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EXPOSURE Response Document: Response Relationships: Study Design, Data Analysis, and Regulatory Applications

September 3, 1999

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This Exposure Response Document focuses on human studies with the understanding that exposure- response information in animal pharmacology/toxicology studies is also highly useful when integrated into the drug development and regulatory review processes (1—Peck, 1991). Integration of pharmacokinetics and pharmacodynamics (PK/PD) throughout all phases of drug development provides for a series of learn and confirm experiences that improve the value of exposure-response relationships (2—Sheiner). Exposure-response information may be amplified by observing changes in plasma concentration and response over time to allow consideration of exposure-response in terms of PK/PD relationships.

BACKGROUND: FDA GUIDANCES

Exposure-response relationships may be represented conceptually as an input/output response surface with three axes [REF: SHEINER'S ARTICLE]: 1) input, i.e., drug exposure (x axis); 2) output; i.e., one or more pharmacodynamic measures/parameters (y axis); and 3) intrinsic and extrinsic patient factors (z axis). Intrinsic and extrinsic factors define demographic and other characteristics of healthy volunteers and/or patients that influence the input/output relationship. The general approach allows a better understanding of safety, efficacy, dosages, and dosage regimens in the general population and in special populations defined by intrinsic and extrinsic factors. The use of exposure-response relationships is considered implicitly and explicitly in many FDA draft and final guidances for industry. The guidances may be divided into 1) those that provide general statements and 2) those that provide specific recommendations about the use of response-response information to adjust a dosage regimen based on intrinsic and extrinsic factors. The ICH Common Technical Document creates a structure to organize the submission of exposure -response information.

Guidances Providing General Statements

The value of understanding exposure- response relationships, and the use of mechanistic models to predict future relationships, has been well established as evidenced by the numerous domestic and international backgrounders/guidelines that address the topic. Brief abstracts of these guidances and guidelines are provided below to emphasize statements that focus on exposure-response relationships and the impact intrinsic and extrinsic factors on these relationships.

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 to allow a regulatory determination of effectiveness based on both statutory and scientific considerations. The backgrounder focuses on: 1) when effectiveness may be extrapolated entirely from existing efficacy studies, 2) when one single adequate and well-controlled study supported by information from other adequate and well-controlled studies may be acceptable; and 3) when information from a single multicenter study may be acceptable. The

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Guidance also comments on statutory language expressed in Section 115 of the Food and Drug Administration Modernization Act that allows a determination of effectiveness based on one adequate and well-controlled study plus confirmatory evidence.

General Considerations for Clinical Trials (ICH E8)

This guideline describes 1) internationally accepted principles and practices for drug development and the conduct of individual clinical trials, 2) approaches to facilitate acceptance of foreign data, and 3) ways to promote a common understanding of general principles, approaches, and definitions of relevant terms for the drug development and regulatory review processes. The guideline emphasizes the importance of exposure-response information in all phases of drug development. This information allows optimal design of subsequent studies, permits an understanding of safety and efficacy outcomes, helps establish dosage and dosing regimens, and permits adjustment of dosage and dosage regimens in the presence of intrinsic and extrinsic factors.

Exposure Response Information to Support Drug Registration (ICH E4)

This guideline describes the purpose of exposure-response information and the uses of exposure-response data in choosing doses and monitoring therapy within the drug development process. The guideline provides sponsors with advice on how to use exposure-response data in early and late phase clinical studies and in the interpretation of study data. The guideline further comments on the use and shape of population and individual dose-concentration, concentration-and/or dose-response to provide dosage and administration instructions in product labeling. The guideline notes that these instructions should include information about both starting dosages and subsequent titration recommendations, as well as information on how to adjust dose in the presence of factors that are intrinsic (age, gender, race, organ dysfunction, weight, body surface area, differences in ADME) and extrinsic (diet, concomitant medications). The guideline emphasizes the importance of early exposure-response data to allow efficient design of later phase studies and the value of examining the entire database to assess exposure-response relationships. The guideline further comments on strengths and limitations of various study designs to assess exposure-response. Generally, the recommendations in this guidance focus on acute, or short-term, exposure-response relationships, which require observations at steady-state and do not consider the impact of fluctuations in drug concentrations and response over time. It is important to recognize, however, that time-dependent or delayed alterations in the exposure-response relationship may occur. The guideline comments briefly on the use of models to amplify understanding of exposure-response relationships and indicates that a well-controlled exposure-response study may serve as primary evidence of effectiveness.

Ethnic Factors in the Acceptability of Foreign Clinical Data (ICH E5)

This guideline provides definitions 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 guideline further defines

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a PD study as one that describes the relationship between a pharmacological or clinical benefit effect in relation to dose or drug concentration. The guideline 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 and efficacy and dosage and dosage regimen determinations. The guideline indicates an additional set of factors that indicate whether a drug may or may not be sensitive to ethnic factors (linear pharmacokinetics, flat PD curve, wide therapeutic range). The guideline focuses on the additional bridging studies that are needed, if any, to achieve acceptance in a new region of a clinical data package developed in another region(s).

Guidances Providing Specific Statements

FDA has finalized or has published in draft a series of 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 exposure-response information may be used to determine the need to adjust dosages and dosing regimens in the presence of age, gender (demographic factors), impaired organ function (intrinsic factors) or concomitant medications and diet (extrinsic factors). In certain circumstances, where the assumption is made that the exposure-response relationships are not disturbed by these factors, PK data alone may be used to guide dosages and dosing regimens. This principle is evident in the following FDA guidances:

- *Studies in Support of Special Populations: Geriatrics*
- *Guideline for the Study of Gender Differences in the Clinical Evaluation of Drugs*
- *General Considerations for Pediatric Pharmacokinetic Studies for Drugs and Biological Products (draft)*
- *Guidance on PK/PD in Patients with Impaired Renal Function: Study Design, Data Analysis and Impact on Dosing and Labeling;*
- *Guidance on PK/PD in Patients with Hepatic Insufficiency: Study Design, Data Analysis and Impact on Dosing and Labeling (draft);*
- *Guidance on In Vivo Metabolism/Drug Interactions Studies: Study Design, Data Analysis and Recommendations for Dosing and Labeling (draft)*
- *Food-Effect Bioavailability and Bioequivalence Studies (draft)*

The ICH Common Technical Document for Efficacy

Based on harmonization efforts now occurring in ICH, a Common Technical Document (CTD) is now in development to serve as a core data package for submission in the ICH regions. Module V/Section C in the draft CTD provides for submission of exposure-response information as follows 1) bioavailability and bioequivalence, 2) human biomaterials, 3) human pharmacokinetic studies; 4) human pharmacodynamic studies; 5) and efficacy and safety studies. Together with the ICH CTD, FDA backgrounders (to include those harmonized in ICH) will provide a rational approach to allow consideration of input/output relationships between exposure and response and

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how this relationship is altered by intrinsic and extrinsic factors. The general objective of these studies is to provide support for safety and efficacy determinations and indicate dosages and dosing regimens that describe optimal drug product use for patient labeling.

INPUT AND OUTPUT MEASUREMENTS OVER TIME

Dose-response information may be generated at steady-state without consideration of the impact of fluctuations in concentration and response over time. Plasma concentration-response data allow a more complete understanding of the impact of the time-dependent fluctuations in PK/PD relationship to amplify information about drug safety, efficacy, dosages, and dosing regimens.

Input: Dose and Concentration-Time Relationships

Dose-response information may be generated at steady-state without consideration of the impact of fluctuations in plasma drug concentrations and response over time. PK/PD studies allow a more complete understanding of the impact of concentration-dependent fluctuations in response to amplify information about drug safety, efficacy, doses and dosage regimens.

1. Dosages and Dosing Regimens

As noted in the FDA guidance for industry *Dose-Response Information to Support Drug Registration*, exposure-response information can help identify an appropriate starting dose and determine the best way to adjust dosage to the needs of a particular patient. Concentration-response information that consider fluctuations over the time of a dosing interval or duration of therapy can also indicate a dose beyond which increases would be unlikely to provide added benefit or that would produce unacceptable side effects. Depending on the drug and its intended use, these general statements may be supplemented by the following more specific information to indicate: 1) whether the usual or average effective dose should be used initially or whether titration is more reasonable; 2) when a dose should be changed and by what magnitude, and 3) time-variant effects on drug action (e.g., induction, tolerance, chronopharmacologic effects). When taken together, this information about input can be expressed in the Dosage and Administration section of product labeling to allow optimal use of the drug product by patients and practitioners.

2. Plasma Concentration-Time Relationships

As stated at 21 CFR 320.26 [CHECK THIS REF], PK studies in healthy individuals and patients describe the time course of an active drug ingredient, therapeutic moiety and/or its metabolites(s) in an accessible biologic fluid such as blood/plasma/serum (hereafter plasma) or urine. The FDA guidance, *Ethnic Factors in the Acceptability of Foreign Data* also defines a PK study as one which determines how a medicine is handled by the body, usually involving measurement of blood drug/metabolite(s) concentrations and

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sometimes concentrations in urine or tissues as a function of time. Pharmacokinetic studies are used to characterize absorption, distribution, metabolism, and excretion of a drug, either in plasma or in other pertinent body regions.

Even though dose is the measure of drug exposure most often used in clinical trials, plasma concentration measures are more directly related to the concentration of the drug at the target site. Even better might be to measure the concentration of drug at the effect site itself. While this is becoming more feasible with the advent of modern imaging technologies to measure labeled drug at the receptor site, current methods generally do not allow this to be done routinely. For this reason, the plasma concentration of the active species is usually chosen as the best PK predictor of clinical response, and the exposure measure is derived from it. Using plasma concentrations rather than dose obviates the problem of intersubject and intraindividual variability in the dose-exposure relationship when attempting to correlate exposure with response. Concentration measurements over a dosing interval makes it possible to describe the temporal change in response with change in exposure and account for variability in the dose-exposure relationship between subjects. PK information may be developed from traditional discrete, or two-stage, studies that depend upon frequent sampling following administration of one or more doses. PK information may also be based on sparse-sampling studies (see the FDA guidance for Industry *Population Pharmacokinetics*).

Output: Response and Response-Time Relationships

PD studies in healthy individuals and patients can describe the time course of positive and negative drug and/or metabolite effects. These effects can be expressed at the subcellular, cellular, tissue, organ, organ system and/or whole body levels. As for PK studies, PD data may be obtained from traditional, discrete sample-rich studies or through population studies based on sparse sampling. PD studies may be incorporated into the design of later phase confirmatory clinical trials that are intended to evaluate the safety and efficacy of a drug as well as into the design of other drug development studies. Careful consideration should be given to the relative value of biomarkers in linking to the PK measures/parameters on one hand, and to the clinical endpoints on the other hand.

Input/Output Linkages

PK/PD studies allow concurrent measurement of changes in concentration and response over time, including the onset and offset of positive and negative responses.. Given the many questions about dosage and administration that may be needed for a particular drug, dose-response information may provide only limited information for the dosage and administration section of product labeling. This is particularly true when the number or range of doses may be limited or the study population constrained in some way, as may occur in late phase confirmatory trials. For this reason, the types of PK/PD information discussed in this backgrounder may substantially amplify the amount of useful information generated in the drug development

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process about how to use a drug in the general population and in specified special populations defined on the basis of intrinsic and extrinsic factors.

DESIGN OF PHARMACOKINETIC/PHARMACODYNAMIC STUDIES

Population vs Individual Exposure-Response

Exposure-response relationships based on data from parallel studies, in which each treatment group receives only one dose, provide only an estimate of the distribution of individual responses at that dose, and not of the distribution of individual dose-response. Administration of several doses to each study participant provides information about the distribution of individual exposure-response. Individual data allows examination of the relative steepness or flatness of the individual PK/PD relationship and distinguishes between responders and non-responders.

Measuring Exposure

1. Chemical Species for Measurement

Active Species

To the extent possible, PK/PD studies should measure the active species which may be the parent drug and/or its metabolite(s). Measurement of all active species is especially important when the route of administration of a drug is changed, given that different routes of administration may result in different concentrations of parent compound and metabolites. Similarly, changes in routes of elimination in the presence of certain intrinsic and extrinsic factors (e.g., hepatic or renal impairment) may also alter the relative proportions of a drug and its active metabolites in plasma.

Racemates and Enantiomers

Many drugs are optically active and are usually administered as the racemate. Enantiomers often differ in both their pharmacokinetic and pharmacodynamic properties. Early elucidation of the pharmacokinetic and pharmacodynamic properties of the individual enantiomers may help in designing a dosing regimen and in deciding whether it may be of value to develop one of the pure enantiomers as the final drug product. Further information 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*.

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Complex Mixtures

Complex drug substances may include drugs derived from animal or plant materials, drugs derived from traditional fermentation processes (yeast, mold, bacterium, or other microorganism), and certain rDNA biotechnology drugs. For some of these drug substances, identification of individual active moieties/ingredients is difficult or impossible. In this circumstance, measurement of only one or more moieties may be useful as "markers" in understanding PK/PD relationships and may even be used to identify the major active moieties.

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 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 may necessitate adjustments in daily dosing schedule, as is seen in some treatment regimens for hypertension. For these reasons, consideration of the endogenous ligand concentration may be needed to explain drug concentration-response relationships.

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 may alter the binding of drugs to proteins and, consequently, their distribution and elimination from the body. These changes can influence the understanding of PK and PK/PD relationships. Where feasible, studies should be performed to determine the extent of protein binding and to understand whether this binding is or is not concentration-dependent. For highly protein bound drugs, PK and PK/PD modeling may be more informative using unbound drug concentrations, particularly if there is significant variation in binding among patients or in special populations of patients.

2. Exposure Measures

PK concentration-time curves for a drug and/or its metabolites may be summarized to express exposure using such measures as AUC, C_{max}, or, C_{min}. Pharmacokinetic models are frequently used to quantify the time course of absorption, distribution and elimination of the active species in terms of a relatively small number of parameter (clearance, volume of distribution, etc.). Models can be estimated from full concentration-time profiles, from trough samples alone, or from even less well-controlled sampling times. To extent that PK parameters are used to summarize and computer exposure, individual-specific values will be more useful as they will reveal inter-and intra-individual exposure variability.

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Full Concentration-Time Profile

In traditional, discrete (two-stage) PK studies, collection and measurement of the active species is possible in a sufficient number of plasma samples in either healthy individuals or patients to fully characterize the concentration versus time profile over a dosing interval for each individual. This approach clearly yields relatively detailed exposure information, and consequently will provide a solid basis for exposure response.

Peak Concentrations

Peak plasma concentrations of drug may be associated with PD response, especially adverse events, but in general, is adequate to describe exposure only for "hit and run" drugs; i.e., those rapidly affecting, and virtually permanently altering their targets. Due to the large interindividual variability in the time to peak, closely spaced sampling times are required to determine the peak level accurately if the estimate used is the observed peak. The design of the sampling scheme should account for variability due to demographics, disease states and food effects, if any.

Trough Concentrations

During chronic therapy, collection of multiple plasma samples over a dosing interval is often not practical. As a substitute, a trough plasma sample may be collected just before the next dose is administered at scheduled study visits. Trough levels are often proportional to AUC, as they do not reflect drug absorption transients, as peak levels may. For drug that act slowly relative to the rates of their PK processes, trough levels, AUC, and other smoothed estimates of the time-integral of drug concentrations may capture most of the variation in levels relevant to effects, and hence make good exposure measures. If trough levels are used, consideration should be given to variations in trough values arising from different doses and dosing intervals. In an individual the same daily dose given at different intervals will yield different trough values. Historical data coupled with observed trough values can be used to assess the impact of the dosing regimen on average exposure.

Sparse Sampling

An increasingly common sampling scheme in clinical trials is to obtain plasma samples randomly, or at prespecified, but different times, at scheduled visits to measure both blood chemistries and drug concentration. With only two or three samples per subject, usual pharmacokinetic data analysis methods cannot be used to determine precise estimates of the set of individual PK parameters. In these circumstances, population PK analysis combined with Bayesian estimation methods can be used to approximate population and individual PK parameters, thereby providing a basis for measuring exposure that is more complete than that available from trough or peak levels, yet not so onerous to obtain as a full kinetic profile.

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This approach is recommended when relatively complete PK information is desired, but it is difficult or unethical to sample repeatedly, e.g., in pediatric and geriatric populations (see the FDA *guidance for Industry Population Pharmacokinetics/February 1999*).

Pharmacodynamic Measures/Parameters

1. General Response Endpoints

Broadly speaking, both positive (efficacy) and negative (safety) effects of a drug may be expressed in terms of biological effect markers (biomarkers), surrogate endpoints, and clinical benefit or outcome endpoints. A quantifiable pharmacological biomarker, surrogate endpoint, or clinical benefit endpoint is one that exhibits a change closely linked in time to the administration of a drug. Generally speaking, biomarkers will more closely relate, in terms of PK-PD understanding, to the administration of a drug and its resulting concentration-time relationships than to clinical benefit endpoints. In many cases, multiple response endpoints are better than single endpoints for use as pharmacodynamic measures/parameters. In all cases, response endpoints should be standardized to conform across studies and between study sites and/or laboratories. As with PK measures of exposure, it is important to determine the interindividual and intraindividual variability in response measures/parameters and the sources of variability. PD measurements should be validated and standardized to conform across studies and between laboratories. The same principles of quality control and quality assurance that are applied to measurements for PK purposes should apply to measurement of PD responses.

Biomarker

Biomarkers may include a broad range of physical signs or quantitative biochemical or physiologic measurements. Biomarkers must be linked by valid scientific theory to expected clinical outcomes through a biologically plausible mechanism of action. From a regulatory perspective, a biomarker is not considered to be an acceptable (surrogate) endpoint for a determination of effectiveness or safety for market authorization, unless it has been empirically shown to function as a valid indicator of clinical benefit/safety: theoretical justification alone does not meet the evidential standards required for market access. Many biomarkers may never undergo the rigorous statistical evaluation needed to establish their value as a surrogate endpoint to allow a determination of effectiveness or safety. This does not mean that they lack utility for drug development and regulation. Biomarkers typically exhibit a different time course compared to clinical endpoints and often are more directly related to the time course of plasma drug concentrations. For this reason, PK/PD relationships based on biomarkers may provide very useful information in the drug development process to establish starting and maintenance doses, to support proof of concept conclusions, to study the impact of drug treatment on the course of a disease, and to suggest the time course of adverse events. To indicate the impact of drug treatment, normal ranges for a biomarker should be adjusted based on subject demographic factors.

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Surrogate Endpoint

Surrogate endpoints are biomarkers that have been successfully demonstrated to be useful predictors of one or more clinical benefit outcomes. A surrogate endpoint, like biomarkers, can be a physiological response, laboratory measurement, or physical sign that is induced by the pharmacological effect of a drug. A goal of the drug development process may be to develop information not only about drug efficacy and safety but also information that establishes the usefulness of a biomarker as a safety and/or efficacy surrogate endpoint. Proof of the suitability of a biomarker as a surrogate endpoint requires that a correlation between the potential surrogate endpoint and one or more positive and/or negative clinical outcome endpoints be demonstrated. While a general approach to establishing a surrogate endpoint is still under study, information supporting the surrogacy of a biomarker may include: 1) information about the pathophysiology and time course of the disease; 2) a mechanistic understanding of drug action relative to the time course of disease pathophysiology; 3) empirical data indicating how much of the clinical benefit outcome of interest is or is not explained by the surrogate endpoint; and 4) development of a convincing PK/PD model reflective of important exposure-response relationship.

Clinical Benefit or Outcome Endpoints

Clinical benefit or outcome endpoints are defined as meaningful endpoints such as survival, onset of serious morbidity, or symptomatic response that can be used as a primary response variable in a clinical trial of effectiveness or as a measure of safety.

2. Specific Types of Response Endpoints

Continuous response

Continuous responses have enjoyed the widest application of PK/PD modeling analysis. The advantage of a graded response is that the change in response can be related to changes in drug concentration over time. The transformation of a continuous response into a binary outcome (with respect to some threshold or cut-off point) inevitable entails a loss of information, and is therefore to be avoided, if no clear pharmacological or clinical rationale support it.

Challenge response

Sometimes it is not practical to wait for episodic events to occur in patients. In these situations, drug effects are often assessed, in a graded fashion, by a physiological or pharmacological challenge such as exercise-induced tachycardia; arrhythmias induced by electronic pacing, methacholine-induced bronchoconstriction, or the isoproterenol stimulation for β -adrenergic blocking drugs. The conditions of the challenge must be well standardized not only within a study but also across studies so that the results are comparable (Holford and Ludden 1994). It is important to keep in mind that to fully understand the PK/PD relationship

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it may be necessary to invoke a pharmacodynamic model that allows for interaction between multiple active moieties i.e. endogenous compound or challenge compound. In some cases, the pharmacokinetics and pharmacodynamics of a challenge compound may be as relevant as that of the primary compound of interest.

Categorical response

In many trials, an important clinical or surrogate response may not be a continuous variable, and at times it may be desirable to describe the time course of a discrete response. In this setting, rather than attempting to define the direct relationship between degree of response and plasma concentrations, the relationship between the probability of each level of response to exposure can be. Logistic regression has usually been used with steady-state data (Perry, 1987) of this type. However, this approach can also be useful in the non-steady-state situation using time and other patient demographics, such as drug concentration, age, weight and gender, as covariates. This approach has been successfully applied to the PK/PD analysis of analgesics (Sheiner, 1994).

Survival response

When the response is time to the occurrence of an event, it is natural to model the time-course of the risk of the event as a function of an exposure covariate. A popular semi-parametric approach, to doing so is the Cox proportional hazards model (Cox, 1974). This approach describes the hazard or risk of a certain event occurring by a certain time as the product of a baseline non-parametric function times a relative (proportional) risk term, given by, the exponential of a linear combination of relevant covariates (exposure, demographics, etc.). This type of model has been used to model the risk relapse during methotrexate maintenance in the treatment of acute lymphoblastic leukemia (George, 1988) and for the assessment of the risk of developing renal dysfunction during cyclosporine therapy (Yee, 1988). The method applies equally well to time-to-cure or to time-to-an-adverse-event. The standard approach requires that the relative risk term be constant over time, although an expanded analysis can accommodate time-varying covariates. A problem with this approach however, is that it is not predictive, as the baseline hazard is non-parametric and is therefore unique therefore to the particular data set being analyzed. Fully parametric survival-type models that may be more predictive are also possible, and these can more easily accommodate non-constant and non-linear influences on the hazard.

Rate response

When the response data are in the form of counts (e.g., seizure frequency), models for the distribution of these integer-valued responses must be used; e.g., Poisson regression models. Counts, like continuous variables are sometimes reduced to a dichotomy so that they can be analyzed e.g., logistic regression. As for continuous variable reducing counts to fewer categories loses information and should be avoided. For example, after administration of an antiepileptic agent, reduction in seizure frequency is often reduced to "response" vs. "no

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response” depending on reaching some clinically meaningful reduction in seizures (e.g., 50% reduction). Regression analysis of the actual counts data using exposure as a covariate would provide a more informative approach, and does not add appreciably to the difficulty of the analysis.

MODELING OF PK/PD RELATIONSHIPS

General Considerations

The conduct of adequate and well-controlled clinical studies in the late phase of drug development to confirm a specific drug effect have become a standard way to allow regulatory decision-making and to allow market access. FDA’s approach to adequate and well-controlled studies is provided in 21 CFR 314.94 and more recently in the ICH Guideline for Industry *Ethnic Factors in the Acceptability of Foreign Clinical Data (ICH E5)*. Empirical or descriptive model based analysis do not establish causality or provide a mechanistic understanding of drug effect, and they are not based on formal scientific/mechanistic models. Scientific (casual, predictive) PK/PD modeling creates a science-based theory to better understand exposure-response relationships. Adequate and well-controlled clinical studies that investigate several doses and are analysed using scientifically reasonable causal models can establish predictive PK/PD relationships for safety and/or efficacy. Simulations of PK profiles and PD outcomes using such models can provide plausible hypotheses about the effects of dosage patterns not actually tested, thereby suggesting dosage regimens with and/or efficacy advantages. Creating a theory of exposure-response through modeling and simulation will allow interpolation and extrapolation to better doses and responses in the general population and to subpopulations defined by certain intrinsic and extrinsic factors. In principle, the exposure/response relationship can be inverted to select the an optimal dosage regimen.

Modeling Strategy

The process of PK/PD modeling should contain the following steps:

1. Statement of the Problem

The objectives of the modeling, the study design and the available PK and PD data should be clearly identified.

2. Statement of Assumptions

The assumptions of the model should be clearly laid out. The assumptions may be related to PK, PD and/or one 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,

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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/parameters, distributions of intra- and inter-individual errors, inclusion and/or exclusion of specific patient data, definition of fixed and/or floating model parameter values. The assumptions should be justified based on previous data or from the results from the current analysis.

3. Selection of the Model

The answer to the question of what constitutes an acceptable model is complex. The model selected should be based on the assumptions that were made and the intended use of the model in decision making. If the assumptions cannot lead to a mechanistic model, an empirical model can be selected by examining the data. In the latter case, the validation of the model predictability becomes especially important. The availability of data may 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 for goodness of fit using one of several objective function criteria. New assumptions can be added when emergent evidence from the data indicates that this is appropriate. The final selection of the model should be the simplest possible, have reasonable goodness of fit, and provide a level of predictability appropriate for its use in decision making.

4. Validation of the Model

The issues of model validation is not totally resolved. Generally, models can be validated based on internal and/or external data. The ultimate test of a model is its prediction power. The predictability is especially important when the model will be used to provide supportive evidence of efficacy and/or safety, justify doses and dosing regimens for different clinical situations, such as change in route of drug administration, and for dosage adjustments in special populations. For details of model validation, see the “Population PK/PD” guidance.

REGULATORY APPLICATIONS (EXAMPLES IN APPENDIX)

This section provides examples of the use of exposure-response relationships in regulatory decision-making. The examples are not intended to be comprehensive, but rather to represent the scope of possible situations where a better understanding of exposure-response relationships may be useful. Sponsors should refer to other FDA guidances for a discussion of the use of exposure-response relationships (see Section II).

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Information to Support the Drug Discovery and Development Processes

The drug development and regulatory review processes may be viewed as a series of explanatory followed by confirmatory phases that provide information about drug efficacy and safety at defined dosages and dose regimens. During drug discovery, screens for PK/PD input/output relationships offer many opportunities to focus on lead compounds. From a drug development perspective, PK/PD linkages between dose and response may be critical in understanding that a drug merits further study, as assessed in early phase 'proof of concept' studies. During clinical trials, PK/PD links can help define doses and dosage regimens for later phase confirmatory trials for safety and efficacy. Depending on the drug and its intended use, drug development scientists may wish to use PK/PD information to allow transition of a biomarkers to a surrogate endpoint. Understanding the exposure/response surface (see Sheiner 1997, CPT) via PK/PD links between exposure and response can amplify understanding of how to determine a dosage and dosing regimen in the general population and adjust this regimen based on intrinsic and extrinsic patient factors. With this information, product labeling can be developed to allow optimal patient and practitioner use.

Information to Support a Determination of Safety and Effectiveness

A regulatory determination of effectiveness and safety based on submission of efficacy and safety data relies primarily on adequate and well-controlled confirmatory clinical trials. General approaches for the design and execution of these studies are considered in E9 and E10. These testing studies require few assumptions, use intent to treat analyses, adopt an inferential mode that seeks to test hypotheses (claims), rather than develop predictive models, generally do not permit interpolation and extrapolation, but offer a high degree of certainty in support of regulatory decision-making. In contrast, PK/PD models linking exposure to response adopt an inferential mode suitable to estimating predictive model, build from prior knowledge, work to establish causality via a mechanistic understanding of drug action, allow interpolation and extrapolation, and may require many assumptions. PK/PD studies offer opportunities to: 1) support a regulatory determination when lesser certainty is appropriate; 2) supplement late phase confirmatory studies to increase certainty when data from empirical studies are not fully capable of supporting a regulatory judgment of safety and effectiveness; and 3) extend the use of a drug to a new patient population and/or to a patient population with a closely related disease. Generally, the PK/PD links between exposure and response with these various approaches focus on the y axis in the response-surface relation, where the response is considered either in terms of a surrogate endpoint or one or more clinical outcomes of interest.

1. Accelerated Approval

When the pathophysiology of a disease and the mechanism of action of a drug are well understood, market access may be allowed based on a specific validated surrogate endpoint predictive of clinical benefit, which may be supported by a demonstrated dose- and or concentration-response (PK/PD) relationship. The general approach has been established in FDA's accelerated approval regulations (cite) and subsequently codified in FDAMA. Post-

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approval clinical efficacy and safety data is needed as part of the accelerated approval regulations.

Example (accelerated approval where a surrogate was used and a PK/PD model helped)

2. Supplement Late Phase Empirical Studies

PK/PD information may be used as evidence of safety and/or effectiveness when the primary clinical evidence is equivocal, confusing or if the trial design failed to take into account important PK/PD characteristics of the drug. In some circumstances, PK/PD information can provide important insights that can allow a better understanding of the clinical trial data. Even when the clinical efficacy data is convincing, there may be a safety concern which PK/PD data can resolve. PK/PD data thus can add to the weight of evidence of an acceptable risk/benefit ratio to support a regulatory decision to allow market access.

Example (empirical evidence not entirely there—PK/PD models helped.)

3. New Target Population

A PK/PD relationship or data from a PK/PD study may be used to support market use of a previously approved drug to a new target patient population. This approach is discussed specifically in E5 where PK/PD bridging studies may allow extension of clinical trial information performed in one region to another. Similarly, PK/PD information may be used to extend the use of a drug to patients with a closely related disease. This may be appropriate when high prior certainty exists about a drug's mechanism of action and in the presence of a sound understanding of the pathophysiology of both disease conditions.

Example:

Information to Support Dosages and Dosing Regimens

The exposure response relationship is frequently used to establish 1) the optimal dose in the general patient population; 2) to determine whether a drug has a narrow or wide therapeutic range; 3) to interpolate and/or extrapolate to new dosages and dosage regimens not well studied in late phase confirmatory trials; 4) to allow line extensions (new drug products); 5) to support drug administration via different routes of administration from the one initially studied in confirmatory safety and efficacy studies; 6) to document unchanged product performance (bioequivalence) in the presence of changes in components and composition and method of manufacture. Generally, these uses of PK/PD information to link dose and response focus on the horizontal axis (x axis) of the exposure/response surface.

1. Choosing a Good Dose

BACKGROUNDER

Example

2. PK/PD to establish a therapeutic index

Information about the therapeutic index of a drug is fundamental to designing safe and effective doses and dosing regimens, and for deciding if it is appropriate to adjust a dosing regimen when there is a change in systemic exposure as a result of patient factors. The classical definition of therapeutic index is the ratio of the dose that is toxic in 50% of subjects, to the dose that is efficacious in 50% of the subjects. A functional definition of therapeutic index is the distance between, or relative position of, an exposure-response curve for efficacy (therapeutic benefit), and an exposure-response curve for safety (side effects). Ideally, a dose and dosing regimen should be selected on the basis of achieving maximal clinical benefit by adjusting the input rate of a drug to achieve a balance between the two exposure-response curves.

Example

3. PK/PD to allow other doses

PK/PD data to make regulatory decisions regarding new doses, dosing schedules (e.g., twice a day to once a day). PK/PD information provide insight into the range of concentrations achieved with these changes and whether or not this will lead to a satisfactory therapeutic response. PK/PD data and an appropriate model may be used to approve a dosing regimen that was not studied in clinical efficacy trials. The approved regimen is usually within the range of regimen studied clinically, but could not be used to extend an approved dose range without additional clinical safety and efficacy data.

Example (ketorolac)

4. Line Extensions

PK/PD data may support market access for a new drug delivery system, e.g., a modified-release dosage form, when the pharmacokinetic profile changes intentionally relative to an approved product, e.g., an immediate-release dosage form. In principle, a known PK/PD relationship is used by regulatory authorities to determine the clinical significance of the magnitude of PK change, and to determine if additional clinical efficacy and/or safety trial data is necessary.

5. New Routes of Administration

Words

Example:

6. Changes in Components/Composition and Method of Manufacture

BACKGROUNDER

PK/PD data may be used to justify market access for a to-be-marketed formulation that is pharmaceutically equivalent and otherwise unintentionally different from the formulation used in the clinical trials to demonstrate efficacy and/or safety. Some type of in vitro and/or in vivo bioequivalence testing may be used to document that the performance of a to-be-marketed formulation is equivalent to that used to generate the primary efficacy and safety data. At times, these BE studies may fail to meet the standard bioequivalence intervals of 80-125% using a 90% confidence interval. Rather than reformulating the product or redoing the BE study, a sponsor may make a claim, based on PK/PD, that the wider confidence interval does not indicate a risk of safety or a loss of effectiveness. This example is similar to extrapolation to a new dose. It also relates to setting the goalposts and the use of population and individual BE criteria.

Adjustment in Dosages and Dose Regimens in Subpopulations Defined on the Basis of Intrinsic and extrinsic factors

PK/PD information linking dose and response can support regulatory decisions about dosage adjustments in patients where pharmacokinetic differences are expected or observed to occur because of one or more intrinsic and/or extrinsic factors. As defined in E5, PK/PD data is strongly encouraged as the basis for label language related to specific adjustments in starting or maintenance doses for these special patient populations. Sponsors may use PK/PD data to establish population and/or individual goalposts for therapeutic equivalence. In this way, a sponsor can provide a rational basis to make a label claim that dosage adjustments are not needed for specific changes in pharmacokinetics, e.g., in the presence of a drug-drug interaction. Use of PK/PD information to link dose and response in this setting focuses on the z axis of the exposure response surface.

1. Intrinsic Factors

An important regulatory use of the distribution of individual PK/PD relationships is to determine the clinical significance of intrinsic (e.g., gender, race, age, renal and hepatic disease) and extrinsic (e.g., drug-drug interactions, smoking, diet) factors that result in differences in pharmacokinetics between patients. This leads to appropriate label language to assist prescribers in choosing the starting dose of a drug based on individual patient characteristics. PK/PD information could also lead to recommendations in the label on when to alter the dose.

Example:

2. Extrinsic Factors

Diet

On occasion a sponsor may wish to make a label claim of no food effect based on a food effect bioavailability or BE study. However, if the food effect is greater than $\pm 20\%$ or

BACKGROUND

exceeds a confidence interval of 70-143% , the absence of a food effect cannot be claimed. However, a sponsor may be allowed to make such a claim in this case if there is a known PK/PD relationship.

Example:

SUBMISSION INFORMATION: PK/PD STUDY REPORT

The general format and content of a clinical study report should follow ICH E3. Components of a PK/PD study report that should be emphasized include: 1) summary, 2) introduction, 3) objectives, hypotheses, and assumptions, 4) materials and methods, 5) results, 6) discussion, 7) application of results, 8) appendix, and 9) electronic format files. These sections are discussed briefly here.

Summary

The summary should provide an overall synopsis of the PK/PD study. It should include information on the context of the study and an indication of the PK/PD study's findings and conclusions.

Introduction

The introduction should briefly state the general intent of the study. It should include enough background information to place the PK/PD study in its proper context within the drug's clinical development and indicate any special features of the PK/PD study.

Objectives, Hypotheses, and Assumptions

All objectives of the study and analysis should be stated clearly. Any modifications made to the objectives retrospectively should be noted and explained. The report should state clearly what assumptions have been made including the rationale. Typically a statement of the hypothesis being tested is included.

Materials and Methods

This section should describe the study procedures, including the study design, planned sample size, and patient selection information, which would contain selection criteria and specific center information. Information about the medication (the drug, dose, timing of doses, compliance) should be documented. Assay and data collection and analysis methods should be described in detail (see below). When multiple PK and/or PD studies are pooled for analysis, such demographic data should also be listed separately for each of the PK or PD studies. Pooling of studies of different designs should be justified.

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1. Exposure measures

This section should contain a description of the assay method(s) used in quantitating drug concentrations. (if they are components of the exposure measure). Assay performance (quality control samples), sample chromatograms, and standard curves should also be included, where applicable. The validity of the method(s) should be described.

2. PD measures

This section should contain a description of the pharmacodynamic measure and its relationship to the clinical outcome. The reliability and repeatability of the measure should be documented.

3. Data Collection

The report should contain the response variable and all covariate information and explain how they were obtained. The report should include a description of the sampling design used to collect the PK and PD measures and a description of the covariates, including their distributions and, where appropriate, the accuracy and precision with which they were measured. Data quality control and editing procedures should be described in this section.

4. Data Analysis Methods

This section should contain 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 should be described here: (1) the chosen PK/PD model, (2) the assumptions and underlying rationale for model components (e.g., parameterization, error models), and (3) the chosen model-fitting method. In addition, this section should contain a description of the treatment of outliers and missing data (where applicable), as well as a flow diagram(s) (if possible) of the analysis performed and representative control/command files for each significant model building/reduction step

Results

The actual sample size (number of patients and number of PK or PD measurements) should be given. Mean, median, standard deviation and range of pertinent demographic data for patients included in the PK/PD analysis should be provided. Protocol violations as well as type should be noted. The key results of the analysis should be compiled in comprehensible tables and plots. Diagnostic plots used to develop the model and test reliability should be included. To aid interpretation and application, a thorough description of the results should be provided. Complete output of results obtained for the final PK/PD model and key intermediate steps should be included. A comprehensive discussion of model building and validation is available in the Backgrounder for Industry: Population Pharmacokinetics.

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Discussion

The report should include a comprehensive statement of the rationale for model building and reduction procedures, interpretation of the results, impact of protocol violations, and discussion and presentation of supporting graphs. The outcome of the modeling should also be discussed in terms of predictive performance.

Application of Results

A discussion of how the results of the analysis will be used (e.g., to support labeling, individualize dosage, safety, or to define additional studies) should be provided. A discussion of the relationship between statistical significance and clinical relevance should also be included. In addition, the use of graphics to communicate the application of a PK/PD model (e.g., for dosage adjustment) is recommended.

Appendix

The appendix should contain a representative portion of the data set used in PK/PD analysis. The programming codes along with the printouts of the results of the final model should be included, as well as any additional plots that are deemed important. Whether the analysis was performed as a result of an add-on to a clinical study or a stand-alone PK/PD study, the original study protocol as well as amendments should be included in the appendix.

Electronic Files

FDA's guidance for Industry *Providing Regulatory Submissions in Electronic Format-NDA*s includes information on how to submit the PK/PD study report in electronic format. FDA is still actively working on standardizing data file formats for PK/PD and other clinical pharmacology data and plans on providing these standards in future versions of the electronic backgrounder document. In the meantime, sponsors are encouraged to submit both the reports and data files with NDA submissions in electronic format. Until the details are included in the electronic NDA guidance document, sponsors should confer with the clinical pharmacology/biopharmaceutics reviewer or team leader on the data sets to be provided and elements to be included in the data sets.

Labeling

Where PK/PD model parameter estimates are included in the label, the total number of subjects used for the analysis and the precision with which the parameters were estimated should be included. Where the results of the PK/PD analysis provide descriptive information for the label, it should be stated that the information was obtained from a PK/PD analysis.