpoint)

- Support, or in some cases provide primary evidence for, approval of different doses, dosing regimens, or dosage forms, or use of a drug in different populations, when effectiveness is already well-established in other settings and the study demonstrates a PK-PD relationship that is similar to, or different in an interpretable way from the established setting

In general, the more critical a role that exposure-response information is to play in the establishment of efficacy, the more critical it is that it be derived from an adequate and well-controlled study (see 21 CFR 314.126), whatever endpoints are studied. Thus, we recommend that critical studies (1) have prospectively defined hypotheses/objectives, (2) use an appropriate control group, (3) use randomization to ensure comparability of treatment groups and to minimize bias, (4) use well-defined and reliable methods for assessing response variables, and (5) use other techniques to minimize bias.

In contrast, some of the exposure-response studies considered in this document include analyses of nonrandomized data sets where associations between volunteer or patient exposure patterns and outcomes are examined. These analyses are often primarily exploratory, but along with other clinical trial data may provide additional insights into exposure-response relationships, particularly in situations where volunteers or patients cannot be randomized to different exposures, such as in comparing effects in demographic subgroups.

1. Contributing to Primary Evidence of Effectiveness and/or Safety

A dose-response study is one kind of adequate and well-controlled trial that can provide primary clinical evidence of effectiveness. The dose-response study is a particularly informative design, allowing observations of benefits and risks at different doses and therefore providing an ability to weigh the benefits and risks when choosing doses. The dose-response study can help ensure that excessive doses (beyond those that add to efficacy) are not used, offering some protection against unexpected and unrecognized dose-related toxicity. Captopril, for example, was a generally well-tolerated drug that caused dose and concentration-related agranulocytosis. Earlier recognition that daily doses beyond 75-150 milligrams were not necessary, and that renal impairment led to substantial accumulation, might have avoided most cases of agranulocytosis.

Dose-response studies can, in some cases, be particularly convincing and can include elements of internal consistency that, depending on the size of the study and outcome, can allow reliance on a single clinical efficacy study as evidence of effectiveness. Any dose-response study includes several comparisons (e.g., each dose vs. placebo, each dose vs. lower doses). A consistent ordering of these responses (most persuasive when, for example, several doses are significantly different from placebo and, in addition, show an increasing response with dose) represents at least internal (within-study) replication, reducing the possibility that an apparent effect is due to chance. In principle, being able to detect a statistically significant difference in pairwise comparisons between doses is not necessary if a statistically significant trend (upward slope) across doses can be established, as described in the ICH E4 guidance on dose-response. It may be advisable, however, if the lowest dose tested is to be recommended, to have additional data on that dose.

In some cases, measurement of systemic exposure levels (e.g., plasma drug concentrations) as part of dose-response studies can provide additional useful information. Systemic exposure data are especially useful when an assigned dose is poorly correlated with plasma concentrations, obscuring an existing concentration-response relationship. This can occur when there is a large degree of interindividual variability in pharmacokinetics or there is a nonlinear relationship between dose and plasma drug concentrations. Blood concentrations can also be helpful when (1) both parent drug and metabolites are active, (2) different exposure measures (e.g., Cmax, AUC) provide different relationships between exposure and efficacy or safety, (3) the number of fixed doses in the dose-response studies is limited, and (4) responses are highly variable and it is helpful to explore the underlying causes of variability of response.

2. Providing Support for Primary Efficacy Studies

Exposure-response information can support the primary evidence of safety and/or efficacy. In some circumstances, exposure-response information can provide important insights that can allow a better understanding of the clinical trial data (e.g., in explaining a marginal result on the basis of knowledge of systemic concentration-response relationships and achieved concentrations). Ideally, in such cases the explanation would be further tested, but in some cases this information could support approval. Even when the clinical efficacy data are convincing, there may be a safety concern that exposure-response data can resolve. For example, it might be reassuring to observe that even patients with increased plasma concentrations (e.g., metabolic outliers or patients on other drugs in a study) do not have increased toxicity in general or with respect to a particular concern (e.g., QT prolongation). Exposure-response data thus can add to the weight of evidence of an acceptable risk/benefit relationship and support approval. The exposure-response data might also be used to understand or support evidence of subgroup differences suggested in clinical trials, and to establish covariate relationships that explain, and enhance the plausibility of, observed subgroup differences in response.

Exposure-response data using short-term biomarkers or surrogate endpoints can sometimes make further exposure-response data from clinical endpoint exposure-response studies unnecessary. For example, if it can be shown that the short-term effect does not increase past a particular dose or concentration, there may be no reason to explore higher doses or concentrations in the clinical trials. Similarly, short-term exposure-response studies with biomarkers might be used to evaluate early (e.g., first dose) responses seen in clinical trials.

3. Supporting New Target Populations, Use in Subpopulations, Doses/Dosing Regimens, Dosage Forms, and Routes of Administration

Exposure-response information can sometimes be used to support use, without further clinical data, of a drug in a new target population by showing similar (or altered in a defined way) concentration-response relationships for a well-understood (i.e., the shape of the exposure-response curve is known), short-term clinical or pharmacodynamic endpoint. Similarly, this information can sometimes support the safety and effectiveness of alterations in dose or dosing interval or changes in dosage form or formulation with defined PK effects by allowing assessment of the consequences of the changes in concentration caused by these alterations. In some cases, if there is a change in the mix of parent and active metabolites from one population (e.g., pediatric vs. adult), dosage form (e.g., because of changes in drug input rate), or route of administration, additional exposure-response data with short-term endpoints can support use in the new population, the new product, or new route without further clinical trials.

a. New target populations

A PK-PD relationship or data from an exposure-response study can be used to support use of a previously approved drug in a new target patient population, such as a pediatric population, where the clinical response is expected to be similar to the adult population, based on a good understanding of the pathophysiology of the disease, but there is uncertainty as to the appropriate dose and plasma concentration. A decision tree illustrating the use of a PK-PD relationship for bridging efficacy data in an adult population to a pediatric population is shown in Appendix B. Possible use of PK-PD bridging studies assessing a well-described PD endpoint (e.g., beta-blockade, angiotensin I or II inhibition) to allow extension of clinical trial information performed in one region to another region is discussed in the ICH E5 guidance on *Ethnic Factors in the Acceptability of Foreign Clinical Data*.

b. Adjustment of dosages and dosing regimens in subpopulations defined on the basis of intrinsic and extrinsic factors

Exposure-response information linking dose, concentration, and response can support dosage adjustments in patients where pharmacokinetic differences are expected or observed to occur because of one or more intrinsic (e.g., demographic, underlying or accompanying disease, genetic polymorphism) or extrinsic (e.g., diet, smoking, drug interactions) factors. In some cases, this is straightforward, simply adjusting the dose to yield similar systemic exposure for that population. In others, it is not possible to adjust the dose to match both Cmax and AUC. Exposure-response information can help evaluate the implications of the different PK profiles. In some cases, exposure-response information can support an argument that PK changes in exposure would be too small to affect response and, therefore, that no dose or dose regimen adjustments are appropriate.

c. New dose regimens, dosage forms and formulations, routes of administration, and minor product changes.

A known exposure-response relationship can be used to (1) interpolate previous clinical results to new dosages and dosing regimens not well studied in clinical trials, (2) allow marketing of new dosage forms and formulations, (3) support different routes of administration, and (4) ensure acceptable product performance in the presence of changes in components, composition, and method of manufacture that lead to PK differences. Generally, these uses of exposure-response information are based on an understanding of the relationship between the response and concentration, and between dose and concentration.

Exposure-response data can sometimes be used to support a new dose or dosing schedule (e.g., twice a day to once a day) that was not studied in safety and efficacy clinical trials. Exposure-response information can provide insight into the effect of the change in concentrations achieved with these changes and whether or not this will lead to a satisfactory therapeutic response. The new regimen would usually be within the range of total doses studied clinically, but in

certain circumstances could be used to extend an approved dose range without additional clinical safety and efficacy data. For example, a once-daily dosing regimen could produce a higher Cmax and a lower Cmin than the same dose given as a twice-daily regimen. If exposure-response data were available, it might be considered reasonable to increase the recommended daily dose to maintain a similar Cmin, even without further studies. Exposure-response data are not likely to be useful in lieu of clinical data in supporting new dosing schedules unless the relationship of the measured responses to relevant safety and efficacy outcomes is well understood.

In some cases, exposure-response data can support the approval of a new drug delivery system (e.g., a modified-release dosage form) when the PK profile is changed intentionally relative to an approved product, generally an immediate-release dosage form. A known exposure-response relationship could be used to determine the clinical significance of the observed differences in exposure, and to determine whether additional clinical efficacy and/or safety data are recommended.

Exposure-response data can also support a new formulation that is unintentionally pharmacokinetically different from the formulation used in the clinical trials to demonstrate safety, or efficacy and safety. In the case of new drugs, in vitro and/or in vivo bioequivalence testing alone is usually used to show that the performance of a new formulation (e.g., to-be-marketed formulation) is equivalent to that used to generate the primary efficacy and safety data. It is possible to demonstrate differences in exposure that are real but not clinically important, even when the 90% confidence interval for the bioequivalence measures fall within the standard of 80-125%. It is possible for these bioequivalence studies to fail to meet the standard bioequivalence acceptance intervals of 80-125%. Rather than reformulating the product or repeating the bioequivalence study, a sponsor may be able to support the view that use of a wider confidence interval or accepting a real difference in bioavailability or exposure would not lead to a therapeutic difference. In other cases, where the altered bioavailability could be of clinical consequence, adjustment of the marketed dosage strength might be used to adjust for the PK difference.

In the case of biological drugs, changes in the manufacturing process often lead to subtle unintentional changes in the product, resulting in altered pharmacokinetics. In cases in which the change in product can be determined not to have any pharmacologic effects (e.g., no effect on unwanted immunogenicity), exposure-response information may allow appropriate use of the new product. Exposure-response data are not likely to obviate the need for clinical data when formulation or manufacturing changes result in altered pharmacokinetics, unless the relationships between measured responses and relevant clinical outcomes are well understood.

Exposure-response information could also be used to support a change in route of administration of a drug. An established exposure-response relationship would allow interpretation of the clinical significance of the difference in PK related to the different route. Such information about active metabolites could also be important in this situation.

IV. DOSE-CONCENTRATION-RESPONSE RELATIONSHIPS AND EFFECTS OVER TIME

Depending on the purpose of the study and the measurements made, exposure-response information can be obtained at steady state without consideration of the impact of fluctuations in exposure and response over time, or can be used to examine responses at the various concentrations attained after a single dose during the dosing interval or over the course of treatment. Where effectiveness is immediate and is readily measured repeatedly in the course of a dosing interval (e.g., analgesia, blood pressure, blood glucose), it is possible to relate clinical response to blood concentrations over time, which can provide critical information for choosing a dose and dosing interval. This is standard practice with antihypertensives, for example, where effect at the end of the dose interval and at the time of the peak plasma concentration is routinely assessed and where 24-hour automated BP measurements are often used. Controlled-release decongestants have also been assessed for their effects over the dosing interval, especially the last several hours of the dosing interval.

Often, however, the clinical measurement is delayed or persistent compared to plasma concentrations, resulting in an exposure-response relationship with considerable hysteresis. Even in this case, exposure-response relationships can be informative. Furthermore, safety endpoints can have a time-dependent concentration-response relationship and it could be different from that of the desired effect.

A. Dose and Concentration-Time Relationships

As noted in the ICH E4 guidance for industry on *Dose-Response Information to Support Drug Registration*, dose-response information can help identify an appropriate starting dose and determine the best way (how often and by how much) to adjust dosage for a particular patient. If the time course of response and the exposure-response relationship over time is also assessed, time-related effects on drug action (e.g., induction, tolerance, and chronopharmacologic effects) can be detected. In addition, testing for concentration-response relationships within a single dosing interval for favorable and adverse events can guide the choice of dosing interval and dose and suggest benefits of controlled-release dosage forms. The information on the effects of dose, concentration, and response can be used to optimize trial design and product labeling.

Although dose is the measurement of drug exposure most often used in clinical trials, it is plasma concentration measurements that are more directly related to the concentration of the drug at the target site and thus to the effect. Relationships between concentration and response can, of course, vary among individuals, but concentration-response relationships in the same individual over time are especially informative because they are not potentially confounded by dose-selection/titration phenomena and inter-individual PK variability.

B. Concentration-Response Relationships: Two Approaches

There are two fundamentally different approaches to examining plasma concentration-response relationships: (1) observing the plasma concentrations attained in patients who have been given various doses of drug and relating the plasma concentrations to observed response; and (2) assigning patients randomly to desired plasma concentrations, titrating dose to achieve them, and relating the concentration to observed response. In some cases, concentration-response relationships obtained from these studies can provide insight over and above that obtained through looking at the dose-response relationship.

The first kind of study (# 1 above) is the usual or most common way of obtaining exposure-response information, but this kind of study can be misleading unless it is analyzed using specialized approaches (e.g., Sheiner, Hashimoto, and Beal 1991). Even when appropriately analyzed, potential confounding of the concentration-response relationship can occur and an observed concentration-response relationship may not be credible evidence of an exposure-response relationship. (See ICH E4). For example, if it were found that patients with better absorption, and thus higher concentrations, had greater response, this might not be related to the higher concentrations but to another factor causing both the greater absorption and the greater response. Similarly, renal failure could simultaneously lead to increased plasma concentrations and susceptibility to adverse effects, leading to an erroneous conclusion that concentration is related to adverse effects. Also, a study that titrated only nonresponders to higher doses might show a lower response with higher concentrations (i.e., a *bell-shaped* concentration-response (or dose-response) curve, a result that would not reflect the true population exposure-response relationship). Thus, although it is useful to look in data for such relationships, we suggest that they be subjected to further evaluation. The potential problem of interrelated factors leading to both an effect on pharmacokinetics and an effect on response and therefore an erroneous concentration-response relationship when individuals are not randomized to concentrations generally does not occur when concentration-response relationships in the same individual are observed over time (e.g., over a dosing interval).

The second kind of study (# 2 above) is the randomized, concentration-controlled trial (e.g., Sanathanan and Peck 1991). While less common than the first kind of study, it is a credible controlled effectiveness study. Unlike the first approach, this approach is not affected by the potential confounding factors noted above, such as an unrecognized relationship between pharmacokinetics and responsiveness, or by the random imbalance of influential factors in the way patients are chosen to receive higher doses.

V. DESIGNS OF EXPOSURE-RESPONSE STUDIES

As noted above, exposure-response studies can examine the relationships between randomly assigned dose or plasma concentration and PD response (biomarker, surrogate, or clinical endpoint) or examine the relationship between attained plasma concentration and PD response. The appropriate designs depend on the study purpose. Randomization of patients to different doses or concentrations is an essential aspect of the design of well-controlled studies to establish efficacy, but other designs can also be informative or can suggest further study. The designs of

exposure-response studies discussed here thus also include nonrandomized approaches that can assume mechanistic models for relationships and that do not rely on randomization for making comparisons.

A. Population vs. Individual Exposure-Response

Exposure-response relationships based on data from randomized parallel studies in which each treatment group receives a single dose level provide an estimate of the distribution of individual responses at that dose, but do not provide information about the distribution of individual dose-response relationships. Administration of several dose levels to each study participant (crossover study) can provide information about the distribution of individual exposure-response relationships. The individual data allow examination of the relative steepness or flatness of an individual exposure-response relationship and the distinctions between responders and nonresponders. In such crossover studies, it is important to take sequence and duration of dosing into account, as well as the possibility of sequence and carryover effects.

B. Exposure-Response Study Design

The various exposure-response study designs and their strengths and limitations have been extensively discussed in the ICH E4 guidance on *Dose Response Information to Support Drug Registration.* The statistical considerations in designing dose-response studies are briefly considered in the ICH E9 guidance on *Statistical Principles for Clinical Trials*.

In this section, important study design issues for exposure-response analyses are emphasized and summarized without repeating details already described in the ICH E4 guidance. In general, the rigor of the design (e.g., whether or not the study is adequate and well-controlled) for an exposure-response study depends on the purpose of the study. During the drug discovery and development stage, the exposure-response studies can be more exploratory, because they are intended to gather information for designing later, more definitive studies. In addition, as emphasized in the ICH E4 guidance, it is important to examine the entire drug development database for potentially interesting exposure-response relationships. For example, gender differences in response can sometimes be explained by observed gender-related PK data obtained during trials (population PK data) or in studies obtaining blood samples for measuring plasma concentrations in patients with adverse effects. When an exposure-response study is designed to support regulatory decisions by providing evidence of efficacy, randomization to exposure (dose or concentration) is critical.

The strengths and limitations of various exposure-response study designs are described in the ICH E4 guidance and are briefly summarized in Table I.

Table 1. Points for Consideration in Different Study Designs from the Exposure-Response Perspective

Study Design	Points to Consider in Study Design and Exposure-Response Analysis
Crossover, fixed dose, dose response	• For immediate, acute, reversible responses • Provide both population mean and individual exposure-response information • Safety information obscured by time effects, tolerance, etc. • Treatment by period interactions and carryover effects are possible; dropouts are difficult to deal with • Changes in baseline-comparability between periods can be a problem
Parallel, fixed dose, dose response	• For long-term, chronic responses, or responses that are not quickly reversible • Provides only population mean, no individual dose response • Should have a relatively large number of subjects (1 dose per patient) • Gives good information on safety
Titration	• Provide population mean and individual exposure-response curves, if appropriately analyzed • Confounds time and dose effects, a particular problem for safety assessment
Concentration-controlled, fixed dose, parallel, or crossover	• Directly provides group concentration-response curves (and individual curves, if crossover) and handles intersubject variability in pharmacokinetics at the study design level rather than data analysis level • Requires real-time assay availability

C. Measuring Systemic Exposure

There are many important considerations in selecting one or more active moieties in plasma for measurement and in choosing specific measures of systemic exposure. Some of these considerations are summarized below.

1. Chemical Moieties for Measurement

a. Active moieties

To the extent possible, it is important that exposure-response studies include measurement of all active moieties (parent and active metabolites) that contribute significantly to the effects of the drug. This is especially important when the route of administration of a drug is changed, as different routes of administration can result in different proportions of parent compound and metabolites in plasma. Similarly, hepatic or renal impairment or concomitant drugs can alter the relative proportions of a drug and its active metabolites in plasma.

b. Racemates and enantiomers

Many drugs are optically active and are usually administered as the racemate. Enantiomers sometimes differ in both their pharmacokinetic and pharmacodynamic properties. Early elucidation of the PK and PD properties of the individual enantiomers can help in designing a dosing regimen and in deciding whether it can be of value to develop one of the pure enantiomers as the final drug product. Further description on how to develop information for a drug with one or more chiral centers is provided in an FDA Policy Statement, Development of New Stereoisomeric Drugs.[2]

c. Complex mixtures

Complex drug substances can include drugs derived from animal or plant materials and drugs derived from traditional fermentation processes (yeast, mold, bacterium, or other microorganisms). For some of these drug substances, identification of individual active moieties and/or ingredients is difficult or impossible. In this circumstance, measurement of only one or more of the major active moieties can be used as a "marker of exposure" in understanding exposure-response relationships and can even be used to identify the magnitude of contribution from individual active moieties.

d. Endogenous ligand measurements

The response to a drug is often the result of its competition with an endogenous ligand for occupancy of a receptor. For example, a beta-blocker exerts its effect by competing with endogenous catecholamines for receptor sites. Taking into

[2] This document is available on the Internet at http://www.fda.gov/cder/guidance/stereo.htm.

account endogenous catecholamine concentrations as well as drug concentrations may help explain the overall physiological response in patients with different concentrations of circulating catecholamines. Biorhythms can affect the concentrations of endogenous compounds, which can make adjustments in daily dosing schedule important, as seen in some treatment regimens for hypertension. Consideration of the endogenous ligand concentration and the drug concentration in various tissues, and of the relative affinities of the ligand to the drug can be important to explain concentration-response relationships.

e. Unbound drug and/or active metabolite (protein binding)

Most standard assays of drug concentrations in plasma measure the total concentration, consisting of both bound and unbound drug. Renal or hepatic diseases can alter the binding of drugs to plasma proteins. These changes can influence the understanding of PK and PK-PD relationships. Where feasible, studies to determine the extent of protein binding and to understand whether this binding is or is not concentration-dependent are important, particularly when comparing responses in patient groups that can exhibit different plasma protein binding (e.g., in various stages of hepatic and renal disease). For highly protein bound drugs, PK and PK-PD modeling based on unbound drug concentrations may be more informative, particularly if there is significant variation in binding among patients or in special populations of patients.

A special case of protein binding is the development of antibodies to a drug. Antibodies can alter the pharmacokinetics of a drug and can also affect PK-PD relationships by neutralizing the activity of the drug or preventing its access to the active site.

2. Exposure Variables

Pharmacokinetic concentration time curves for a drug and/or its metabolites can be used to identify exposure metrics such as AUC, Cmax, or Cmin. These simple measurements of exposure ignore the time course of exposure, in contrast to the sequential measurement of concentration over time. The most appropriate representation of exposure will depend on the study objectives, the study design, and the nature of the relationship between exposure and response. If response varies substantially with time within a dosage interval, then the maximum information on exposure-response will normally be retrieved by relating response to concentration within the group and individual subjects. When a single pharmacodynamic response is obtained once on a given sampling day, it may be more appropriate to represent the exposure by more simplified metrics such as AUC, Cmax, or Cmin.

a. Area under the concentration-time profiles (AUC)

The area under the concentration-time full profile is a typical pharmacokinetic variable used to represent the average drug concentration over a time period. It is also a variable that can be used to compare exposure to a drug after multiple doses to single dose exposure. It is frequently useful to correlate long-term drug effects to steady-state AUC, as the effects usually reflect the daily exposure to drug following multiple dosing.

b. Peak plasma concentrations (Cmax)

Peak plasma concentrations of a drug can be associated with a PD response, especially adverse events. There can be large interindividual variability in the time to peak concentration, and closely spaced sampling times are often critical to determining the peak plasma concentration accurately in individual patients. It is important to have a well-designed sampling plan for estimating peak concentrations and be able to account for expected differences in PK profiles (e.g., in Tmax, time to Cmax) due to demographics, disease states, and food effects, if any.

c. Trough plasma concentrations (Cmin)

During chronic therapy, collection of multiple plasma samples over a dosing interval is often not practical. As a substitute, a trough plasma sample can be collected just before administration of the next dose at scheduled study visits. Trough concentrations are often proportional to AUC, because they do not reflect drug absorption processes, as peak concentrations do in most cases. For many of the drugs that act slowly relative to the rates of their absorption, distribution, and elimination, trough concentration and AUC can often be equally well correlated with drug effects.

d. Sparse plasma concentrations

An increasingly common sampling practice in clinical trials is to obtain plasma samples at randomly selected times during the study, or at prespecified but different times, to measure drug concentration and, in some cases, response. With only two or three samples per subject, the usual pharmacokinetic data analysis methods will not be able to make precise estimates of individual PK parameters. In these circumstances, a specialized technique, population PK analysis combined with Bayesian estimation method, can be used to approximate population and individual PK parameters, providing an exposure variable that is more readily correlated to response than the sparse plasma concentrations themselves. This approach is particularly useful when relatively complete PK information is desired, but it is difficult or unethical to sample repeatedly C for example, in pediatric and geriatric populations (see the FDA guidance for industry on *Population Pharmacokinetics*).

e. Plasma concentration-time profiles

In traditional PK studies (not sparse sampling), the concentrations of active moieties are measured over time. This allows not only calculation of AUC but also the determination of concentration versus time profiles over a dosing interval for each individual, as well as the population. This approach yields relatively detailed exposure information that can be correlated to the observed response in individuals. The exposure-response relationship based on concentration-time profiles can provide time-dependent information that cannot be derived from AUC or Cmin.

D. Measuring Response

Broadly speaking, both positive (efficacy) and negative (safety) effects of a drug can be characterized using a variety of measurements or response endpoints. These effects include clinical outcomes (clinical benefit or toxicity), effects on a well-established surrogate (change in blood pressure or QT interval), and effects on a more remote biomarker (change in ACE inhibition or bradykinin levels) thought to be pertinent to clinical effects. All of these measurements can be expected to show exposure-response relationships that can guide therapy, suggest efficacy or safety, dose and dosing intervals, or suggest a hypothesis for further study.

In many cases, multiple response endpoints are more informative than single endpoints for establishing exposure-response relationships. Specifically, less clinically persuasive endpoints (biomarkers, surrogates) can help in choosing doses for the larger and more difficult clinical endpoint trials and can suggest areas of special concern. In most cases, it is important to standardize the measurement of response endpoints across studies and between study sites and/or laboratories.

1. Biomarkers

Biological marker (biomarker) refers to a variety of physiologic, pathologic, or anatomic measurements that are thought to relate to some aspect of normal or pathological biologic processes (Temple 1995; Lesko and Atkinson 2001). These biomarkers include measurements that suggest the etiology of, the susceptibility to, or the progress of disease; measurements related to the mechanism of response to treatments; and actual clinical responses to therapeutic interventions. Biomarkers differ in their closeness to the intended therapeutic response or clinical benefit endpoints, including the following:

- Biomarkers thought to be valid surrogates for clinical benefit (e.g., blood pressure, cholesterol, viral load)
- Biomarkers thought to reflect the pathologic process and be at least candidate surrogates (e.g., brain appearance in Alzheimer's Disease, brain infarct size, various radiographic/isotopic function tests)

- Biomarkers reflecting drug action but of uncertain relation to clinical outcome (e.g., inhibition of ADP-dependent platelet aggregation, ACE inhibition)
- Biomarkers that are still more remote from the clinical benefit endpoint (e.g., degree of binding to a receptor or inhibition of an agonist)

From a regulatory perspective, a biomarker is not considered an acceptable surrogate endpoint for a determination of efficacy of a new drug unless it has been empirically shown to function as a valid indicator of clinical benefit (i.e., is a valid surrogate). Theoretical justification alone does not meet the evidentiary standards for market access. Many biomarkers will never undergo the rigorous statistical evaluation that would establish their value as a surrogate endpoint to determine efficacy or safety, but they can still have use in drug development and regulatory decision making. Changes in biomarkers typically exhibit a time course that is different from changes in clinical endpoints and often are more directly related to the time course of plasma drug concentrations, possibly with a measurable delay. For this reason, exposure-response relationships based on biomarkers can help establish the dose range for clinical trials intended to establish efficacy. In some cases, these relationships can also indicate how soon titration should occur, and can provide insight into potential adverse effects. Biomarkers can also be useful during the drug discovery and development stage, where they can help link preclinical and early clinical exposure-response relationships and better establish dose ranges for clinical testing.

2. Surrogate Endpoint

Surrogate endpoints are a subset of biomarkers. A surrogate endpoint is a laboratory measurement or physical sign used in therapeutic trials as a substitute for a clinically meaningful endpoint that is expected to predict the effect of the therapy (Temple 1999). A well-validated surrogate endpoint will predict the clinically meaningful endpoint of an intervention (Lesko and Atkinson 2001), with consistent results in several settings. FDA is able to rely on less well-established surrogates for accelerated approval of drugs that provide meaningful benefit over existing therapies for serious or life-threatening illnesses (e.g., acquired immunodeficiency syndrome). In these cases, the surrogates are reasonably likely to predict clinical benefit based on epidemiologic, therapeutic, pathophysiologic, or other scientific evidence. However, generally, in trials examining surrogate endpoints, even where the endpoint is well correlated with a clinical outcome, surrogates will be unable to evaluate clinically relevant effects of the drug unrelated to the surrogate, whether these are beneficial or adverse (Temple 1999).

3. Clinical Benefit or Outcome Endpoints

Clinical benefit endpoints are variables that reflect how a patient feels, functions, or survives. Clinical endpoints reflect desired effects of a therapeutic intervention and are the most credible response measurements in clinical trials.

VI. MODELING OF EXPOSURE-RESPONSE RELATIONSHIPS

A. General Considerations

Safety information and adequate and well-controlled clinical studies that establish a drug's effectiveness are the basis for approval of new drugs. Exposure-response data can be derived from these clinical studies, as well as from other preclinical and clinical studies, and provide a basis for integrated model-based analysis and simulation (Machado et al. 2000; Sheiner and Steimer 2000). Simulation is a way of predicting expected relationships between exposure and response in situations where real data are sparse or absent. There are many different types of models for the analysis of exposure-response data (e.g., descriptive PD models (Emax model for exposure-response relationships) or empirical models that link a PK model (dose-concentration relationship) and a PD model (concentration-response relationship)). Descriptive or empirical model-based analysis does not necessarily establish causality or provide a mechanistic understanding of a drug's effect and would not ordinarily be a basis for approval of a new drug. Nevertheless, dose-response or PK-PD modeling can help in understanding the nature of exposure-response relationships and can be used to analyze adequate and well-controlled trials to extract additional insights from treatment responses. Adequate and well-controlled clinical studies that investigate several fixed doses and/or measure systemic exposure levels, when analyzed using scientifically reasonable causal models, can predict exposure-response relationships for safety and/or efficacy and provide plausible hypotheses about the effects of alternative doses and dosage regimens not actually tested. This can suggest ways to optimize dosage regimens and to individualize treatment in specific patient subsets for which there are limited data. Creating a theory or rationale to explain exposure-response relationships through modeling and simulation allows interpolation and extrapolation to better doses and responses in the general population and to subpopulations defined by certain intrinsic and extrinsic factors.

B. Modeling Strategy

In the process of PK-PD modeling, it is important to describe the following prospectively:

1. Statement of the Problem

The objectives of the modeling, the study design, and the available PK and PD data;

2. Statement of Assumptions

The assumptions of the model that can be related to dose-response, PK, PD, and/or one or more of the following:

- The mechanism of the drug actions for efficacy and adverse effects
- Immediate or cumulative clinical effects
- Development of tolerance or absence of tolerance
- Drug-induced inhibition or induction of PK processes
- Disease state progression
- Response in a placebo group

- Circadian variations in basal conditions
- Influential covariates
- Absence or presence of an effect compartment
- Presence or absence of active metabolites and their contribution to clinical effects
- The PK model of absorption and disposition and the parameters to be estimated
- The PD model of effect and the parameters to be estimated
- Distribution of PK and PD measures and parameters
- Distributions of intra- and inter-individual variability in parameters
- Inclusion and/or exclusion of specific patient data

The assumptions can be justified based on previous data or from the results of the current analysis.

3. Selection of the Model

The answer to the question of what constitutes an appropriate model is complex. In general, the model selected will be based on the mechanism of action of the drug, the assumptions made, and the intended use of the model in decision making. If the assumptions do not lead to a mechanistic model, an empirical model can be selected. In this case, the validation of the model predictability becomes especially important. The available data can also govern the types of models that can be used. The model selection process can be a series of trial and error steps. Different model structures or newly added or dropped components to an existing model can be assessed by visual inspection and tested using one of several objective criteria. New assumptions can be added when emerging data indicates that this is appropriate. The final selection of the model will usually be based on the simplest model possible that has reasonable goodness of fit, and that provides a level of predictability appropriate for its use in decision making.

4. Validation of the Model

The issue of model validation is not totally resolved. Generally, we recommend that the predictive power of a model be dealt with during the study design as well as in the data analysis stages and that the study be designed to yield a predictive model. When plausible exposure-response models are identified based on prior knowledge of the drug before conducting an exposure-response study, the predictive power of the final models derived from the study results becomes a function of study design factors, such as number of subjects and sampling plan. The predictive power can be estimated through simulation, by considering distributions of pharmacokinetic, pharmacodynamic, and study design variables. A robust study design will provide accurate and precise model parameter estimations that are insensitive to model assumptions.

During the analysis stage of a study, models can be validated based on internal and/or external data. The ultimate test of a model is its predictive power and the data used to

estimate predictability could come from exposure-response studies designed for such a purpose. A common method for estimating predictability is to split the data set into two parts, build the model based on one set of data, and test the predictability of the resulting model on the second set of data. The predictability is especially important when the model is intended to (1) provide supportive evidence for primary efficacy studies, (2) address safety issues, or (3) support new doses and dosing regimens in new target populations or subpopulations defined by intrinsic and extrinsic factors or when there is a change in dosage form and/or route of administration.

VII. SUBMISSION INFORMATION: EXPOSURE-RESPONSE STUDY REPORT

It is advisable for the general format and content of a clinical study report to be based on that presented in the ICH E3 guidance on the *Structure and Content of Clinical Study Reports*, modified to include measurements of exposure and response and planned or actual modeling and simulation. It is helpful to include a description of the assay methods used in quantifying drug concentrations (if they are components of the exposure measure) as well as assay performance (quality control samples), sample chromatograms, standard curves used, where applicable, and a description of the validity of the methodologies. The report could also contain:

- The response variable and all covariate information
- An explanation of how they were obtained
- A description of the sampling design used to collect the PK and PD measures
- A description of the covariates, including their distributions and, where appropriate, the accuracy and precision with which the responses were measured
- Data quality control and editing procedures
- A detailed description of the criteria and procedures for model building and reduction, including exploratory data analysis

The following components of the data analysis method used in the study would also ordinarily be described: (1) the chosen dose-response or PK-PD model, (2) the assumptions and underlying rationale for model components (e.g., parameterization, error models), (3) the chosen model-fitting method, (4) a description of the treatment of outliers and missing data, where applicable, and (5) diagrams, if possible, of the analysis performed and representative control/command files for each significant model building and/or reduction step. In presenting results, complete output of results obtained for the final dose-response, or PK-PD model, and important intermediate steps can be included.

A complete report would include a comprehensive statement of the rationale for model building and reduction procedures, interpretation of the results, impact of protocol violations, discussion and presentation of supporting graphs, and the ability of the model to predict performance.

It is helpful if an appendix is provided containing the data set used in the dose-response or PK-PD analysis, the programming codes along with the printouts of the results of the final model, and any additional important plots.

Whether the analysis was performed as a result of an add-on to a clinical study or as a stand-alone exposure-response study, it is important that the original study protocol and amendments be included in the appendix.

The FDA's Center for Drug Evaluation and Research (CDER) guidance for industry on *Providing Regulatory Submissions in Electronic Format C NDAs* includes information on how to submit the exposure-response study report in electronic format. Information on electronic submissions to FDA's Center for Biologics Evaluation and Research (CBER) can be found in the guidance for industry on *Providing Regulatory Submissions to the Center for Biologics Evaluation and Research (CBER) in Electronic Format C Biologics Marketing Applications (Biologics License Application (BLA), Product License Application (PLA)/Establishment License Application (ELA) and New Drug Application (NDA))*. FDA is still actively working on standardizing data file formats for exposure-response and other clinical pharmacology data, and plans to provide these standards in future versions of the electronic guidance document. In the meantime, sponsors are encouraged to submit both the reports and data files with BLA or NDA submissions in electronic format. Until the details are included in an electronic BLA or NDA guidance document, sponsors can consult the clinical pharmacology and biopharmaceutics reviewer or team leader on the data sets to be provided and elements to be included in the data sets.

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APPENDIX A: RELATED GUIDANCES[3]

The use of exposure-response relationships is considered in many FDA guidances for industry as well as in various ICH guidances. These guidances can be divided into those that provide general advice and those that provide specific recommendations about the use of exposure-response information to adjust a dosage regimen based on intrinsic and extrinsic factors. The ICH Common Technical Document (ICH M4, Efficacy) suggests a structure to organize the submission of exposure-response information. In addition, the statistical considerations for dose-response studies are briefly described in the ICH E9 *Guidance on Statistical Principles for Clinical Trials.*

A. Guidances Providing General Statements

The value of understanding exposure-response has been recognized in numerous domestic and international guidances. Brief abstracts of these guidances are provided below to focus on exposure-response relationships and the impact of intrinsic and extrinsic factors on these relationships.

1. *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products*

   This guidance provides general information about the efficacy standard (section I) and comments further on the quantity (section II) and quality (section III) of efficacy information needed for a regulatory determination of efficacy based on both statutory and scientific considerations. The guidance focuses on (1) when efficacy for a new product can be extrapolated entirely from existing efficacy studies, (2) when one adequate and well-controlled study of a particular condition, regimen, or dose supported by information from other adequate and well-controlled studies may be appropriate, and (3) when information from a single multicenter study may be appropriate.

2. *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application*

   This guidance provides a description of the format and content of the clinical and statistical data package required as part of a new drug application under Title 21, Code of Federal Regulations (CFR) § 314.50. It emphasizes the importance of conducting an integrated analysis of all clinical and preclinical exposure-response data that forms the foundation for dose and dosing regimen determinations and dose adjustments for subpopulations.

3. *ICH E4, Dose Response Information to Support Drug Registration*

[3] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at http://www.fda.gov/cder/guidance/index.htm or the CBER guidance page at http://www.fda.gov/cber/guidelines.htm.

This guidance describes the purpose of exposure-response information and the uses of dose-response and/or concentration-response data in choosing doses during the drug development process. The guidance emphasizes the importance of developing exposure-response data throughout development. It further comments on the use of population and individual dose-concentration, and concentration- and/or dose-response relationships to provide dosage and administration instructions in product labeling. The guidance notes that these instructions can include information about both starting dosages and subsequent titration steps based on response to the drug, as well as information on how to adjust dose in the presence of factors that are intrinsic (age, gender, race, organ dysfunction, body size, differences in absorption, distribution, metabolism, and excretion) and extrinsic (diet, concomitant medications). The guidance emphasizes the importance of early exposure-response data to allow efficient design of later studies and the value of examining the entire database to assess exposure-response relationships. The guidance further comments on strengths and limitations of various study designs to assess exposure-response. The guidance comments briefly on the use of models to amplify understanding of exposure-response-relationships and, consistent with 21 CFR 314.126, indicates that a well-controlled dose-response study may be one type of study that supports efficacy.

4. *ICH E5, Ethnic Factors in the Acceptability of Foreign Clinical Data*

This guidance provides descriptions of PK and PD studies and expresses PD endpoints as safety and/or efficacy measures of activity thought, but not documented, to be related to clinical benefit (biomarkers), surrogate endpoints, and clinical benefit endpoints. The guidance further defines a PD study as one that describes the relationship between a pharmacological effect or clinical benefit effect in relation to dose or drug concentration. The guidance establishes a classification system of intrinsic (genetic polymorphism, age, gender, height, weight, lean body mass, body composition, and organ dysfunction) and extrinsic (medical practice, diet, use of tobacco, use of alcohol, exposure to pollution and sunshine, practices in clinical trial design and conduct, socioeconomic status, compliance with medication) ethnic factors that can affect safety, efficacy, dosage, and dosage regimen determinations. The guidance provides an additional set of factors that indicate whether a drug may be sensitive to ethnic factors (linear PK, flat PD curve, wide therapeutic range). It focuses on the bridging studies that may be critical for an application in a new region based on a clinical data package developed in another region. These bridging studies range from those that establish similarity of exposure-response relationship in the two regions for a well-established PD effect (e.g., ACE inhibition or short-term blood pressure response) to a controlled trial in the new region, preferably a dose-response study, using the pertinent clinical endpoint.

B. Guidances Providing Specific Statements

FDA has issued final or draft[4] guidances that focus on how to adjust dosages and dosing regimens in the presence of selected intrinsic and extrinsic factors. A general theme of these guidances is that information relating exposure to response can be used to adjust dosages and dosing regimens in the presence of influences on PK such as age, gender (demographic factors), impaired organ function (intrinsic factors), or concomitant medications and diet (extrinsic factors). In many circumstances, where the assumption can be made that the exposure-response relationships are not disturbed by these factors, PK data alone can be used to guide dosages and dosing regimens. This principle is articulated in the following FDA guidances:

1. *ICH E7, Studies in Support of Special Populations: Geriatrics*

2. *Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*

3. G*eneral Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products (draft)*

4. *Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data Analysis and Impact on Dosing and Labeling*

5. *Pharmacokinetics in Patients with Hepatic Insufficiency: Study Design, Data Analysis and Impact on Dosing and Labeling (draft)*

6. *In Vivo Metabolism/Drug Interactions Studies: Study Design, Data Analysis and Recommendations for Dosing and Labeling (draft)*

7. *Population Pharmacokinetics*

[4] Draft guidances have been included for completeness only. As draft documents, they are not intended to be implemented until published in final form.

APPENDIX B: PEDIATRIC DECISION TREE INTEGRATION OF PK-PD