*International Journal of Pharmaceutics*, 82 (1992) 9–19
Elsevier Science Publishers B.V.



IJP 02773

# Opportunities for integration of pharmacokinetics, pharmacodynamics and toxicokinetics in rational drug development

*Sponsored by the American Association of Pharmaceutical Scientists, U.S. Food and Drug Administration and American Society for Clinical Pharmacology and Therapeutics*

April 24–26, 1991, Arlington, VA

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(Received 9 January 1992)
(Modified version received 27 January 1992)
(Accepted 27 January 1992)

This report derives from the conference on 'The Integration of Pharmacokinetic, Pharmacodynamic and Toxicokinetic Principles in Rational Drug Development,' held on April 24–26, 1991 in Arlington, VA. The conference was sponsored by the American Association of Pharmaceutical Scientists, U.S. Food and Drug Administration and American Society for Clinical Pharmacology and Therapeutics. The objectives of the conference were: (1) To identify the roles and the interrelationships between pharmacokinetics (PK), pharmacodynamics (PD) and toxicokinetics (TK) in the drug development process. (2) To evolve strategies for the effective application of the principles of pharmacokinetics, pharmacodynamics and toxicokinetics in drug development, including early clinical trials. (3) To prepare a report on the use of pharmacokinetics and pharmacodynamics in rational drug development as a basis for the development of future regulatory guidelines.

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## Introduction

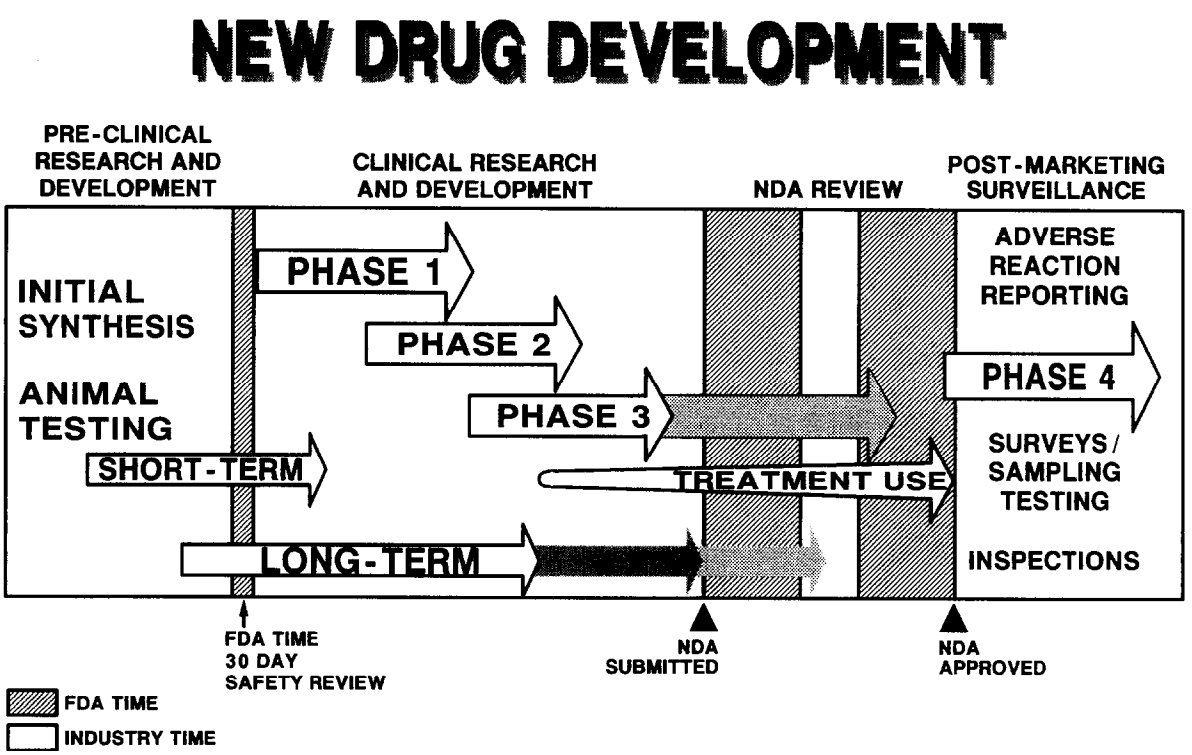
The development process for a new drug involves a series of developmental and evaluative steps carried out (in the U.S.A.) under an Investigational New Drug application (IND) and leading to submission of a New Drug application (NDA). The steps involved in this process and FDA evaluation are illustrated in Fig. 1 and are summarized below. The process includes preclinical research and development and clinical trials, commonly divided into phases 1–3, and NDA review by FDA. For drugs that are shown to be effective and that can be administered with acceptable toxicity, the process results in NDA approval and marketing of the drug.

(A) *Preclinical studies:* The purposes of these studies in experimental animals are to demonstrate, directly or indirectly, the biological activity against the targeted disease; to provide data for toxicity and safety evaluation; and to provide PK and PD data which may be helpful in human dosing regimen development and dose escalation strategies.

(B) *Clinical studies, phase 1:* These studies in healthy volunteers or patients are intended to define the initial parameters of toxicity, the tolerated dose range and general PK and PD characteristics of the drug. The studies also provide information on relevant PK and PD in special populations and on candidate drug delivery systems.

(C) *Clinical studies, phase 2:* These studies in patients are to assess the drug's therapeutic effectiveness and to develop a rational dosing strategy for phase 3 studies, by providing information on dose-concentration-response relationships suitable for designing dosage optimization/individualization strategies applicable in phase 3.

(D) *Clinical studies, phase 3:* These studies in patients are designed to document the clinical safety and efficacy, to further refine the dose-

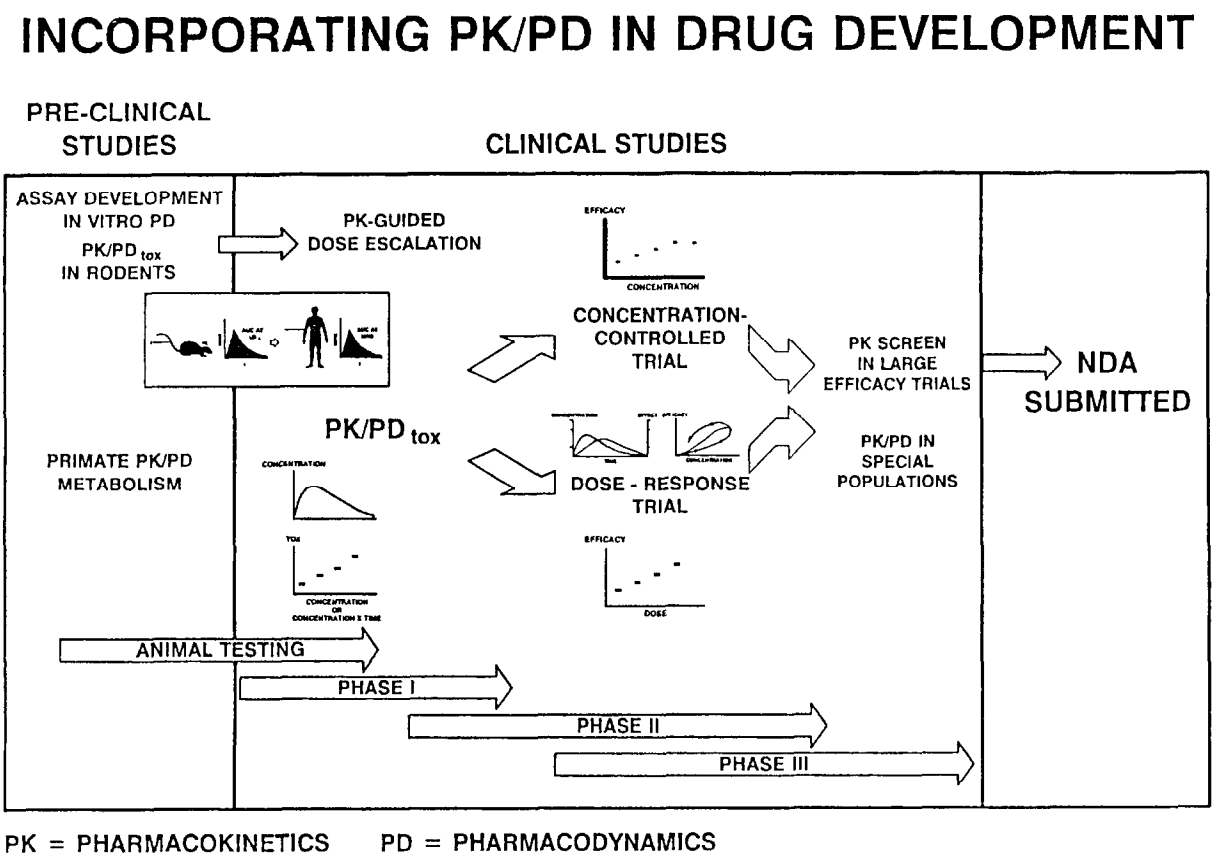


concentration-response relationships and to allow qualitative and quantitative assessment of adverse drug reaction rates.

(E) *Drug labeling / individualization of dosing:* On the basis of data obtained in clinical studies, product information for labeling is generated to provide individualized dosing strategies for optimal use of the new drug.

We believe that the application of PK, PD and TK principles and procedures to the development of a new drug is essential. Incorporation of PK and PD studies along with TK studies in each of these phases, coupled with appropriate and timely evaluation so as to influence subsequent drug development procedures, may lead to earlier identification of optimal dosing regimens, and may contribute to shortening the overall time of drug development. Of equal importance, the increased understanding of drug action derived from PK/PD based drug development leads to a more informative drug development program, especially as regards identification of drug dosage regimens that result in optimal therapeutic outcome through strategies for individualization of dosage. The establishment of this PK/PD information base during premarketing drug development provides an essential framework for continued refinement and improvement during post marketing drug use.

Fig. 2 outlines opportunities for incorporation of these PK, PD and TK assessments at different stages of premarketing drug development. This report summarizes the rationale for incorporating PK, PD and TK in each phase of the drug development process and identifies specific kinds of studies that can/should be carried out.



## Preclinical Pharmacokinetic and Pharmacodynamic Studies

The objectives of preclinical pharmacokinetic and metabolism studies are to obtain information which is useful for: (a) toxicity and safety evaluation studies in animals, by supporting study design, dosing regimen development and interpretation of toxicity data; and (b) initial safety and tolerance studies in man, by providing pharmacokinetic and pharmacodynamic data that may be helpful in dosing regimen development and dose escalation in normal subjects and patients. Informative preclinical information can be helpful in expediting the drug development process.

The following specific kinds of studies will often be of value.

*(A) Development of methodologies for quantitation of drug and metabolite concentrations in biologic fluids*

The availability of specific and sensitive analytical procedures is essential to start any pharmacokinetic or pharmacodynamic research and development program for a new drug. When a major metabolite(s) is (are) known, particularly if pharmacologically active, an appropriate method should be developed for its (their) identification and quantitation in biologic fluids. If the drug and/or its metabolite(s) exhibit chirality, the assay should be stereospecific.

*Note*: Throughout this report, systemic drug concentrations may be used interchangeably with blood, plasma or serum measurements, depending upon which fluid of measurement is most convenient or useful for the drug under study. When analytical methods are developed in plasma or serum, it is useful to know the partition parameter into red blood cells so that drug clearances from blood by organs of elimination may be evaluated relative to organ blood flows.

*(B) Mass balance-metabolism profile and metabolite pharmacology: determination of metabolic pathways and qualitative and/or quantitative measurement of major metabolites in blood, plasma or serum, urine, and other relevant fluids or tissues*

In order to fully understand and interpret toxicology studies, it is essential to determine the fate (absorption, distribution, metabolism and elimination) of the drug in the species used in toxicology testing; it is especially important to discover interspecies differences, including differences from humans. Identification and pharmacologic characterization of individual metabolites is essential in comparing results of preclinical studies with those of human studies.

*(C) Pharmacokinetics and biological fluid concentration monitoring*

Development of a pharmacokinetic data base, which characterizes the time course of drug and metabolite(s) following multiple doses, supports the dosing regimens chosen and is needed to substantiate the extent and duration of exposure in animal toxicology species. Such a data base may also allow results using one dosage form to be extrapolated to another, or may facilitate extrapolation from different animal species to man.

*(D) Relation of systemic drug concentrations to pharmacodynamic endpoints*

Determination of systemic drug concentration ranges that are associated with pharmacological action and toxicological effects of a drug (or its metabolite(s)) may aid in development of human dosing regimens and may indicate the likely steepness of the dose-response curve in man. For planning dose escalation in phase 1 studies in normal subjects and patients, for example, the AUC of $LD_{10}$ in mice of certain oncologic drugs has been shown to correlate with the AUC of the maximum tolerated dose of those drugs in patients.

*(E) Systemic drug concentration monitoring in long-term toxicology studies*

Concentration monitoring is used to determine extent of exposure during safety evaluation studies. This information will allow better interspecies comparisons than simple dose/body-weight comparisons. Knowledge of the intensity and duration of drug exposure is essential for substantiating

safety assessments and will assist in interpretation of unanticipated toxicity.

*(F) Protein binding*

In vitro studies are undertaken to determine the extent of binding to proteins and unbound plasma concentration ranges associated with pharmacological action or toxicity of the drug. The quantitated free fraction values and their concentration dependence can be used to estimate the plasma concentrations of the free drug, which are associated with pharmacological action or toxicity.

*(G) Tissue distribution*

This study is usually conducted with a radiolabeled drug to determine the time course, persistence and potential accumulation of the drug and/or its metabolite(s) in various parts of the animal body. The disposition information can support a metabolism study in man using radiolabeled compound by providing dosimetry data.

*(H) Placental transfer kinetic studies*

These studies may complement reproduction studies.

## Phase 1 Studies

The objective of phase 1 clinical development is to define the initial parameters of toxicity, tolerance and their relation to dosage and the relevant pharmacokinetics of the drug. These studies are usually carried out in healthy volunteers but in the development of drugs to treat AIDS and cancer, where the drugs under study are often highly toxic, phase 1 investigations are undertaken in patients. It is important to realize that 'phase 1' refers both to a stage of development (earliest human exposure) and a kind of study (loosely, any clinical pharmacology), that may occur throughout the clinical development of the drug. The initial (early phase 1) rising dose-tolerance and pharmacokinetic studies are utilized to establish the appropriate dosing program to be incorporated in phase 2 studies. Further phase 1 studies in volunteers and patients, usually carried out during and even after the phase 2 and 3 clinical studies, are intended to characterize the drug's PK and PD in special populations, to optimize the drug delivery system, and to probe potential drug-drug and drug-disease interactions that might be expected to perturb the PK/PD relationship of the drug.

The sequence and timing of phase 1 studies relative to other phases will depend upon the clinical development plan, which will differ depending upon pharmacologic class and pharmacokinetic characteristics of the drug. It is important to incorporate PK/PD studies in the very first dose-tolerance studies in humans since this offers a unique (possibly once only) opportunity to evaluate drug concentration-acute toxic effect relationships of poorly tolerated doses which will be avoided in subsequent studies.

The following description of phase 1 studies does not necessarily reflect the order in which they will be carried out. The major aims in phase 1 studies include the following:

To determine the tolerability and acute toxicity of the drug in normal subjects as a function of dose, duration of dosing, and, where possible, as a function of plasma concentration, prior to initiating phase 2 studies in patients.

To characterize the pharmacokinetics of the drug after a single dose as a function of dose size and, where appropriate after multiple doses.

To characterize the acute pharmacologic effects, and their dose- and plasma concentration-relationships to both the desired clinical outcome and adverse effects.

To assess the suitability (probable predictive value for humans) of the animal models used in toxicology studies with respect to comparability of exposure to the drug and its metabolites.

To evaluate the bioavailability of dosage forms and drug delivery system(s) to be used in clinical studies, including assessment of the effects of food and other clinical variables on the rate and extent of absorption.

To identify special populations or clinical conditions that result in altered pharmacokinetics/pharmacodynamics, requiring dose adjustment during clinical use.

To initiate development of a PK/PD knowledge base for development of algorithms for initi-

ation and adjustment of dosing in individual patients.

The following is a list of the types of studies that relate to these aims.

*(A) Dose-escalation tolerance studies using a variety of designs to expose patients to increasing single, and subsequently multiple doses of drug (often the same patient may receive several doses of the drug)*

These studies can yield at least three kinds of information:

*(1) Dose- and concentration-toxicity relationships* Tolerance studies in humans reveal the first and often the only systematic information in humans at doses near or above maximum tolerated doses, making it possible to correlate acute toxicity with dose and, even better, plasma concentrations of the drug. In addition to systematic blood sampling for PK analysis, whenever possible, in these studies, a blood sample should be taken at each time that an adverse effect is observed. It may also be useful to measure active metabolite(s) at the time of an adverse effect.

*(2) Dose- and concentration-effect (or surrogate for effect) relationship* If a clinically relevant pharmacologic effect can be measured in healthy volunteers and examining it will not compromise the safety outcomes of the study, an initial PK/PD model can be developed. A placebo group (zero dose) may contribute to the validity of such an effort. Where clinically relevant effects are not readily measured, it may be possible in preclinical animal studies to develop surrogate measures which can be used to relate PK parameters to pharmacologic effects. For many drugs, it will not be possible to develop PK/PD models of therapeutic efficacy in phase 1, but a unique opportunity is lost if PK/PD models of acute or subacute toxicity and of some efficacy-related target organ effect(s) are not forthcoming from phase 1 investigations.

*(3) Describing the dose-concentration relationship* Single dose ranging oral studies can yield estimates of PK parameters such as $CL/F$, $V/F$, apparent half-lives, and CLr, as well as the variability and linearity with respect to dose of these parameters in a limited population. The relatively high doses usually employed in dose tolerance tests provide a unique opportunity to study the linearity of pharmacokinetics at concentrations that might occur clinically only through overdosing. Adequate systemic drug concentrations should be obtained following high doses for a sufficiently long period of time so that extrapolated areas will represent only a small fraction of the total area and so that multiple half-lives of disposition may be accurately estimated. The latter is important for determining the relevance of particular half-lives with respect to clearance. If this study is large enough, it may adequately characterize dose proportionality of the drug, but even a small study should detect significant nonlinearity. Parallel measurements of acute drug effects, if possible, will provide data for PD modeling.

*(B) Pharmacokinetic studies to characterize dose and time dependencies or nonlinearities in the same individual after increasing single doses and multiple doses*

In these studies it is important to cover the full range of doses likely to be used clinically. These studies can yield at least two kinds of information:

*(1) Dose-linearity over the therapeutic range after single doses* Crossover single dose studies in healthy volunteers encompassing the dose range anticipated to be studied in phases 2 and 3 provide information on linearity of PK systems and intra- and intersubject variability. If low intersubject variability is encountered in the initial dose-escalation tolerance study such that linearity can be reliably demonstrated, or if PK screening data show clear linearity, these additional crossover single dose studies may not be necessary. This may be especially true if the initial tolerance studies can be designed to allow more than one dose per individual.

*(2) Dose linearity / dose-concentration relationship following multiple dosing* At a dose in the upper end of the anticipated clinical dose range, PK linearity can be evaluated by comparing the PK following a single dose to that during a dosing interval (relevant to the anticipated clinical studies) at steady state in the same volunteers. Multiple dose oral studies yield measures of $CL/F$ and

apparent half-life. Linearity of CL/$F$ with increasing concentrations stability with time of PK parameters or their time dependency (metabolic inhibition, induction) can be determined.

*(C) Intravenous single dose study (with comparison to oral dosing) to rigorously characterize PK*

This study can establish the absolute bioavailability of the drug and a precise model for the disposition characteristics of the drug. When an i.v. solution can be devised, a crossover study of an intravenous dose with an oral dose in healthy volunteers will provide unambiguous measures of $F$, CL, $V$ and allows characterization of the absorption time course profile of the oral dose. Metabolite profiles following oral and i.v. drug administration may provide information on the nature and site of biotransformation. These studies are critical to the complete characterization of the PK and are also important in dosage form development. To facilitate this goal the regulatory agencies should review and attempt to minimize any barriers to i.v. studies in humans for scientific purposes.

*(D) Radioactive tracer studies to assess mass balance and further characterize metabolism and routes of elimination*

Determination of mass balance and the time course of elimination of drugs and major metabolites is highly desirable. If most of the drug and its metabolites can be accounted for in blood and urine (with the guidance provided by animal studies), it may not be necessary to utilize tracer studies. They will be helpful, however, where there is insufficient information on the routes and metabolic pathways of elimination from studies not involving radiolabeled tracers.

It may be useful in some cases to combine administration of an oral radiolabeled dosage form with an i.v. dosage form, particularly when there is significant first-pass metabolism but adequate chemical methods for the identification and quantification of metabolites are not available. Comparison of metabolite ratios following i.v. and oral dosing is important in evaluating first pass metabolism. If the drug is optically active, chiral assays may be employed to investigate stereospecific differences in biotransformation.

*(E) Evaluation of the suitability of preclinical animal models to predict pharmacologic effects in humans*

Data from the studies described in the above sections, referred to as A–D, that characterize the pharmacokinetics of the drug can be used to evaluate the suitability of preclinical animal species used in toxicity studies.

Differences in pharmacokinetics between the small number of animals available for toxicity testing and man may lead to toxicity data that are of limited relevance to clinical use. An adequate preclinical animal model is one that can be dosed such that it will attain blood or tissue levels of drug and active metabolites at least equal to and preferably higher than those attained in humans during therapeutic usage. While this issue is often most critical with respect to the interpretation of carcinogenicity and reproduction studies, it is pertinent also to the earliest human studies. If humans form a major metabolite not seen in animals it may be necessary to study the metabolite in animals by direct administration. However, this would not account for possible reactive intermediate metabolites.

Measures such as AUC, $C_{max}$, $C_{min}$, average steady-state concentrations and degree of fluctuation may be used to compare systemic exposure in toxicology species and humans. Plasma protein binding and the plasma : red blood cell concentration ratio may be factors that influence the concentration of the drug in a target site. The frequency of dosing in the animal model compared to dosage regimens used clinically may be critical in terms of effective exposure because of differences in half-lives and therefore, in degrees of concentration fluctuation at fixed dosage intervals.

The qualitative and quantitative comparison of active and potentially active metabolites with those found in early studies in humans is necessary to validate the animal model. Consideration should be given to chirality of active metabolites.

A complete understanding of the pharmacokinetics of the drug in both preclinical animal mod-

els and humans, including delineation of the relative drug distribution to the organs and routes of elimination, is important to all subsequent development, particularly in anticipating drug and disease state perturbations of PK/PD relationships that should be evaluated in late phase 1 studies.

*(F) Evaluation of the drug formulations and delivery systems*

The importance of the dosage form is often unappreciated, leading to premature commitment to suboptimal formulations. It is unwise to prematurely commit to a particular dosage form prior to full characterization of PK/PD relationships, particularly GI absorption and first-pass elimination characteristics. It is advisable to initiate clinical studies in man using an experimental dosage form that is likely to have good systemic availability based on in vitro stability and dissolution data, and that is flexible in dosage. This is often a solution, suspension or 'neat' capsule. Even these dosage forms must be considered with caution until absolute bioavailability and its variability are documented. Drugs delivered as solutions may have limited bioavailability due to instability in the gastric or intestinal environment. Some suspensions have poor dissolution and absorption due to the suspending agent or decreased effective surface area.

To maximize flexibility and ability to act on information attainable in early studies, the final dosage form can be chosen just prior to the conduct of clinical trials in phase 3, even though candidate formulations may have to be developed earlier for stability studies. The final dosage form should be based on PK/PD relationships established in phase 1/2. Significant differences in rate and extent of absorption between the formulation used in clinical studies and the formulation to be marketed should be avoided, because they may complicate interpretation of the trials. Because it is not always feasible to develop the final dosage form prior to phase 3 clinical studies, it is critical to establish the bioavailability relationships of the to-be-marketed form to the dosage forms used in trials and to evaluate the clinical importance of differences.

The effect of food on the availability of the clinical dosage form should, if at all possible, be known before the pivotal clinical trials are carried out. The effects of food on the systemic availability of a drug may be quite complex. The sponsor should consider the physical-chemical properties of the drug, the performance characteristics of the dosage form and the degree of first pass metabolism in selecting an appropriate test meal(s) for a new drug product. A high fat meal may not be appropriate in all circumstances. Details on the types of food studies that should be done on the marketed dosage form have been listed in the AAPS/FDA Workshops on 'In Vitro and In Vivo Testing and Correlation for Oral Controlled/Modified-Release Dosage Forms' (*Pharm. Res.*, 7 (1990) 975–982).

*(G) Studies in special populations to identify patient characteristics that influence pharmacokinetics and/or pharmacodynamics and therefore require altered dosing or special monitoring*

Depending on the pharmacologic class and the pharmacokinetic and metabolic characteristics of the drug, studies should be carried out in those types of individuals likely to exhibit clinically significant deviations from usual PK/PD behavior. These include patients with dysfunction of the drug elimination systems (e.g., hepatic and renal) that are relevant to the drug; patients with disease states that alter distribution (e.g., obesity or congestive heart failure); patients with genetically determined drug metabolism rates; and patients who are likely to be taking concomitant medication that may interact with the drug. The development plan should also address, using specific studies, or population approaches (see phases 2 and 3 below), methods that allow effects of age, race, body weight and gender to be evaluated. Studies in pediatric and elderly patients are essential when drug use is likely in these age ranges, the therapeutic index is narrow and/or pharmacokinetic variability is high.

Study of these patient and clinical variables is intended to provide information for the package insert to assist the clinician in tailoring drug dosage to optimize therapeutic outcome in individual patients. Therefore, the determinants of

drug dosing rate should use those patient variables that would normally be conveniently available to or measurable by the practitioner (for example, age, body weight and creatinine clearance).

**Phase 2 and 3 Studies**

With the exception of drugs for a few diseases such as AIDS or cancer, phase 2 studies are the first controlled trials in individuals with the disease or condition intended to be treated by the drug. They are usually of relatively short duration and focus on the effects of the drug on clinical and/or valid surrogate endpoints of therapeutic effectiveness. The principal goal of phase 2 is to provide unequivocal evidence of the desired therapeutic effect. Hence, optimal experimental conditions are often employed, including use of relatively uncomplicated patients (little or no concomitant illness or disease), particularly close monitoring and attention to compliance, and attempts to use an unequivocally adequate dose by, e.g., titrating patients to the highest tolerated dose or blood concentration, use of a relatively short inter-dosing interval and use of a variety of therapeutic endpoints to gain an idea as to which is most satisfactory.

A second major goal is to gain information that will guide the additional clinical trials, generally larger and longer, carried out in phase 3, such as the best dose range and titration scheme to use, the optimal dosing interval, needed adjustments of dose for people with organ dysfunction and concomitant medications, etc.

Often, a commercial sponsor does not want the phase 2 (is the drug active in the disease?) to be prolonged and hence, the extra time needed to explore the full dose range and various dose intervals to obtain good dose and concentration response information may not be committed. Moreover, having established some effect at some dose, it is tempting to obtain the wider exposure in phase 3 without ever defining these relationships, hoping that the efficacy will be evident in the further studies and that the adverse effects will be acceptable. Undoubtedly, this approach can be successful and it can be rapid. But on too many occasions failure to define dose-concentration-response relationships leads to unacceptable toxicity or adverse effect rates, marginal evidence of effectiveness (e.g., because the wrong dosing interval or dose was chosen), and a lack of information on how to individualize dosing. This is especially true when phase 3 is designed with a series of concurrent studies, that allow no opportunity for the results of one trial to influence the design of subsequent trials.

Phase 3 studies overlap in intent and design with phase 2 studies and include:

(A) Additional controlled trials to establish effectiveness and dose-concentration-response.

(B) Comparative trials with standard therapy.

(C) Add-on or interaction studies, where the effect of the new agent is examined when added to other therapy.

(D) Studies in special populations, e.g., patients with concomitant illness, varying severity of disease, and specific demographic features (age, gender, race).

(E) Longer-term studies, active-drug controlled or uncontrolled, to establish long-term safety. These usually are only marginally (at best) useful for establishing effectiveness, but can be enhanced by employing randomized dose allocation (e.g., two or more doses of the test drug to gain dose-response information) or a randomized withdrawal phase.

(F) Studies of long-term effectiveness or of clinical effects where only a surrogate end-point has been tested in phase 2.

(G) Studies of different regimens (q.d., where b.i.d. had been studied), titration schemes, or use of loading doses.

While there are no firm guidelines regarding how much of this information should be obtained in phase 2 vs. phase 3, it seems obvious that there must be opportunity, for adaptive modification(s) whether this occurs after phase 2 or during phase 3. Moreover, the 'unexpected' (toxicities, marginal (or lack of) efficacy, etc.) should be anticipated and possible means of understanding it and seeking it out should be utilized. This leads to two important principles.

(1) Dose-concentration and concentration-response information, including an estimate of the lowest useful concentration, the concentration beyond which greater response is not seen (if toxicity does not preclude determination of this parameter), the highest concentration that is tolerated, and understanding of the concentration-effectiveness and concentration-toxicity curves, should be obtained as early in drug development as possible. Similarly, acceptable dose interval(s) should be defined early.

(2) Throughout phases 2 and 3, systemic drug concentration data, apart from those related to concentration-response trials should be routinely obtained on a survey basis to help explain unusual responses, to suggest the possibility for either the presence of or lack of drug-drug and drug-disease interactions, and to identify other unanticipated variability such as metabolic heterogeneity.

Specifically, applying these principles:

(1) Ideally, the first or second phase 2 controlled trial should be a concentration-response study, exploring the full tolerated range (found in phase 1) of the drug. Concentration-response data may be derived retrospectively from randomized dose-response trials or more unambiguously from randomized concentration-controlled trials. While most experience to date is with parallel design trials, it is possible that titration-design trials, if properly analyzed, can provide useful concentration-response and dose-concentration response data. Designs that expose a substantial fraction of the study group to more than one dose level are, however, the only designs that can provide information on the typical shape and distribution of individual dose-response curves. This information is important for dosage optimization, so that some such design (random sequence crossover, dose titration, or other) should be used in at least some studies. Early concentration-response studies should be possible for drugs in a well-developed class, where the basic activity of the drug is readily demonstrated and is highly probable based on clinical pharmacologic measures. Where the fundamental activity of the drug is not clear (first member of a new class) it may be reasonable to use maximum tolerated doses early, turning to concentration-response later, but even here, the lack of prior information about toxicity argues that it is a desirable precaution to include one or more lower dose groups.

(2) A well-designed phase 3 trial will have an organized approach to establishing long-term safety, effectiveness and safety in relevant demographic and disease subgroups, clinical effectiveness where surrogates have been used, identifying the best dose-interval and dose adjustments needed in particular subsets (e.g., age, race, gender, patients with organ system dysfunction).

Even a well-developed and carefully planned program cannot anticipate all possibilities. Moreover, specific studies of all possible subsets and interactions are costly, time-consuming, and, probably unnecessary. The pharmacokinetic screen (a small number of blood level measurements taken in some or all patients), coupled with the sorts of integrated overview analyses of effectiveness and safety data called for in FDA's Guideline to the Clinical and Statistical Sections of an NDA, or using more formal population models, can be used to identify and quantify important demographic and other subset differences. It will therefore be necessary to study formally only those interactions that require very precise definition or that would not be discerned in ordinary clinical studies because the correct measurements have not been taken.

## Drug Labeling / Individualization of Dosing Using PK / PD

It is the objective of labeling to advise the prescriber regarding the safe and effective method of use for a new drug in individual patients. Once the diagnosis has been made and the drug is chosen for use in treatment, then practical pharmacokinetic and pharmacodynamic information should be available in an organized and logical format to serve, when appropriate, as a basis for selection of dose and dosage interval. The known relationships between dose, plasma concentration and drug effects in typical patients may be used as a starting point in dosage individualization. The modifying effects of age, body weight, dis-

ease, and interacting drugs should be disclosed to practitioners, to help them adjust the dose or target exposure to suit the individual patient's needs and the practitioner's therapeutic goals. The entire clinical experience during phases 1–3, in relationship to the derived exposure vs effect relationships should be the basis of dosing recommendations for individualized treatment. The information derived therefore can be utilized in the following ways:

(A) To guide practitioners when monitoring the desired and adverse effects of the drug, in relation to dose or plasma concentrations.

(B) To assist practitioners in optimizing the use of the drug in a variety of patients, the algorithms for dosing particular subsets of patients are incorporated into the Dosing and Administration section. Ideally, labeling will include:

(1) For systemic concentration monitoring (if indicated), the usual therapeutic concentration range, and suggested blood sampling times.

(2) The methods that were used to assess drug response and drug toxicity so that therapeutic/toxic endpoints can be related to dose, exposure or systemic concentrations.

(3) Alerts to the need for dose adjustments for concomitant use of interacting drugs, with attention to interactions that modify PK, PD or both.

(4) The impact of variable compliance on therapeutic or toxic endpoints, if known, and, how this should affect dosing.

(C) To help practitioners appreciate the existence of interpatient variability in response and its causes, and the way to avoid adverse drug experiences due to such variability.

Wording on the label should be developed to communicate to prescribers relevant kinetic and dynamic relationships, including some appreciation of intra- and inter-patient variability and its causes, so that they will be able to individualize treatment. In particular, variability can be expressed as ranges, standard deviations, coefficients of variation, etc. Information about intra-patient as well as inter-patient variability and their sources may be present in formulas, tables, or scattergrams.

## Conclusions

The authors believe that a full understanding of the pharmacokinetics and pharmacodynamics of a new drug in preclinical animal species and humans, provides a scientific framework for efficient and rational drug development. Integration of the principles and practices outlined in this conference report into the drug development process should lead to identification of dosing regimens for individual patients that optimize therapeutic outcome.

## Glossary

| | |
|---|---|
| AUC | area under curve (plasma concentration time profile) |
| CL | clearance |
| CLr | renal clearance |
| $C_{max}$ | maximum concentration |
| $C_{min}$ | minimum concentration |
| $F$ | fraction of dose absorbed |
| $V$ | volume of distribution |

*Disclaimer*

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