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Getting the Dose Right: Report From the Tenth European Federation of Pharmaceutical Sciences (EUFEPS) Conference on Optimizing Drug Development

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This report highlights the main points emerging from a meeting sponsored on "Getting the Dose Right" in clinical development, jointly sponsored by the European Federation of Pharmaceutical Sciences and the European Center of Pharmaceutical Medicine, as part of the Workshop Series on Frontiers in Drug Development, in Basel, Switzerland on December 9–12, 2002.

KEY WORDS: meeting report; dose; response; drug development.

INTRODUCTION

"Dosis Venenum-the dose makes a poison" Paracelus (1493–1541). This report highlights the main points that emerged from a meeting focused on "Getting the Dose Right" in clinical drug development, jointly sponsored by the European Federation of Pharmaceutical Sciences (EUFEPS) and the European Center of Pharmaceutical Medicine (ECPM) Workshop Series on Frontiers in Drug Development in Basel, Switzerland on December 9–12, 2002. The primary aims of this meeting were twofold:

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- To assess the current situation with respect to dose estimation during drug development, and, importantly.
- To examine how the role of drug exposure and response, linked via pharmacokinetic and pharmacodynamic modeling and analysis, together with associated innovations, can contribute to an improved likelihood of getting the dose right for patients.

Within the context of the meeting, exposure was taken to mean drug dose or concentration, and response to be any measure of effect produced following drug administration. This includes a change in a biomarker, in a surrogate endpoint, in clinical effectiveness, or in a safety endpoint. The meeting formed part of a continuum of the EUFEPS annual meetings aimed at optimizing the science of drug development. The first of these considered generally opportunities for improved candidate selection and accelerated evaluation in human (1). Subsequent meetings have dealt with specific topics such as biomarkers (2) and drug–drug/food interactions (3).

SETTING THE STAGE

The pharmaceutical industry is facing many challenges and issues. These include the seemingly ever increasing cost of research and development, the increasing loss of patent life and generic competition for large revenue drugs, which challenge the sustainability of the previous double digit growth in the pharmaceutical industry, and finally, the decreasing stock price and market capitalization of much of the industry (4). Mergers and acquisitions have provided temporary economic relief, but have not changed the fundamental principles governing the success and cost of drug development. An additional societal concern is that if the cost of drug development is too high, new medicines will be so expensive as to be unaffordable in parts of the developed world, and hence, in practice, unavailable in the developing world.

The present drug development process appears to represent the mature end of an S-shaped growth period; small incremental modifications of current practices will no longer suffice to improve productivity and reverse the upward trend in cost of drug development. A paradigm shift toward increased productivity and lower development costs is needed, if the pharmaceutical industry is to stay profitable. As the clinical drug development process undergoes detailed scrutiny due to the above issues, "getting the dose right" for patients becomes a fundamental issue as it can optimize the utility of the drug. Failure to do so can lead to ineffective therapy in some patients or excessive toxicity in others. In the limit,

this can lead to the drug being withdrawn from the market, always a very costly affair.

Two measures suggest that the current approach to drug development is generating incomplete information on dose. First, is the frequency of regulatory required dose adjustments in product labels and second, is the still large number of reported adverse drug effects post-drug approval.

Insight into the frequency of dosage adjustment, post-approval comes from a recently published retrospective evaluation of dosage changes that occurred in 499 new molecular entities (NME) approved by the FDA between 1980 and 1999 (5). Of the 354 drugs that had evaluable information, one in five had had a dosage change post approval, with 20% of these resulting in an increase in dose and, importantly, 80% in a decrease. While there are likely to be many reasons for these required changes in dosage, there has been no apparent amelioration of the frequency of such adjustments with time; the likelihood of a dosage change, adjusting for market exposure, was three times higher for drugs approved in the 1995–1999 period than in the 1980–1984 period. This study also demonstrated that far too often (ca. 20% of instances), current drug development does not capture completely the dose information needed for safe therapeutic use. To address this issue it was suggested that improved PK/PD information be gathered in early Phase 2, which is earlier than is often currently the case, in order to better facilitate individualized dosing and utilization. It was also suggested that, if possible, improved knowledge of the probability of adverse effects be obtained prior to marketing approval. This last proposal may not be feasible for certain drugs until much greater patient exposure is available. Generally, this occurs post-marketing. Currently regulatory agencies do not systematically document the frequency that the initially approved drug dosing paradigm must be changed following post-approval patient exposure. This limits our ability to evaluate the quality of dose information that is generated in the pre-approval drug development process.

Adverse drug reactions, which can also reflect incorrect drug dosing, fall into three broad categories. The first category covers baseline risks within the population that are found to be statistically correlated to events that may or may not be identified as drug related. Attention to correct dosing will not influence the occurrence of this type of adverse effect. The second covers so-called idiosyncratic adverse reactions, thought to be more related to the patient than dose, although dose is likely to be a factor. Here also it is unlikely that this category could be prevented by paying more attention to dosing. The last category, and the most common, encompasses adverse effects that are directly related to the pharmacological effect(s) of drugs. These effects are often predictable and hence

potentially avoidable. Without doubt these adverse drug effects, with their attendant physical, emotional, and financial costs to patients, family, and society, represent a serious "cost" of getting the dose wrong.

Generally, risk increases with increasing dose and a confounding factor is that frequently, dose is associated with the severity of the disease or condition. Adverse drug reactions are also a cause of some patients stopping their medication, thereby limiting harm but also efficacy. Given the evidence that current drug development practices often fail to arrive at correct doses, the meeting sought to define and address scientifically-driven approaches to better understand and define dose-response relationship(s) during drug development. Fundamental to this drive for improvement is a consideration of why excessive doses are so common. One may speculate that it is due to an inappropriate emphasis on completing regulatory requirements. Phase 2A typically seeks to demonstrate "proof of concept" —that the drug can cause efficacy at *some* dose. Since most dose-response curves are monotone and non-decreasing, the most efficient phase 2A will be one that uses the maximal tolerated dose (MTD). If then, clinical development time is of the essence, the natural decision is to carry forward into phase 3 the dose that was demonstrated to work in phase 2. If, indeed, the positive efficacy in phase 2A was real, and the MTD is sufficiently nontoxic, phase 3 will succeed, and approval will be granted for the MTD, without any information on whether that dose is on the "flat of the (efficacy) curve," and hence whether a lower, and possibly less toxic, dose might yield just as much efficacy.

If the above speculation applies at all then there should exist not only drugs whose dose is lowered due to excess toxicity (as documented above), but also those whose dose is lowered because adequate efficacy can be obtained at a lower-than-approved dose, and hence for a lower drug cost (price). Such "marketplace" dose adjustments are not expected to be reflected in labeling changes as these are seldom initiated by the manufacturer, and regulatory agencies request such changes exclusively in response to safety concerns post-approval and not to evidence of 'excessive' efficacy. Despite the lack of easily accessible public records of such dose adjustments (in contrast to approved label changes), anecdotal evidence bears out this prediction. Some notable examples are zidovudine and cimetidine; both drugs were approved at doses that were higher than the doses currently used.

If the above reasons are even partly responsible for failed dose-finding programs during drug development, then greater attention to "learning" in phase 2, using the "learn-confirm" concept of drug development as proposed by Sheiner (6), must be encouraged. A suggestion for beginning this process is as follows. Regulatory agencies might begin to

require an explicit "learning" goal, specifically, a decision-analysis-based justification for the manufacturer-suggested dose. This justification would have to involve (i) estimates of the probability of at least one important (beneficial and adverse) drug effect as a function of dose, and (ii) an explicit clinical utility function, balancing the relative "value" of these effects on the same clinical scale. For the time being, the regulatory decision to approve or not would continue to be based solely on demonstration of safety and efficacy at the suggested dose, as at present, until greater familiarity with the decision-analytic approach was gained. Nonetheless, the exercise would emphasize the reasoning behind choosing doses, and would place a premium on gathering dose–response information during phases 2 and 3.

While further progress is clearly needed to improve on existing approaches to determining the right dose, early indications are that increasing attention to exposure-response is moving drug development and regulatory appraisal towards a more scientific (as opposed to purely empirical) enterprise. These indications are:

- An increasing number of exposure–response orientated international conferences and scientific publications (7).
- An increasing number of exposure–response examples in current clinical development (8,9).
- Exposure-response concepts are now part of regulatory guidances (10).
- FDA and statutory laws recognize the role of exposure–response and are using it to optimize clinical drug development programs.

INTEGRATING PRE-CLINICAL EXPOSURE-RESPONSE FOR CLINICAL DOSE FINDING

Although it may be argued that there is no substitute for data in humans, and in particular patients, substantial understanding of exposure–response relationships can be gained through preclinical investigation. Quantitative exposure–response relationships can be performed in most preclinical models, from tissue cultures to intact small animals, for many classes of drugs such as anti-infectives, steroids, and endocrine hormones. Results from innovative experimental methodologies applied in small animals can be quantified using mechanistic modeling, and then—through appropriate physiological scaling—mapped to humans. A program to determine which such scalings are *a priori* more reliable than others will help direct efforts in this regard. For example, it seems likely that the

metabolic fate of drugs, and hence their pharmacokinetics, will show considerable inter-species variability, especially when the species have evolved to exploit very different food environments (e.g., herbivores vs. carnivores), whereas affinities of drugs for pharmacological receptors involved in the regulation of highly conserved and similar physiological processes across species are less likely to show large inter-species variation.

In recent years, the reason for drug attrition has markedly shifted from a poor bioavailability profile to lack of clinical efficacy and excessive toxicity, indicating that preclinical pharmacokinetic methodology has markedly improved the selection of drugs with adequate oral absorption. Notwithstanding the comment in the previous paragraph, there have also been significant advances in scaling pre-clinical animal pharmacokinetics, coupled with data from *in vitro* human systems, to predict human pharmacokinetic behavior and thus aid in the choice of initial doses for testing in human. The remaining challenge here—perhaps, as suggested above, less formidable than it might appear—involves pharmacodynamic scaling: understanding how to extrapolate the concentration–effect relationship seen in preclinical models to humans.

Mechanism-based pharmacodynamic modeling as a basis for predicting exposure response is an emerging powerful pre-clinical approach to help bridge the animal–human divide. It involves using a "systems biology analysis" to characterize the mechanistic behavior of a drug's exposure–response–time relationship. This approach holds the promise, at least partially demonstrated for some drugs (adenosine A(1) agonists, GABA (A) modulators (11,12)), of predicting human *in vivo* dose–response by using semi-mechanistic PK–PD models, developed in whole animal and *in vitro* models, comprising (i) *in vitro* drug-receptor affinities and (ii) animal pharmacokinetic parameters, appropriately scaled to humans. In the ideal case, all the new human data required to make initial decisions might be obtainable from *in vitro* drug affinities for key pharmacokinetic (metabolic, transporter) and pharmacodynamic (receptor) sites.

Mechanistic models characterize the time dependant transduction and homeostatic feedback mechanisms that follow subsequent to the binding of drug to its receptor. An important feature of such mechanistic models is that they separate transduction—a property solely of the biological system and independent of the drug—from drug–receptor interaction, a property of both the biological system and the drug, so that full use can be made of prior scientific systems knowledge. This is a very powerful principle only available by using mechanistic models. Namely, new data are used to quantify only those system properties that depend on the drug (i.e. parameters describing the direct physical interaction between biological and drug molecules), not those that do not (i.e. all interactions

and mechanisms that occur subsequent to the drug–biological molecule interaction). Contrast this with empirical models of dose–response; in such models all parameters are functions of both drug and system, and hence advantage cannot be taken of (i.e. efficiency gained from) prior scientific knowledge. In particular, the investment in characterizing transduction and effector mechanisms for non-lead compounds in a series acting via a common mechanism, as will often be investigated during early drug development, represents an accumulation of valuable knowledge permitting more efficient development of the lead compound, rather than representing resources wasted on a "false lead."

Mechanistic system modeling, however, requires significant investment in understanding both pharmacology and physiology, and may not be so readily and rapidly applied to first-in-kind or first-in-class drugs. An additional problem that could well limit the rate of progress in this important field is the increasing shortage of adequately skilled and trained pharmacologists in systems biology working with *in vivo* animal models. The solution to this problem lies primarily within academia, but without strong industrial support it is not likely to be forthcoming, since in most countries government funding is directed more to basic research, such as molecular biology, genomics and proteomics, rather than what is seen as "applied clinical research."

Recent advances in molecular and genetic biology are beginning to help facilitate the use of preclinical markers for safety assessment. Useful preclinical safety markers may be defined as those that give a reasonable measure of the probability that an event may occur in humans, and as such represent an observation in non-humans that can be extrapolated to humans. However, the explosion of genomic screening and protein expression methodologies that are now available, while having enormous promise, creates a significant informatics and data analysis challenge, as the vast number of "signals" arising in gene/protein screening represents an "ill-posed inverse problem", when trying to discover which subsets of those signals are potentially causal for some outcome of interest.

NEW, EFFICIENT AND MORE INFORMATIVE ALTERNATIVES FOR ESTIMATING DOSE-RESPONSE

Traditional approaches in drug development to defining the "right dose" vary greatly with the therapeutic area of a drug. Most drug development programs have traditionally focused on demonstrating drug efficacy as defined by a "beating placebo" framework to achieve regulatory approval. Along with demonstrating unambiguous drug efficacy, drug

development programs focus on finding a dosing paradigm that will be simple and easy for physicians and patients to understand and utilize. This frequently results in the concept of a dosing strategy where "one size fits all" To a lesser extent, suggested dosing may differ within patient 'categories,' based on known *a priori* patient characteristics (e.g. elderly vs. young).

A number of new approaches to studying and defining "the right dose" are now available. Alternative "individualization" strategies are possible but even within the *a priori* individualization strategy, considerable improvement, often with only a surprisingly small number of distinct regimens, can be obtained by defining regimens within categories and category boundaries, using decision-theoretic concepts. The first requirement is to define a utility function that properly projects potential positive and negative consequences of drug-taking onto a single common "value" scale. This function, combined with an appropriate population pharmacokinetic and/or pharmacodynamic model to generate the probabilities of all of the outcomes in the utility function, given alternative dosing strategies and baseline patient covariate values, allows one to explore, through simulation, alternative dosing approaches to find the optimal (or near optimal) one(s), conditional on covariates. This strategy would then be tested in phase 3 of development, with the expectation that it would become the label-recommended dosage.

For some drugs with narrow therapeutic indices, *a priori* individualization is insufficiently precise. A well known approach in such cases (used far more often by physicians than drug labels) is *a posteriori* individualization (dose adjustment) based on measurements of individual patient drug effects, side effects, a biomarker, a drug concentration, or a mixture of such measurements. A Bayesian formulation of this procedure has been known for many years. Truly optimal control, explored by engineers in aerospace and other industries but rarely applied to drug therapy, is a very complex affair, involving not only adjustments for past responses, as in the *a posteriori* approach just mentioned, but also a continuous trade-off between learning (about the system to be controlled) and exercising control (to keep the system within tolerance).

Dose response may be efficiently studied using enrichment trials, which, in essence, attempt to choose study subjects who are likely to show the drug response of interest. Study groups can be "enriched" for responders in many ways, for example, by using inclusion criteria based on known response markers (e.g. excluding those lacking expression of a target receptor), or by enrolling for the main study only those subjects showing a good response during a short pre-test phase. The main phase of the enrichment trial then randomizes the selected population to either

active treatment or placebo. While this approach may have considerable efficiency for the qualitative conclusion that a drug has efficacy (at least within a selected population), it is difficult to know how to extrapolate the quantitative results (e.g. dose–response) of such studies to the general population with the indication for which approval is sought. One important factor impacting enrichment trials is the correlation between the treatment response and the placebo response, a factor that is not often studied or utilized in the design of enrichment trials.

Another innovative trial design that may allow efficient dose selection does so by seeking to learn about dose–response only in the "region" of useful doses, rather than in general. So-called adaptive designs are well suited to this goal (13). As its name implies, this approach involves using a model (here, not necessarily mechanistic, hence easier to define) of the dose–response that is adaptively and continuously updated as each subject's response is observed. Using the updated model the (optimal) probability of allocation of each new patient to a treatment arm (essentially favoring allocation to those arms with better accumulated outcomes to date) is computed, and new patients are randomly allocated to arms according to these frequencies. An arm is discontinued when its allocation probability drops below a specified threshold. The "learn-as-you-go" approach has the potential to minimize the number of individuals studied at ineffective or toxic doses. Essentially one studies only as many as required to conclude with a specified degree of certainty that the dose is less useful than some other, thereby improving the efficiency with respect to both time and number of subjects for the characterization of the dose–response relationship *in the region of greatest interest*. Clearly, such adaptive designs will only work well when subject accrual rates are slow relative to the time-course of response so that outcomes of previous patients are known as new patients accrue.

INTEGRATION OF EXPOSURE-RESPONSE AND CLINICAL TRIAL SIMULATION INTO CLINICAL DEVELOPMENT

The exposure–response relationship has fundamental clinical relevance. It is also an integral part of any model of drug action, and such models are finding increasing use in drug development, notably for clinical trial simulation. Some reasons for this increase use of modeling in general, and clinical trial simulation in particular, include:

- It is clear that it is inefficient, indeed impossible, to study dose–response experimentally for all possible clinical situations. If near

optimal dosing is desired, one cannot confine one's choice of dose only to those actually studied, a vanishingly small subset of all possible doses. Instead, one must extrapolate and interpolate between and from experimentally observed "points' on the high-dimensional response surface to find the optimum. Semimechanistic models provide the most credible means of so doing.

- By accounting for all possible deviations from protocol (e.g. noncompliance), clinical trial simulation allows more realistic estimates of true study power, and helps avoid, or at least minimize, the likelihood of likely-to-fail studies being undertaken, prior to committing resources to them.
- More powerful statistical tests (which preserve type-I error rates under the null) wherein the null hypothesis is contrasted with a scientifically valid alternative can be devised using a model and simulation based reference (null) distribution. This minimizes the likelihood of type-II error, and allows more efficient confirmatory trials.
- A model of drug action updated in real time can be used to minimize the loss of knowledge during drug development by efficiently storing generated knowledge in a format that allows interrogation by individuals with varying backgrounds, since it can generate distributions of *observable* consequences of drug use, e.g., dose response, *and properly accounts for all sources of uncertainty*.

Models and clinical trial simulation can be used as a component of knowledge management in drug development. It is possible to use modeling and simulation of clinical trials to integrate and drive decision-making in clinical development (9).

REGULATORY PERSPECTIVES

Within both European and United States regulatory agencies there is considerable support for randomized, parallel-group, fixed dose–response trial designs, in terms of simplicity of design and analysis. This is, in contrast to cross-over or titration designs, responsible for the continued reliance on this design for assessing dose–response relationships. From the regulatory viewpoint, specifying initial and maximal dosage, or optimal dosage, defined as that dosage yielding the most favorable population average benefit-to-risk ratio, is of paramount interest when defining dose–response curves for efficacious and toxic drug effects. As both types of such curves are directly estimated using data averages from parallel dose trials, this interest provides a justification for favoring such designs.

In the opinion of the authors, the exclusive emphasis on population average response neglects the importance of individual dose–response which can only be estimated using designs that administer several different doses to at least some individuals using repeated measures designs, such as cross-over or dose escalation. Knowledge of individual dose–response allows one to forecast the results of individual titration, a common clinical practice in chronic therapy, but frequently neglected in drug labeling. Parallel dose designs do not provide the information required to estimate the distribution of individual dose–response relationships, a contrast to repeated measures design.

The problems and challenges with repeated measures designs are not trivial. Depending on the particular design, a more complex model-based data analysis that requires scientifically plausible assumptions are required. These assumptions may not be testable on the study data and their validity may not be known with certainty. For example, when titration-type repeated measure designs are used, wherein doses are raised until a prespecified drug effect is seen, the dose is not randomized and dose/time can be confounded, especially for safety. Because of spontaneous improvements and regression to the mean, it can appear that higher doses add to the drug effect when in fact they do not. Thus, naïve analysis of such trials, contrasting average observed effects at final doses has been known to often produce severely biased estimates of dose–response. Model-based analysis methods can be used to mitigate such biases, but when inference is paramount (ie, for confirmatory trials) since these methods are sensitive to assumptions that are not testable on the data at hand, it seems prudent to use less problematic designs such as the parallel dose design. Thus, in our view, there is a place for both types of designs in modern drug development.

MEETING SUMMARY

The problem facing the pharmaceutical industry is one of unsustainable economics. The cost of drug development has increased exponentially while the rate of market entry of innovative new molecular entities and the magnitude of financial returns has remained flat, or possibly has decreased. Moreover, a reversal of this trend is not predicted. Thus, increased spending on drug development has not generated the needed return in investment over the recent short term. Big pharmaceutical and biotechnology company mergers have not solved this problem.

The societal impact of the above is significant. The cost of innovative, new medications is seen as too expensive in the developed world and

unaffordable in the developing world. While molecular and genetic biology has created an explosion of therapeutic opportunity, the translation of this knowledge into affordable and innovative medication for mankind has become a rate limiting factor. The economic health of the biopharmaceutical industry affects many people, countries and economies. Clinical drug development, specifically the phases from the identification of promising compounds that are ready to enter human testing up to the final regulatory approval of these compounds as drugs, is where improvement is needed. Since this meeting, the Food and Drug Administration in the United States has proposed a Critical Path program to attempt to deal with this issue (14). Getting the dose right is fundamental to the future of the pharmaceutical industry.

Current clinical drug development appears to result in incorrectly suggested doses approximately 20% of the time, with attendant potential for significant adverse outcomes and negative therapeutic impact. A consensus is emerging that "model-based methods" of study design and analysis—methods which differ from those currently in routine use—offer potential for more efficient estimation of dose/exposure–response.

Adaptive clinical trial design is an especially exciting and efficient concept for early clinical development that has the potential to create considerable drug development efficiency. Clinical trial modeling and simulation in both early and late clinical development can create significant advantage. Exposure–response relationships captured from a variety of sources generate a fundamental opportunity and challenge for knowledge management in the pharmaceutical industry. Economic models, linked to decision analysis, can be integrated with exposure–response models to provide a quantitative foundation not only with respect to getting the dose right but also for clinical drug development decision making, in general.

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