Optimizing the Science of Drug Development: Opportunities for Better Candidate Selection and Accelerated Evaluation in Humans*,[7]

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INTRODUCTION

This report is a distillation of two tandem conferences, the first entitled "AAPS, ACCP, ASCPT, FDA Symposium on Clinical Pharmacology: Optimizing the Science of Drug Development," held in September, 1998 in Arlington, Virginia, USA, and the second entitled "5th EUFEPS Conference on Optimizing Drug Development: Fast Tracking into Human," held in December, 1998 in Wiesbaden, Germany. The collective aims of these conferences were:

- To identify critical issues which currently limit drug candidate selection and the early phases of human drug development.
- To explore those modern scientific and technological innovations which could further improve preclinical and clinical development.
- To assess the impact of using modern approaches of clinical pharmacology in the early stages of drug development on the time, cost, quality, and regulatory decisions associated with this process.
- To assess the implications of the new standards for the definition of evidence of efficacy in the US as they relate to International Conference on Harmonisation (ICH) and US regulatory guidances, with special emphasis on the characteristics of confirmatory evidence.
- To generate recommendations for the design and analysis of early phase, state-of the-art clinical studies in healthy volunteers and patients that allow bridging of information from nonclinical to late-phase clinical studies designed to demonstrate safety and efficacy.
- To prepare a combined summary of the two conferences to facilitate communication of these new ideas for optimizing drug candidate selection and early-phase clinical development, as well as to provide a rationale for the development of future regulatory guidances.

Drug discovery, lead candidate selection, and pre-clinical development are undergoing rapid changes, driven in part by scientific advances in areas such as combinatorial chemistry, molecular and cell biology, and high throughput technology, but also by fierce competition and economic forces. As a result, the pressure to accelerate drug discovery and development is increasing, especially in the phases leading up to and during early human clinical testing, where a clear bottleneck exists. Too often, however, the thrust of change has been on process rather than on scientific content. The underlying thesis of both conferences is that there are numerous opportunities for employment of modern pharmaceutical sciences and principles of clinical pharmacology at every step of the development process, to move from an essentially empirical mode to a more mechanistic and predictive one. Doing so will not only provide better therapeutic agents with lower risk, but will also find failures faster, resulting in a more economical and informative development program.

The fundamental concepts which underpin the application of clinical pharmacological methods in the drug development process were laid out in a report published in 1992 from a landmark conference entitled "Opportunities for Integration of Pharmacokinetics, Pharmacodynamics, and Toxicokinetics in Rational Drug Development." (1) The major point made then—and now increasingly accepted—is that the coordinated application of pharmacokinetics (PK) and pharmacodynamics (PD) provides a rational approach to efficient and informative drug development. The general sequence of scientific and regulatory processes involved in drug development are depicted in Fig. 1. These broadly comprise the pre-

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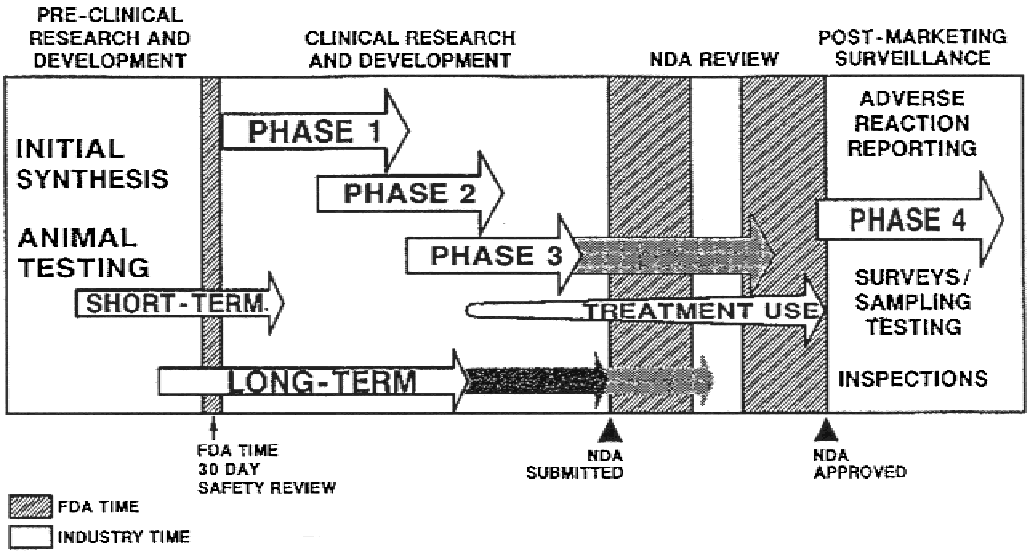

Fig. 1. New drug development. From C. C. Peck, W. H. Barr, L. Z. Benet, J. Collins, R. E. Desjardins, D. E. Furst, J. G. Harter, G. Levy, T. Ludden, J. H. Rodman, Peck, C. C., Barr, W. H., Benet, L. Z., Collins, J., Desjardins, R. E., Furst, D. E., Harter, J. G., Levy, G., Ludden, T., Rodman, J. H., Sanathanan, L., Schentag, J. J., Shah, V. P., Sheiner, L. B., Skelly, J. P., Stanski, D. R., Temple, R. J., Viswanathan, C. T., Weissinger, J., and Yacobi, A. Opportunities for integration of pharmacokinetics, pharmacodynamics, and toxicokinetics in rational drug development. *Clinical Pharmacology and Therapeutics,* **51,** 465, (1992).

clinical or nonclinical phase, sometimes referred to as Phase 0, and the three clinical phases, 1, 2, and 3. Post-marketing surveillance (pharmacovigilance) is commonly referred to as Phase 4.

Regulatory reviews generally take place just before first administration to human volunteers or patients, at the end of Phase 2, at the end of Phase 3 prior to submission, and then intermittently once a drug is marketed. Ideally, the entire process from discovery, lead candidate selection through development, and registration is highly integrated, with overlap and sharing of the informational content across the various phases. In practice, the sharing of information across the phases is often suboptimal.

A Summary of the Pre-marketing Phases of Drug Development

Preclinical Phase (Phase Zero).

As part of the drug discovery process, using chemical library profiling and lead compound optimization, the many thousands of compounds synthesized and tested in high-throughput biological activity screens are narrowed down to relatively few compounds that will be evaluated in Phase 1. The purpose of the preclinical phase is to further narrow drug candidate selection for subsequent evaluation in humans. This is achieved through *in vitro* studies using human cell fractions and cultures, whole animal investigations of metabolism, pharmacokinetics and toxicokinetics, the development and use of biomarkers believed to provide early signals of efficacy and toxicity, and considerations involved in developing an acceptable clinical formulation. A broad, general goal is to integrate knowledge gained from this phase into the decision-making process in the design and conduct of early clinical studies. When it occurs and is bidirectional, this integrative process provides a better understanding of the mechanism of drug action, suggests improved animal models to evaluate drug targets and drug–disease interactions, and helps to design animal experiments which, as second-generation compounds are studied, provide more clinically useful information, predict drug class liability with respect to safety, and generate exposure–response relationships for efficacy and safety which can be extrapolated from animals to humans.

Phase 1

The goals of this phase, conducted in healthy subjects or, in some cases, patients, is primarily to provide information on acute tolerability and safety, dose–plasma concentration profiles, maximum safe doses and concentrations, routes of metabolism and elimination, and initial estimates of the variability associated with these measurements. These data are highly relevant to selecting formulation, dose, dosing regimen and route, and administration in the target patient population. Increasingly, some PD data addressing proof of therapeutic concept using a clinically relevant biomarker may be possible during this phase.

Phase 2

In the first component of this phase (Phase 2A), the primary aim is assessment and confirmation of proof of therapeutic concept (efficacy), and affirmation of acute tolerability, maximum safe dose and plasma concentration, and lack of acute safety issues in patients. In the second component (Phase 2B) concurrent aims are further evidence of efficacy and the exploration of dosage regimens which will be administered to the general target population in Phase 3. This exploration of dosing regimens will include strategies to optimize dosage for individual subgroups of patients, by identification of relevant patient, disease, and external factors influencing exposure (PK) and exposure–response (PK–PD) relationships. Pharmacogenetics and pharmacogenomics will play an increasingly greater role in designing and interpreting Phase 2 studies.

Phase 3

In this confirmatory phase, studies in larger numbers of patients are intended to provide documentation of clinical efficacy and safety, a more complete adverse reaction profile, as well as sources (covariates) and estimates of variability in dose–response due to both PK and PD. This information guides product labeling and strategies for individualized dosing regimens in special populations such as patients with renal or hepatic dysfunction, or the elderly.

Advances in humanized cell based systems, human transgenic animal models, analytical technologies, and computational methods and informatics, combined together with the development of biomarkers and potential surrogate endpoints, modeling and simulation, noninvasive imagining, and functional genomics, if integrated well, will provide a tremendous opportunity to improve and accelerate the drug selection and development processes. Examination and refinement of the regulatory review process, based on sound scientific, legal, and ethical principles will help to encourage such developments.

ADVANCES AND IMPROVEMENTS NEEDED, ORGANIZED BY DEVELOPMENT PHASE

The two conferences focused on domains for advances and improvements that are needed during all phases of drug development, recognizing that these phases are commonly overlapping and integrated. The following were the key domains:

In Vitro and Preclinical Studies (Phase 0)

An initial objective of the early studies in Phase 0 is to identify lead compounds—from the myriad produced—that are most likely to have desirable biopharmaceutical, PK, PD, and clinical properties in humans. High volume preliminary biological screens, requiring little compound, provide relatively coarse information, but allow a subset of potentially useful compounds to be identified. By using greater amounts of material in more specific screening procedures, more refined and detailed information is then obtained on these remaining compounds to facilitate further selection of only the most promising candidates for subsequent evaluation in humans. The point at which discovery research is said to end, and early development and investigation in human begins, varies from one organization to another. This juncture often occurs when the decision is made to invest major resources in a compound to advance into Phase 1, and to obtain the information needed to meet regulatory requirements.

Prediction of Human Pharmacokinetic Properties

Significant progress has been made over the last five years in predicting human absorption and metabolism properties, using data from cell-based systems and from whole animal studies, based on the premise that fewer compounds are likely to be rejected in Phase 1 because of poor PK performance. Many of the improvements in prediction have occurred because of the increasing availability of high throughput biological screens utilizing human cell lines and enzyme systems, and with the associated relevant process rate data incorporated into suitable mathematical models. Nonetheless, there is still room for significant improvement. Many approaches are still largely qualitative, and the goal for the future is to make them more mechanistic and predictive. Among the areas requiring further development are:

- A need to improve and increase the number of human-derived *in vitro* systems, including normal intestinal and brain cell lines, hepatocytes, and transport systems and tissues pertinent to PK and PD, and to validate predictions made using these systems. While some validation of the various methodologies may be done in animals, ultimately, prediction must be tested against actual human data.
- Greater use of suitably-refined whole-body physiologically-based PK models, which use and integrate *in vitro* and whole animal data, is needed to facilitate better prediction (both mean and variability) of human plasma and tissue concentration–time profiles. This mechanistic approach will facilitate, through scale-up and simulation, exploration of various scenarios affecting exposure (*e.g.,* disease, regimens, interactions) likely to arise during drug development.
- Coupling of PK with *in vitro–in vivo* PD responses at the preclinical stage. This would contribute to drug selection and help define the target plasma and tissue concentration–time profiles, as well as the appropriate route and rate of administration, likely to achieve optimal therapeutic response.
- Better and earlier studies of plasma protein binding. Protein binding is a major determinant of the pharmacokinetic features of a compound. Currently, methods to determine protein binding are relatively tedious and time-consuming. Better and more rapid screening methods would facilitate this information being available at an earlier time in the drug selection process.
- Better understanding of structure–PK relationships. This is needed to help the medicinal chemist to more efficiently design molecules with the optimal biological properties. Existing computational methods to relate structure to Absorption, Distribution, Metabolism and Excretion (ADME) and PK profiles are embryonic, and significant improvements are needed if these are to be of greater value.
- More robust bioinformatic software. This is critical for capturing, organizing, and interrelating data among disciplines. A vast amount of data are produced from high throughput screens of ADME and PK processes, and these must be readily accessed throughout drug development.
- More precise and informative PK (and PD) data. The quality and quantity must increase progressively over time, from lead candidate selection through dosing decisions made at all phases of drug development.

Prediction of Biopharmaceutical and Formulation Properties

Many a developmental program falters because a compound has poor biopharmaceutical properties—such as low intestinal permeability and poor absorption—or has problems with dissolution of the compound from the pharmaceutical formulation, leading to low and highly variable bioavailability. The challenge is to reduce or remove these limitations at

the preclinical stage, and if possible have the "optimal" formulation at the time of entry into humans, or alternatively rapidly gain the necessary information to achieve this objective during Phase 1. The issues and improvements needed here are:

- Better computational methods, determined by critically examining structure–function relationships between physicochemical properties, which could substantially reduce the number of compounds that need to be tested.
- Development of nanotechnology approaches that require only minute quantities of compound to characterize the material properties of substances that would also facilitate the selection process at an earlier stage.
- An improved quantitative understanding of the interactions between excipient and compound that would greatly help in selecting the appropriate formulation and reducing subject-by-formulation interactions and intrasubject variability.
- Improved methods are needed to calculate the likely maximum bioavailable dose, a critical parameter that helps determine the maximum possible unit dose strength of the formulation and dosage regimen. Open-minded consideration of all possible routes and rates of administration (including transdermal, intranasal, inhalation, etc.), novel drug delivery systems, and formulation techniques (*e.g.,* nanoparticles, liposomes, etc.) is advised in order to optimize availability of the new drug at its site of action, while minimizing effects at undesirable sites.

Preclinical Efficacy and Safety Data to Facilitate Rapid Entry into Human

Preclinical efficacy and safety assessment strategies to support fast tracking into humans are undergoing significant changes, driven by advances in molecular biology and more mechanistic understanding of drug action. And, while *in vitro* cellular systems (cell lines, subcellular fractions etc.) are increasingly used, it is strongly recommended that traditional animal models continue to be employed. This is because animal studies often provide important insights at an early stage into PK–PD relationships and optimal dosing regimen strategies, as well as allow evaluation of potential risks in teratology, reproduction, and cardiac and hepatic toxicity. Animal models allow evaluation of drug targets as well as target–disease interactions, and can be used to study concentration–response-time relationships associated with a variety of dosing strategies which cannot be readily undertaken in human.

Recent advances in proteomics and pharmacogenomics promise to provide an opportunity to establish better predictive biomarkers and surrogate endpoints for early indication of delayed-onset and/or long-term efficacy and safety outcomes. Preclinical relationships between exposure and biomarkers will also provide scientific support for the rapid assessment of proof of concept (efficacy and safety) in humans.

There is a critical need to develop data bases that permit integration of *in vitro* and *in vivo* data from functional toxicology and exposure–response information, and that facilitate toxicokinetic–toxicodynamic mathematical and/or physiological modeling to provide a "bridge" to assess the range of dosage regimens proposed for clinical assessment of pharmaceuticals in healthy human subjects and/or patients. These data bases could also be used in both retrospective and prospective analyses of safety and toxicology data to provide direction for future changes in preclinical safety testing.

Some further areas needing progress in preclinical assessment include:

- Earlier exploration of genomically identified novel targets involved in the pathogenesis and progression of disease to identify compounds and facilitate informed decisions at the outset of the drug development process.
- Evaluation of a two-stage testing paradigm in which a single tracer dose human clinical trial, justified by a single dose animal toxicology study, serves as a guide to animal species and dosage regimen selection for more extensive animal multidose and carcinogenicity studies. The tracer dosage would be sub-pharmacological, using cold or radioactive or stable isotope-labeled tracer drug doses—if bioanalytical methods are available—to enable safe human exposure.
- Continued discussions of the use of cassette dosing in animals and the development of the screening Investigational New Drug Application (IND) for human testing, both of which are neither routine nor feasible under the current preclinical safety testing programs.

Phase 1 Studies

Historically, the primary objective of Phase 1 first-in-man studies was to assess acute tolerability and safety, and to define the maximum tolerated dose (MTD). Subsequently, with the advent of suitable bioanalytical methods, the objective(s) were expanded to characterization of the biopharmaceutical performance, PK and metabolic profiles, and the relationship between plasma concentrations of drug (and metabolites) and desirable and undesirable effects. As currently practiced, Phase 1 often includes all studies involving healthy subjects or patients who are not the intended population to receive the drug, *e.g.,* patients with renal impairment. These include studies of food and drug interactions, radiolabelled mass balance, dose proportionality assessments as well of effects of various diseases, and various formulations and comparative bioavailability. In the past, bioanalytical work was invariably performed some time after completion of the acute tolerability study, whereas today the design is increasingly more adaptive, with analysis performed during the study to guide subsequent dosing within the same or a subsequent study.

The information gained from Phase 1 studies is sometimes used to select the relevant animal species and the degree of systemic exposure needed for future toxicological, teratogenic, and carcinogenicity assessments. Phase 1 results are also used to guide the design of Phase 2 studies, particularly the dose size and range, frequency and route of administration, and appropriate dosage form, as well as to predict drug exposure in certain patient groups defined by both intrinsic (*e.g.,* age, gender, disease) and extrinsic (*e.g.,* drugs) factors suspected to influence exposure. Despite the value and progress in the informativeness of Phase 1 studies, there are areas for further improvement and utility.

Pharmacokinetic–Pharmacodynamic Assessments

Two significant differences exist in characterizing PK and PD processes. One is specificity. With modern analytical instrumentation, specific PK data can be obtained for each chemical species independently, but many compounds in the same class may evoke the same or similar PD responses. The second is linearity. Most PK processes (absorption, distribution, and elimination) are not saturable in the pharmacologic or therapeutic dose range. Accordingly, the PK of most compounds are linear or dose-independent. In contrast, nonlinearity of the PD response as a function of dose or concentration is normal.

A few companies have reported that PK specificity and linearity is being used advantageously in preclinical screening by the use of "cassette dosing." Cassette dosing involves the simultaneous administration of a mixture of up to 10 and occasionally more compounds, in order to rapidly identify those compounds with desirable PK profiles. These latter compounds are then taken further into PD screens, which requires each compound to be evaluated separately.

Based on the above considerations, there is an argument for exploring the division of Phase 1 into two phases: Phases 1a and 1b. The objective of Phase 1a would be to assess preliminary PK and especially metabolic properties. This phase would involve the administration of a small dose below that which would provide any measurable pharmacological or clinical effect, preferably in solution, of either a single compound or possibly a mixture of compounds given by the desired route. If more than one compound is given simultaneously, it is assumed that the PK and metabolism of each compound be independent of the other compounds administered, based on animal or *in vitro* data. In some instances, this might require confirmation. Only compounds that had desirable PK properties would be evaluated further. PK and metabolism information from this investigation could also be fed back to the discovery and preclinical toxicology teams for further optimization criteria of candidate lead compounds. It is envisaged that only small quantities of compound would be needed at this stage. The objectives of Phase 1b would be to assess acute tolerability and detailed PK, and the biopharmaceutical characteristics, as is done currently.

This two-stage (Phase 1A and 1B) argument is based on scientific credibility and efficiency gains, but has clear ethical implications. Some ethical and practical advantages of this division of Phase 1 are:

- It would minimize the possibility, which exists currently, of volunteers being unnecessarily exposed in high-dose tolerability studies to new chemical entities with poor PK properties, which are unlikely to be developed further.
- It could reduce the number of animals needed in the preclinical screening programs, as well as reduce the amount of compound needed to be synthesized, for compounds dropped at Phase 1a.
- It would provide a rich human data base for developing relationships between *in vitro* and physicochemical data and human PK data, which ultimately can be used in computer models to evaluate drug development scenarios *in situ.* If the compounds were given both orally and intravenously, this development could be extended to refining absorption and biopharmaceutical properties, prior to evaluating formulation issues.

Phase 2 Studies: Proof of Concept

Assessment of "Proof of Concept" (sometimes called Proof of Principle) may have multiple meanings to drug development scientists, ranging from preclinical *in vitro* or animal investigations that establish a postulated pharmacological action, to human trials that demonstrate a pharmacological or clinical effect predicted from preclinical experiments or other human data. A precise definition of the usual "Proof of Concept" human study in Phase 2 of drug development proposed by 5th EUFEPS Conference participants is "a human trial that provides scientifically sound evidence supporting the postulated effect(s) of a new therapeutic drug product, where 'effects' may be relevant pharmacological action or a change in disease biomarkers, established surrogate endpoints, or clinical outcomes, and may be beneficial and/or toxic in nature." Because the Phase 2 Proof of Concept clinical trial (abbreviated POC hereafter), is often used for "go/no-go" (investment) decisions, it has become one of the most critical trials in the development program. While many advances in this phase have been made, particularly by combining PK with PD, there is still considerable room for improvement.

SOME CANDIDATE PROCEDURES FOR ACCELERATING PROOF OF CONCEPT TRIALS

Whole Animal, Mechanism-based, PK–PD Modeling to Forecast Human PK–PD

This preclinical study, discussed in sections "preclinical phase" and "phase 2" of this report, is reiterated here due to the importance of employing early physiologically-based whole animal PK–PD modeling as one of the frameworks for rational and efficient drug development. Here, "PD" refers to biomarkers, including physiological, laboratory, and anatomical (imaging) measurements. Application of this approach to dose selection and escalation in early human trials has a sound, established conceptual basis, having been demonstrated in animals and humans for more than six classes of antineoplastic drugs (2). Among improvements needed for fuller utilization of this approach are implementation of sparse sampling paradigms for animal PK experiments, and expanded demonstrations of the technique with biomarkers that are measurable in both animals and humans; optimally these biomarkers would be noninvasive.

Biomarkers/Surrogate Endpoints

When clinical effects of the new drug are not easily measured or are slow to develop, POC trials are greatly enhanced by the use of biomarkers that serve as rapid and readily measured effects that are causally related to clinical effects. Panels of biomarkers may also provide greater prediction of delayed toxicity. New classes of biomarkers have been identified for safety assessments based on emerging knowledge of genomics and proteomics, such as damage-specific inducible genes, biochemical markers of cell death, chemokines/surface markers of cell infiltration, tissue-specific markers of cell integrity, signaling molecules as functional markers, and other disease progression markers. It is important to distinguish between a

biomarker and a surrogate endpoint. To avoid surprises, proposed surrogate endpoints are suspect until fully validated. Concern about accepting new surrogate endpoints for drug registration has been expressed within the pharmaceutical industry, and by regulatory authorities, unless they are appropriately linked to clinical endpoints using credible study designs and data analysis procedures. As a result, biomarkers are frequently ignored or abandoned after Phase 2, as attention is turned to clinical outcome measures. Recently, the NIH and the FDA have encouraged advancement of biomarker and clinical endpoint concepts, by proposing strict definitions and a statistical framework for validation (3).

Improvements needed to expand the use of biomarker/surrogate concepts include:

- practical procedures for in-development investigations using biomarkers (particularly for novel mechanisms of action) that generate evidence for linkage with clinical endpoints.
- model-based linkage between disease and pharmacological mechanisms or clinical endpoints.
- a shift in emphasis from criterion (empirical) assessment to mechanistic assessment using biomarkers.

Examples of Accelerating Proof of Concept and Drug Development

Contemporary clinical drug development is changing. This statement is based on a comparison of the current situation to the period up to 1995, when a typical New Drug Application (NDA) had a 7-year clinical development phase, up to 60 clinical trials, and over 3000 subjects. The impact of early-intensified clinical pharmacology on subsequent drug development is of particular importance in the selection of dose and dosage regimens for Phase 1, Phase 2, and Phase 3 studies, in guiding dosage adjustments in special populations, in selecting relevant animal species for toxicology, in making go-no-go decisions using POC trials, and in deciding to discontinue drug development. There has been an estimated time savings of 2–24 weeks in Phase 1 and 4–72 weeks in Phases 2 and 3 in recent examples of the value of clinical pharmacology in the drug development process at one major pharmaceutical company (4). There are numerous examples of strategic use of PK–PD in deriving key information about the clinical pharmacology of the drug. The following three examples illustrate well how application of PK–PD modeling using biomarkers and/or surrogate endpoints accelerated drug development.

Remifentanil

This example illustrates the use of the electroencephalogram (EEG) as an efficacy biomarker in the development of new opioid anesthetics, such as remifentanil (5,6). In particular, "fingerprinting" of new drugs during the investigational development phase, using high resolution PK–PD approaches, allowed rational decisions about the efficacy, safety, and differential profiling of the new compound compared to marketed drugs in the same chemical or therapeutic class (7). The derived benefits of this approach included:

- Development of PK–PD relationships that facilitated the go/no-go decision (POC).
- Application of PK–PD early in Phase 1, which, along with effect site computer models, provided nearly optimal dosages for Phase 2 and Phase 3, as well as a greater understanding of onset and offset of the anesthetic agent.

Taxotere

In this case, the value of nonlinear mixed effects modeling of dose–PK–PD relationships using sparse plasma samples was demonstrated (8). Through this analysis, the plasma clearance was shown both to be significantly decreased in patients with hepatic impairment, and that hepatic function was a significant predictor of clinical neutropenia. Furthermore, PK–PD analysis identified patients at risk for neutropenia, and justified the subsequent safety re-analysis of the clinical data base to address questions posed by both sponsor and regulatory authorities, which allowed the sponsor to confirm the safety profile of the drug without waiting for Phase 3 data. The PK–PD data also provided the basis for the labeling, as well as usage recommendations for patients based on liver function tests. In this case, population PK–PD studies provided many advantages including:

- A scientific and clinical basis by which safety concerns were alleviated.
- Avoidance of a specific clinical trial to assess dexamethasone's effects on taxotere clearance.
- Accelerated approval of the drug for market access.
- Provision of key information in the package insert.

Ritonavir

PK–PD studies involving new models of the dynamics of HIV replication (9) played a key role in the accelerated approval of this and other antiviral drugs for market access for the treatment of AIDS patients. The use of efficacy PD surrogate endpoints for efficacy (CD4, viral load) allowed decisions to be made earlier in time, and to be based on relatively smaller numbers of patients than would otherwise be the case. However, it was important here, as is generally the case, that the PK–PD data was robust, with a complete understanding of the biological plausibility of the surrogate endpoint. In the case of ritonavir, and antiviral drugs in general, surrogate endpoints proved of benefit in:

- Assessing the stage of disease or rate of change in disease status or severity.
- Assessing the effects of therapeutic intervention.
- Predicting clinical benefit.

Clinical Trial Design and Analysis

To effectively utilize tools of modern clinical pharmacology, such as population PK–PD analysis and PK–PD models, clinical trial designs, or paradigms, should be considered that are appropriate to the information requirement at hand. Depending on the phase of drug development, the goals of clinical trials may be confirmatory (late phase) or explanatory (early phase). Study designs with a confirmatory perspective include:

- Intent to treat—in which all randomized patients are included in the analysis regardless of whether or not they received the treatment.

- Fixed-dose and dosing regimen designs with analysis of average results over time—which aggregate and integrate responses over time.
- On-drug analyses (or per-protocol analyses)—which address what happens to patients who remain on therapy, and typically excludes patients with missing or problematic data. Is used in combination with intent-to-treat, and should be logically consistent with it.

The features and results of these study designs include a goal of gross hypothesis testing, the use of a null model, treatment for analysis as assigned, relatively few assumptions, low study power, little ability to interpolate/extrapolate or to individualize therapy, and a high degree of certainty.

In contrast, the features and results of explanatory study designs include a goal of estimation, a causal or mechanistic model, treatment for analysis as treated, many assumptions, high study power, greater ability to interpolate/extrapolate and a relatively low or high degree of certainty depending on assumptions.

Attempts should be made to build an explanatory or "learning" perspective into study designs and data analysis that have a confirmatory focus. Some examples of these study design and methods of data analysis include:

- Modified intent-to-treat—which permits exclusions from analysis based on prespecified baseline criteria.
- Instrumental variable analysis—an analysis technique that relies on the existence of one or more variables that induce substantial variation in the treatment variable but have no direct effect on the outcome variable of interest (10).
- Adaptive strategies—which allow the dose in a trial to be varied according to prior responses.
- Dose or concentration response—trial strategies which use a range of doses or target specific drug concentrations in order to demonstrate dose- or concentration-response relationships.

Modifications of traditional confirmatory studies serve to address problems associated with confirmatory trials. For example, with antiviral drugs, pharmacodynamic measurements or surrogate endpoints could be designed into intent-to-treat clinical trials to (1) evaluate initial response and to identify nonresponders before the end of the trial, and remove them, (2) identify the time period of response following fixed-dose administration before assessing clinical outcomes, and (3) establish criteria for loss of response over time in the trial in order to assess the duration of response.

Population PK–PD has been proposed as an approach to accelerating drug development and maximizing the knowledge gained from confirmatory trials. Its usefulness is most evident when it is clear what target patient covariates are considered pertinent for dosing and/or for labeling. It is also important to determine when and how to incorporate a population analysis of PK and PD measurements into a drug development plan. A priori identification of special populations at risk who may require dosage adjustments is a challenge to drug developers, and no one approach will fit all situations. The use of adaptive designs deserves greater consideration. Dose and concentration response trials provide highly informative information relevant to dose selection, especially in Phase 2B.

Accelerating the Drug Development Process

Implementation of modern clinical pharmacology in drug development also accommodates practical process strategies to accelerate drug development. With the emphasis on acceleration, there are only a limited number of options. They include:

- Telescoping or overlapping phases of clinical development.
- Intensifying efforts in a given phase of drug development.
- Combining multiple objectives and efforts, *e.g.,* combining PK goals with clinical goals in a given trial.
- Simplifying clinical programs and shortening timelines.
- Skipping or postponing studies, which is the accelerated approval paradigm.

The challenge in accelerating drug development is to do so without lowering scientific and clinical standards. Experience with accelerated development of antiviral drugs has demonstrated that it is possible to combine study designs and types of efficacy evidence to achieve accelerated development without compromising quality.

Learning and Confirming

The application of good clinical pharmacology to trial design and analysis—as evidenced in the remifentanil, taxotere, and ritonavir examples—raise the question of when a model-based analysis can contribute to regulatory decisions to allow market access. The main issue in this regard is the role of explanatory versus confirmatory analysis models (11). The features of explanatory models include the goal of estimation, and the model is usually causal or mechanistic in nature. Explanatory models are often used for traditional PK–PD studies as conducted in Phase 1, and to determine optimal dose and dosing regimens in Phase 2B. Explanatory models, because they involve various assumptions to generate the model, are used when the certainty required is relatively low and the results are not being used alone for decisions about marketability. However, the results of these models may be robust because many factors are considered—usually with high power. Explanatory models may be especially useful in making label language decisions or in allowing interpolation or extrapolation within or beyond the results of a given clinical trial, and in some cases as supportive evidence for a single trial using confirmatory models.

Confirmatory models have as their most important goal the testing of the null hypothesis of no difference between two treatments. With strictly empiric, confirmatory models, there is greater certainty because the assumptions are few, and this is often required in certain decision-making situations, especially by drug regulators. For example, confirmatory models are used by industry in Phase 2 to confirm efficacy in small patient populations, and in Phase 3 by regulators to confirm safety and efficacy in large patient populations in the context of clinical use. In some cases, confirmatory models have an explanatory component.

For example, as discussed earlier, collection of sparse numbers of plasma concentrations during a confirmatory trial, followed by a population analysis of plasma drug levels,

provides an opportunity to learn about patient covariates, such as intrinsic (*e.g.,* gender) and extrinsic (*e.g.,* coadministration of drugs) factors that affect pharmacokinetics (PK) and possibly explain differences in clinical responses related to variability or changes in PK.

Further Improvements and Utility

Motivated by the urgent need to drastically improve the efficiency and informativeness of drug development programs even further, pharmaceutical developers are seeking ways to optimize each clinical trial by applying novel approaches to the planning and evaluation of clinical trials. Among the most promising new ideas are simulation of trials and development programs, novel statistical approaches to trial designs, and genome-based subject selection.

Modeling and Simulation

Computer assisted modeling and simulation (M&S) of clinical trials is a rapidly advancing approach for optimization of clinical trial designs that can successfully achieve the trials' scientific and therapeutic goals. The modeling employs sound pharmacokinetic and pharmacodynamic data derived from animal or early human studies. Virtual trials are run using proposed clinical trial designs and real world trial attributes (dropouts, variable compliance, various sources of known and random variability, etc.). Currently, this approach has achieved a sound conceptual basis, various modeling and simulation techniques have been identified, and capable software for M&S has become available (12,13).

Improvements needed include:

- Better disease progression models.
- Better approaches to model optimization and validation.
- Consensus-derived standards and 'good practices' (14).
- Improved data collection for M&S during drug development.
- Prospective implementation of the approach from the very early stages of drug development.
- Widespread training of scientists and statisticians that can understand and implement M&S and can communicate with senior management.

Novel Statistical Approaches

Phase 2 and 3 trials have to date largely employed empirical, frequentist, hypothesis-oriented trials of fixed (often simple) design with minimal assumptions. Although known to be inefficient and minimally informative, fixed-dose in duration, parallel group designs have dominated. Novel statistical approaches have been proposed that aim to achieve greater efficiency in learning and confirming trials, by employment of adaptive clinical trial designs and pharmacologically informed crossover designs. In the limit, such approaches could compress trials in size and duration, or even collapse development phases such that traditional goals of Phases 2 and 3 are achieved in a single adaptively designed clinical trial. Despite these potential benefits, adaptive and crossover designs are currently underutilized. Improvements needed include better training of statisticians in pathophysiology and pharmacology so they can couple knowledge of modern pharmacology with clinical trial designs, analysis, and interpretation. Strategies for increasing awareness and receptiveness of these approaches in the regulatory sector are also needed.

Genome-Based Subject Selection

Advances in pharmacogenetics and genomics may improve the power of human trials by using techniques for trial subject selection on the basis of genetic profiles that improve diagnostic certainty or optimize pharmacogenetic acceptability. Practical pharmacogenetic profiling techniques are currently under development (*e.g.,* chip-based gene screens for human drug metabolizing enzymes) while the impending full sequencing of the human genome promises additional techniques for identification of genetic factors that affect efficacy or safety of new drugs. Advances in the understanding of the genetic basis of disease will also result in new leads in phenotyping of disease states and appropriate selection of patients in clinical trials. Apart from obvious technological and bioinformatics advances needed to reduce these concepts to practical application during drug development, it will take some time to elucidate the strengths and limitations of this approach.

Challenge/Provocative Tests

Proof of concept (POC) trials need not be restricted to Phase 2 patient studies. Proof of concept investigations of pharmacological interventions in disease models can be undertaken by safely provoking, under controlled laboratory conditions, a mild transient pathological state in healthy subjects (or suitable, mildly ill or susceptible patients). This approach may enable investigation of new drug actions on suitable biomarkers, and increase the relevance and precision of POC. Currently, this approach has been used in regulation of generic inhaled beta-agonists and topical corticosteroids. Developments needed include new, safe, highly controlled, induced transient disease state models.

Additional Considerations and Recommendations

The following concepts could also improve overall clinical drug development.

Minimum Dose for Satisfactory Effect (MDSE)

A critical goal of Phase 2 is identification of a dosage regimen that provides a high probability of successful confirmation in Phase 3 that the compound is safe and effective. Frequently, dose-finding for Phase 3 has been imperfect, depending upon the sophistication of the dose–response investigations undertaken, ranging from uninformed "ball park" guesses to scientifically-based optimal dose identification. The traditional goal of Phase 2 dose-finding has been to identify the maximum safe dose (MSD). This has been justified in oncology on medical, ethical, and statistical grounds for maximizing the power in a simple placebo-controlled trial. The MSD strategy, nevertheless, has often resulted in testing (even marketing) of excessively high dosages that ultimately cause safety problems, of which there are many examples. To address this problem the concept of the minimum dose for satisfactory effect (MDSE) is suggested. While currently

available dose–response trial methodology exists for discovery of the MDSE, it is often not applied or utilized in creating the drug label. A potential consequence of this to the drug developer is a reduction in dosing that occurs after marketing and resultant reduction in sales, or the need to develop an additional dosing form. Needed developments to establish this concept include practical dose–response designs for finding the MDSE in Phase 2, and regulatory receptivity and encouragement for identification of unstudied MDSE via interpolation from dose–response modeling. Again, examples of interpolation already exist in the regulatory environment.

Key Documentation—Investigational Brochure and Draft Label

An early (discovery/pre-clinical phase) provision of key information that provides integrated knowledge and visions for the new drug product and the research goals and approaches of the sponsor takes the form of the investigator's brochure (IB) and the draft label. The IB, which should be constantly updated, provides a running summary of the entire knowledge base on the new drug that promotes awareness and knowledge by all members of the product development team. Consideration should be given to maintaining the IB in an online format to facilitate updating and review by investigators.

Training of Ethical Committees

Fast-tracking new drug development requires novel strategies and techniques that may be unfamiliar or even uncomfortable for traditional ethical committees. Training of ethical committees on advances in drug development science in order to increase their receptivity to novel approaches is recommended.

Organizational Behavior

Beyond scientific strategies and tactics, organizational behavior and culture can profoundly influence the success of drug development. Better communication across all disciplines is needed to help guide drug development more efficiently and informatively with regard to strategic decision-making. For example, to become more contributory, clinical pharmacologists should get involved earlier in the drug development process, focusing on a better understanding of preclinical and clinical drug metabolism, scaling of preclinical PK data to humans, and identification of biomarkers to incorporate into the drug development plan. A major problem facing many companies is deciding when, where, and how to obtain high quality clinical data at a reasonable cost. Bi-directional communication between preclinical scientists, clinical pharmacologists, and clinicians is critical to achieve the most valued results. Major obstacles in communication can occur where there is handoff of research data between disciplines, so there is a critical need to improve data collection procedures, to allow exchange data among different data bases, and to archive data in a manner which allows integration with new data from current development programs. These are prerequisites to optimizing corporate decision making and designing focused, information-rich, clinical studies with multiple objectives.

Regulatory Initiatives

International and domestic regulatory initiatives inevitably have a substantial impact on drug development. Some important current initiatives include:

- Definition of efficacy standards under US Code of Federal Regulations [CFR 505(d)].
- Description of confirmatory evidence in the FDA Modernization Act of 1997 (FDAMA), Section 115, that provides an alternative to the efficacy standard of two adequate and well-controlled clinical trials, using PK–PD studies.
- Codification of fast track, accelerated approval regulations.
- Good guidance practices and FDA's Medical Policy Coordinating Committee (Clinical Pharmacology Section) guidances.
- International Conference on Harmonization (ICH) guidances and, in particular, the common technical document (CTD) for efficacy.

CONCLUSIONS

Advances in a whole host of technologies, together with a much better understanding of the way in which compounds are handled by the body and how they act to produce their effects, is facilitating better and more rational design of new therapeutic agents and their preclinical and clinical testing. However, pressures on resources and time demand more efficient approaches. The authors believe that this will best be achieved by the increasing integration of information from all phases of drug selection and development through the application of modeling and simulation methodologies, thereby improving the informational content while reducing the amount of experimentation required.

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