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Impact of Pharmacometrics on Drug Approval and Labeling Decisions: A Survey of 42 New Drug Applications

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ABSTRACT

The value of quantitative thinking in drug development and regulatory review is increasingly being appreciated. Modeling and simulation of data pertaining to pharmacokinetic, pharmacodynamic, and disease progression is often referred to as the pharmacometrics analyses. The objective of the current report is to assess the role of pharmacometrics at the US Food and Drug Administration (FDA) in making drug approval and labeling decisions. The New Drug Applications (NDAs) submitted between 2000 and 2004 to the Cardio-renal, Oncology, and Neuropharmacology drug products divisions were surveyed. For those NDA reviews that included a pharmacometrics consultation, the clinical pharmacology scientists ranked the impact on the regulatory decision(s). Of about a total of 244 NDAs, 42 included a pharmacometrics component. Review of NDAs involved independent, quantitative evaluation by FDA pharmacometricians, even when such analysis was not conducted by the sponsor. Pharmacometric analyses were pivotal in regulatory decision making in more than half of the 42 NDAs. Of the 14 reviews that were pivotal to approval related decisions, 5 identified the need for additional trials, whereas 6 reduced the burden of conducting additional trials. Collaboration among the FDA clinical pharmacology, medical, and statistical reviewers and effective communication with the sponsors was critical for the impact to occur. The survey and the case studies emphasize the need for early interaction between the FDA and sponsors to plan the development more efficiently by appreciating the regulatory expectations better.

KEYWORDS: regulatory decisions, modeling, simulation, FDA, dose-response

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INTRODUCTION

The US Food and Drug Administration (FDA) has 3 primary roles in promoting and protecting the public health through the regulation of new and marketed drugs. First, the FDA decides whether to approve a new drug for the market based on the perceived benefit and risk or removes a drug from the market usually based on safety but, at times, based on product quality. Second, the FDA approves the information in the product label both at the time of marketing and while the drug is on the market. Third, the FDA provides advice to sponsors usually before some action the sponsor is planning to undertake (eg, development plan, trial design, and disease end point selection).

This report describes how quantitative pharmacologic thinking and analysis has had an impact on the first 2 decisions and how the FDA is moving to use these tools in its consultative role. We use the term pharmacometrics to describe how a simultaneous quantitative understanding of the variables that influence drug pharmacokinetics (PK) and pharmacodynamics (PD) are applied to lead or support the above decisions. Work in this area has evolved primarily around the New Drug Application (NDA) approval process over the past 15 years or so. Case studies have been extracted from our experience over the past 4 years to provide an insight on how this information is used to lead the FDA to more quantitatively based decisions on drug approval and labeling. Aside from the specific case studies, we have provided an overall assessment of the impact of the pharmacometrics consultation on the ultimate decisions.

At the FDA, pharmacometricians from clinical pharmacology and biostatistics develop exposure-response models. The pharmacometrics group is currently set up as a matrix function within the Office of Clinical Pharmacology and Biopharmaceutics (OCPB). The clinical pharmacology and pharmacometrics reviewers and the team leaders identify the need for pharmacometric analysis based on the key regulatory questions, the availability of relevant data, and priority. The pharmacometrics consults are generated without regard to the prior existence of this type of sponsor-conducted analysis. The pharmacometrics reviewer and

Table 1. Summary of the Types of Regulatory Decisions Influenced by Pharmacometric Analyses*

Regulatory Decisions	Role of Pharmacometric Analyses
Approval basis	1. Provide evidence of effectiveness 2. Assess benefit-risk 3. Review targeted safety studies (eg, QT [proarrhythmic risk] evaluation) 4. Develop approval criteria 5. Evaluate clinical implications of failed BE studies
Labeling	1. Formulate dosing instructions a. Select dose and regimen b. Individualize doses c. Evaluate dosing in special populations (eg, pediatrics, renal impaired) d. Assess drug interactions e. Describe time course of effects 2. Provide warnings and precautions
Designing trials	1. Select dose or exposure range for registration trials 2. Derive optimal sampling schemes (exposure and response)
Policy	1. Evaluate alternative primary analysis methods 2. Pivotal BE criteria 3. Compare competing recommendations in Guidances

*BE indicates bioequivalence.

team leader then become an integral part of the review team. The key regulatory questions are discussed with other members of the review team, including the clinician, statistician, and pharmacologist, so that the pharmacometrics review aids in the regulatory decision. The clinical pharmacology and pharmacometrics team generates a joint review of the submission. In several cases, the same reviewer performs both the clinical pharmacology and pharmacometric reviews. During these deliberations, several other aspects, which include current clinical practice and benefit-risk ratio (ie, utility, which is predominantly qualitative), are considered. Two aspects of the pharmacometrics reviews are vital to its acceptance and application in regulatory decisions. The first is the overall delivery of the message to stakeholders, including the review team and the sponsor. The second is the comprehensiveness of the review, as well as its utility to address key clinical questions. It is only after these successful communications that pharmacometrics reviews can influence regulatory decisions. The pharmacometric reviews deal with a variety of analyses types including population PK, exposure-response (or PK/PD), biomarker-clinical outcome modeling, and simulations to determine optimal dosing based on benefit-risk assessment. The various regulatory decisions and the roles of the pharmacometric analyses are presented in Table 1.

Few surveys have been published that evaluated the role of pharmacometrics in drug development. Recently, the pharmaceutical industry has published at least 2 surveys that discuss the role of population PK and PD analysis in the drug development process.[1,2] The surveys cited that information derived from these analyses was most commonly used for labeling. A survey of NDAs reviewed by OCPB over a 2-year period (1995 to 1996) has also been published.[3] This survey of 206 NDAs and supplements reviewed by the OCPB of the FDA during fiscal years 1995 and 1996 found that approximately 19% (39 of 206) of the population PK reports contributed to labeling.

In this report, we present the results of an internal survey of 42 NDAs, submitted between 2000 and 2004, that reflect the impact of pharmacometrics in regulatory decisions for the cardiorenal, neuropharmacology, and oncology drug products. We also describe in detail a few case studies to allow greater appreciation of the role of pharmacometric analyses.

This article is also a tribute to the research, teaching, and advice of Lewis Sheiner. As Dr. Sheiner's thinking evolved over the past 35 years, his concepts began to influence the FDA in the late 1970s and have progressively increased ever since. Dr. Sheiner worked on several FDA advisory committees (Cardiovascular and Clinical Pharmacology) and was a frequent consultant over the past 25 years. His influence has been broad in terms of how to think about learning as applied to drug development.

MATERIALS AND METHODS

NDA Survey

The clinical pharmacology team leader involved with a particular review was asked to rank the pharmacometric reviews, along with the clinical pharmacology/pharmacometric reviewer, in the following categories: (1) impact on the decision to approve the NDA, and (2) impact on the labeling.

The 2 categories were succinctly designated as "approval" and "labeling." The first category, although denoted as approval, implies approval-related decisions, that is, approved, approvable, and refused. Typically, approvable implies that the FDA recommended submission of additional information to support approval.

The ranking choices included: "pivotal," "supportive," "no contribution," and "not applicable." Pharmacometric reviews with a critical role in the regulatory decision making were considered as pivotal. For these NDAs, the

pharmacometric analyses were part of the basis for the regulatory decision. Pharmacometric reviews that were worthwhile in confirming the regulatory decision making were considered as supportive. It should be noted that supportive evidence is also required by the FDA to make high-level regulatory decisions, such as approval. Pharmacometric reviews with no role in the regulatory decision making were ranked as no contribution. For these NDAs, the regulatory decision would have been the same without the pharmacometric analyses. If the aim of the pharmacometric review did not answer a particular category, the scientists were asked to rank as not applicable. For each review, the reviewer and the team leader provide 1 rank per category.

To gain insights into the consequences of the reviews, the decisions were additionally subdivided for interpretation purposes. The approval decisions were subcategorized into those that increased or decreased the development time. The labeling decisions were subclassified into those that impacted the Dosage and Administration, Warnings/ Precautions, and Clinical Pharmacology sections.

Case Studies

The role of the pharmacometric review is elaborated for 7 selected NDAs. These case studies should provide a better appreciation for the scope of impact. Details of the pharmacometric analysis were intentionally not provided. Drugs of which the applications are pending approval are masked for confidentiality.

RESULTS

NDA Survey

Pharmacometrics consultation was sought for 42 of a total of 244 NDAs submitted to cardiorenal, neuropharmacology, and oncology drug products. Of the 42 NDAs reviewed, a pharmacometrics component was involved in approval-related issues for 26 NDAs and labeling-related issues in 37 NDAs. In the approval category, the pharmacometrics role was considered pivotal in 14 (54%) and supportive in 12 (46%) of the submissions. In the labeling category, the pharmacometrics role was considered pivotal in 21 (57%), supportive in 11 (30%), and no contribution in 5 (14%) of the submissions.

Of the 14 reviews that had pivotal impact on the approval decision, 5 (36%) identified the need for additional trials, whereas 6 (43%) reduced the burden of conducting additional trials. The other 3 reviews had adequate information to make the regulatory decision, based on quantitative thinking. In general, supportive pharmacometric analyses might not have affected the development time. Of the 32 reviews that influenced labeling decisions (both pivotal and supportive), 15 (47%) contributed to statements in the Dosage and Administration section, 12 (38%) to the safety sections (Precautions or Warnings), and 20 (63%) to the Clinical Pharmacology section. Several reviews contributed to multiple labeling sections.

A majority (90%) of the pharmacometric reviews that affected approval decisions were performed by the FDA pharmacometricians. Similarly, 60% of the (re-) analyses that influenced labeling decisions were conducted by the FDA reviewers. The instances when the FDA pharmacometricians conducted the analysis included cases where the FDA reanalyzed the data, built onto the sponsor model, or performed new analysis.

Case Studies

Table 1 shows the various general types of regulatory decisions and the roles of pharmacometric analyses. Executive summaries of the pivotal impact that the pharmacometric reviews had on regulatory (approval or labeling) decisions for 7 of the 26 NDAs are provided. The relevant background, the key regulatory question(s), the role of pharmacometrics, and the final regulatory action are described.

Case Study 1

Background

The original NDA for nesiritide (Natrecor) was submitted for the treatment of acute decompensated congestive heart failure (CHF) in April 1998. The change in pulmonary capillary wedge pressure (PCWP) was shown to be different from placebo.[4] Nesiritide was discussed at the Cardiorenal Advisory Committee on January 29, 1999.[5] From a clinical viewpoint, the maximum desired effect on PCWP at a given dose does not occur instantaneously, and the desired effects cannot be achieved without undesired effects, such as hypotension. It was recommended that the sponsor optimize the dosing regimen so that the desired effect occurs instantaneously with minimal hypotension. In April 1999, the FDA issued a nonapprovable letter to the sponsor.

Regulatory Question

What is the optimal dosing regimen of nesiritide to achieve a faster decrease in PCWP (benefit) and minimize undesired hypotension (risk)?

Role of Exposure-Response Analysis

Exposure and response data from the original submission were modeled. The developed model was used to explore various alternative dosing scenarios. A bolus dose followed

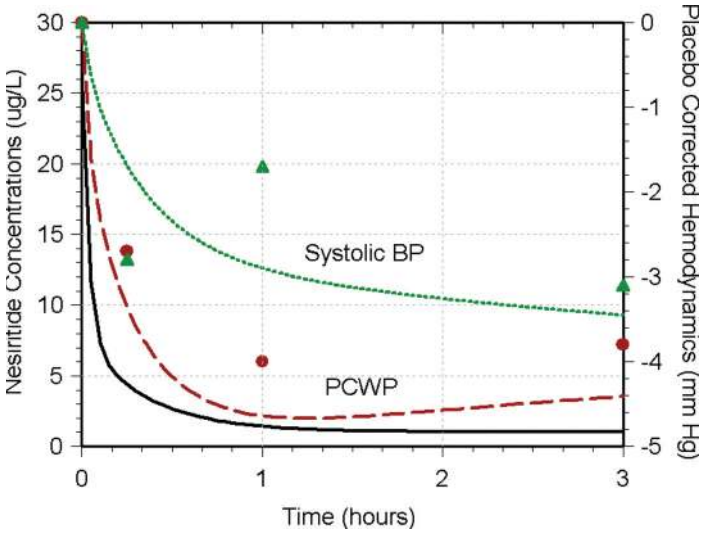

Figure 1. Typical time course of nesiritide plasma concentrations (—), and the effects on the PCWP (● indicates observed; **----** indicates model predicted) and systolic blood pressure (Systolic BP; ▲ indicates observed; **.....** indicates model predicted) after a 2 μg/kg bolus followed by a fixed-dose infusion of 0.01 μg/kg/min. Data for the initial 3 hours are being shown here.

by a maintenance infusion would allow faster achievement of the desired effect. On the other hand, lower dose rates might offer smaller effects on systolic blood pressure. Evidently, 2 μg/kg followed by 0.01 μg/min/kg infusion seems to offer a reasonable benefit-risk profile. This dosing regimen was selected for additional investigation in the Vasodilation in the Management of Acute CHF (VMAC) trial.[6] The results obtained from the VMAC trial and the simulations are in close agreement with those observed (Figure 1).

Regulatory Action

The sponsor submitted the results of the VMAC study in support of a revised dosing regimen. The FDA approved nesiritide for acute CHF in May 2001.

Case Study 2

Background

The sponsor sought approval of apomorphine (Apokyn), subcutaneous injection) for acute use in patients with Parkinson's disease. Along with the registration studies, the sponsor submitted results from a dose-finding (2 to 10 mg) study. In the renal-impaired apomorphine demonstrated a 50% increase in exposure. The FDA conducted exposure-response analysis to aid in evaluating the appropriate dosing instructions for labeling.

Regulatory Questions

Is the maximum recommended dose and the titration strategy proposed by the sponsor appropriate? Is there a need for adjusting dose in the renal impaired?

Role of Pharmacometric Analysis

The data from the dose-finding study indicated a concentration-dependent effect on Unified Parkinson's Disease Rating Scale, which is desired, and blood pressure, which is undesired.[7] Simulations using the exposure-response model suggested only minor additional benefits beyond 6 mg. The concentration-blood pressure relationship implied that titration to a higher dose should not occur before 90 minutes. Also, these results suggested that a dose increment of 0.5 mg, although not tested, might be reasonable. The starting dose for patients with renal impairment was recommended to be 1 mg.

Regulatory Action

Except for the titration step size of 0.5 mg, the dosing recommendations suggested by the exposure-response analysis were incorporated in the labeling after discussions with the sponsor.[7]

Case Study 3

Background

Zoledronic acid (Zometa) is a third-generation bisphosphonate that is approved for the treatment of hypercalcemia of malignancy and for the treatment of osteolytic bone metastases secondary to solid tumors (prostate, breast, lung, and colon) or multiple myeloma. The original NDA and supplemental NDA data, published postmarketing reports and case studies, suggested an increased risk of renal deterioration with zoledronic acid use.[8,9]

Regulatory Questions

Is there a need to adjust the zoledronic acid dose in patients with renal impairment? If so, what doses should be recommended?

Role of Pharmacometric Analysis

The registration studies of zoledronic acid in patients with bone metastases lacked PK evaluations. A population PK model for zoledronic acid, based on early phase PK studies, was critical for imputing the area under the curve (AUC) in the 3,064 patients included in the registration studies evaluating renal deterioration after zoledronic acid

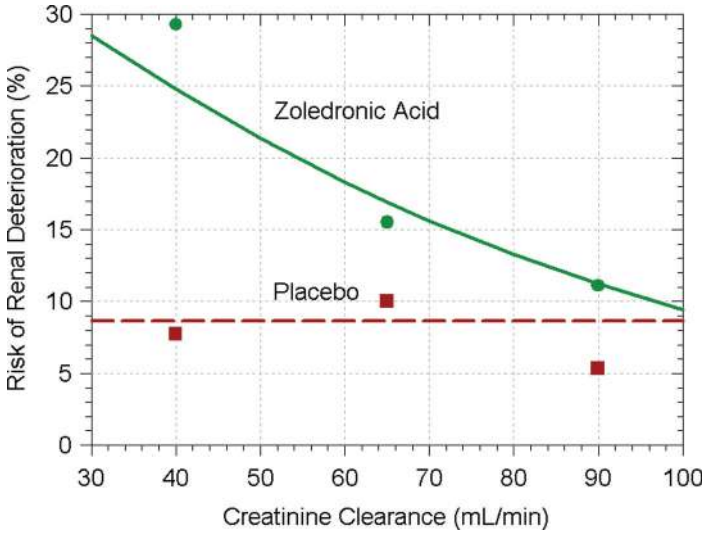

Figure 2. Risk of renal deterioration increases with decreasing renal function (assessed based on baseline creatinine clearance) after 4-mg infusion of zoledronic acid over 15 min (● indicates observed, — indicates predicted) and placebo (■ indicates observed, **----** indicates predicted) in solid tumor and prostate cancer patients.

treatment. The risk of renal deterioration was modeled as a function of treatment and baseline renal function (creatinine clearance) using logistic regression. Other complementary approaches included survival analysis of the time to renal deterioration and linear mixed-effects modeling of the time course of serum creatinine after treatment with zoledronic acid or placebo. All of the analyses consistently suggested that drug exposure was related to an increased risk of renal deterioration (Figure 2). The FDA recommended dose adjustment in mild and moderate renal impairment patients to match the AUC in those with normal renal function.

Regulatory Action

After discussions with the sponsor, the FDA dosing recommendations were incorporated in the labeling.[10] The revisions to the Dosage and Administration and Warnings sections of the prescribing information on the management of patients with advanced cancer and renal impairment were notified to the health care professionals.[11]

Case Study 4

Background

Busulfex is an intravenous formulation of busulfan, a bifunctional alkylating agent that was approved as a part of a combination drug regimen for bone marrow ablation before hematopoeitic stem cell transplantation in adults with chronic myelogenous leukemia. The dose-limiting toxicity associated with busulfan is potentially fatal hepatic venoocclusive disease. Exposures (AUCs) >1,500 μmol/L/min were associated with venoocclusive disease and seizures, whereas AUCs <900 μmol/L/min were associated with leukemic relapse and failure to engraft.[12-15]

The FDA issued the sponsor a pediatric written request to determine the PKs of intravenous busulfan in pediatric patients (between 4 and 17 years of age) who require hematopoietic stem cell transplantation and to derive the optimum dosing regimen that achieves exposures in the target therapeutic window.

Regulatory Question

What is the appropriate dosing strategy for busulfan in pediatric patients?

Role of Pharmacometric Analysis

A population PK model was developed using a 24-pediatric-patient study. The ability of different dosing regimens to achieve a busulfan exposure with the first dose, within the target therapeutic window of 900 and 1,350 μmol/L/min (3.7 to 5.5 μg/h/mL) was explored using the model. For each dosing regimen tested, 1,000 simulations were conducted, and the probability of successfully achieving the target therapeutic window was observed. Regimens with 1 to 7 dosing steps were tested. For regimens with 2 to 7 dosing steps, multiple combinations of weights and doses were tested. Table 2 lists the success rates for each regimen with 1 to 7 dosing steps. All of the dosing regimens achieved a 60% success, at best, with the first dose of busulfan. This appears to occur because the therapeutic target window is narrow, whereas the between-subject variability (25%) for busulfan is relatively large. Consequently, a relatively large proportion of patients fail to achieve the target window with the first dose of busulfan. Importantly, the model also allowed estimation of within-subject variability (6%), which was low, indicating that the between-subject variability is the key determinant of the therapeutic success. This finding provides a scientific rationale for therapeutic drug monitoring in these patients.[12]

Regulatory Action

As a result of this analysis, a 2-step dosing regimen (1.1 mg/kg in children ≤12 kg and 0.8 mg/kg to children >12 kg) was listed in the pediatric section of the product labeling. Instructions on therapeutic drug monitoring were also included to increase the success of achieving the target therapeutic window for busulfan in these patients. The dosing strategy recommended was not directly tested in clinical trials.

Table 2. Percentage of Patients Achieving Target Busulfan Exposure With Different Dosing Regimens*

Dose Levels	Dosage Regimen (mg/kg)	% Subjects With Target AUC (900 to 1,350 μM/min)		
		Overall	Missed LL	Missed UL
One	1.2	50	19	31
Two	0.8, 1.1	56	27	16
Three	0.7, 0.9, 1.0	57	26	17
Four	0.8, 0.9, 1.0, 1.2	60	18	21
Five	0.7, 0.8, 0.9, 1.0, 1.1	59	19	22
Six	0.7, 0.8, 0.9, 1.0, 1.1, 1.2	59	17	23
Seven	0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2	59	19	22

*% Missed LL indicates percentage of subjects below the lower limit of busulfan exposure (900 μM/min; 3.7 μg/h/mL); % Missed UL indicates the percentage of subjects above the upper limit of busulfan exposure (1,350 μM/min; 5.5 μg/h/mL). Note that for each dose level, multiple dosing scenarios were tested. The highest average % of each scenario is listed.

Case Study 5

Background

Sotalol (Betapace) is approved for ventricular and supraventricular tachycardia in adults.[16] Demonstrating benefit based on clinical outcomes is challenging for antiarrhythmics, especially in pediatrics. The FDA agreed with the sponsor, as part of the pediatric written request, to use biomarker data (heart rate and proarrhythmic risk) to derive dosing guidelines in pediatrics such that the effects are consistent with adults. The sponsor conducted 2 clinical trials to investigate the antiarrhythmic potential in pediatrics ages 1 month to 12 years. The sponsor collected sotalol concentration, HR, and proarrhythmic risk data.[17] No specific dosing instructions for children with body surface area <0.33 m^2 were proposed in the submission.

Regulatory Question

Is the pediatric dosing regimen proposed by the sponsor acceptable?

Role of Pharmacometric Analysis

Although the sponsor's dosing recommendations were acceptable for patients aged $\geq$2 years (30 mg/m^2 three times daily as a starting dose with subsequent titration to a maximum of 60 mg/m^2), the FDA preferred specific dosing recommendations for neonates and infants. For this purpose, the FDA modified the exposure-response model developed by the sponsor. The PD effects of sotalol in pediatrics were similar to those in adults for a given exposure. Hence, the exposure in the adults was a reasonable target in pediatrics. The systemic clearance of sotalol increases until the patient reaches 2 years of age independent of body-size, owing to the maturation process of the kidneys. After about 2 years, the clearance of sotalol predominantly depends on body size. Based on the model findings, the FDA proposed a dose in patients <2 years of age that included an age factor (Figure 3).[16]

Regulatory Action

The analysis performed by the sponsor and the FDA concluded that the effects in pediatrics were consistent with those in adults. The dosing recommendations for sotalol in

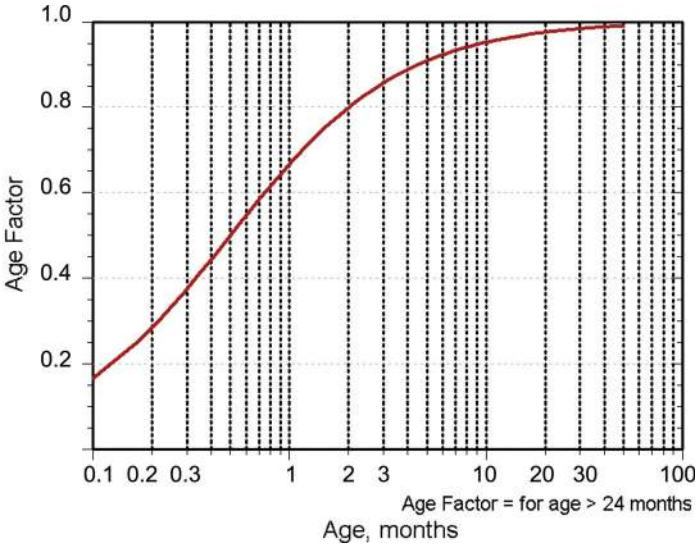

Figure 3. Dose adjustment factor for sotalol in pediatrics aged $\leq$2 years (adapted from approved label for BETAPACE in the Physicians Drug Reference). For children aged $\geq$2 years, with normal renal function, doses normalized for body surface area are appropriate for both initial and incremental dosing.
For children age about $\leq$2 years, the dosing regimen should be reduced by a factor that depends heavily upon age. For a child aged 1 month, the starting dose should be multiplied by 0.68; the initial starting dose would be (30 $\times$ 0.68) =20 mg/m^2, administered 3 times daily.

pediatrics aged 1 month to 12 years old were incorporated in the labeling. More importantly, the modeling efforts led to the specific dosing instructions, which were not directly studied in trials, in patients <2 years of age.

Case Study 6

Background

The sponsor conducted 2 registration trials in patients with an unmet life-threatening rheumatologic disorder. The first study failed to meet its primary end point; however, post hoc analysis showed that a subgroup of the population may derive more benefit from the drug. A second study was conducted to confirm this hypothesis, but it also failed to meet the primary end point. The FDA decided the application was approvable pending the submission of additional evidence of effectiveness. The sponsor was asked to explore higher doses or use an enrichment trial design for evidence of effectiveness. Two issues identified were the dose and the plausibility of a laboratory concentration (biomarker) as a predictor of clinical outcome. The clinical outcome was an undesired event, so fewer events signify benefit.

Regulatory Questions

Is the laboratory concentration predictive of the clinical outcome? What dose should be approved?

Role of Pharmacometric Analysis

The time to event (or survival) analysis showed that the biomarker was predictive of the clinical outcome. The pharmacometrics team expanded the analysis submitted by the sponsor and estimated the reduction required in biomarker to achieve a clinical benefit by simulations. We used the best placebo and drug response rates from the clinical trial and assumed that this laboratory concentration is a surrogate for the clinical end point. The FDA simulation showed that a 65% reduction in the laboratory concentration was required to achieve a significant end point (Figure 4). The sponsor's second trial only had a 37% reduction in the laboratory concentration for the highest dose studied and did not achieve statistical significance.

Regulatory Action

The results of the simulations were discussed internally and also with the sponsor. Because there was a dose-response relationship with this predictive laboratory value, the sponsor was recommended to explore dose(s) that achieve a greater reduction in this laboratory value or a maximally tolerated dose.

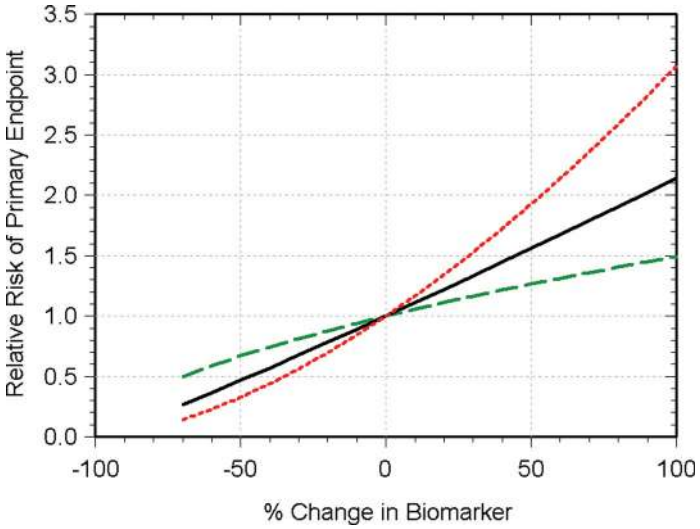

Figure 4. Relationship between the relative risk of the clinical event and the percent change in the biomarker (laboratory concentrations). The best fit (—) and the 95% confidence limits (----) are shown.

Case Study 7

Background

Oxcarbazepine (Trileptal) is approved as adjunct and monotherapies in adult patients and as adjunct therapy in pediatric patients with partial seizures (original submission). The Code of Federal Regulations (21 CFR 201.57(f)(9)(iv)) makes allowance for approving pediatric indications without controlled trials, provided certain criteria are met. The FDA in its approval letter indicated that the sponsor might be able to obtain a claim for the use of oxcarbazepine as monotherapy in the pediatric population without a controlled trial. In response, the sponsor provided a rationale for approving oxcarbazepine monotherapy in pediatrics.

Regulatory Questions

Is there adequate evidence for approving oxcarbazepine monotherapy in pediatric patients without the need for additional controlled clinical trials? What are the appropriate dosing instructions for this indication?

Role of Pharmacometric Analysis

Exposure-seizure frequency data collected from adult and pediatric patients submitted originally was subjected to qualitative analysis and to build an exposure-response model to test whether placebo responses in adult and pediatric patients were similar, test whether the exposure-response relationships in the 2 populations were similar, and derive reasonable dosing recommendations for monotherapy in

pediatric patients. Mixed-effects modeling indicated no important differences in the placebo and drug effects between adults and pediatrics. Equivalence testing suggested that the effect of oxcarbazepine adjunct therapy in pediatrics, on an average, is 85% of that in adults. Dosing recommendations in pediatrics to match the exposure in adults for monotherapy were derived using the exposure-seizure reduction model.

Regulatory Action

Based on the pharmacometric analysis conducted by the sponsor and the FDA and clinical judgment, oxcarbazepine monotherapy in pediatric patients was approved without the need for specific controlled clinical trials. Furthermore, the exposure-response model-derived dosing instructions were provided in the labeling.

DISCUSSION

Survey

The current survey of 42 NDAs submitted during a 4-year period (2000 to 2004) clearly shows that the OCPB management (including team leaders) appreciates and supports pharmacometrics in regulatory reviews. Pharmacometric analyses were pivotal in regulatory decision making in more than half of the 42 NDAs. The present survey is limited to opinions of the OCPB scientists. A similar survey should be conducted with all of the drug review team members (including clinical and statistics). However, the translation of OCPB recommendations into regulatory actions implies acceptance from clinical divisions.

Approximately 90% of the pharmacometric analyses that affected approval decisions were either performed or initiated by the FDA pharmacometricians. Approval-related decisions are probably the most important regulatory decision for both the public and the sponsors. About 60% of the analyses that influenced labeling decisions were conducted by the FDA reviewers. The survey supports the notion that the FDA reviewers proactively engage in quantitative analysis where applicable. The instances when the FDA pharmacometricians conducted the analysis included cases where the FDA reanalyzed the data, built onto the sponsor model, or performed new analysis. It is important to realize that the instances when the FDA performed a completely new analysis are fewer. Also, this result does not imply that the sponsors had no role in the analysis. Without adequate design and data collection by the sponsor, perhaps none of the analyses could have been feasible. Also, the regulatory decision making involves scientific discussions and negotiations both within the FDA and with the sponsors.

Case Studies

Our 7 case studies demonstrate the influence that pharmacometric analyses had on a variety of aspects ranging from optimizing dosing (sotalol and busulfan), accelerating drug development (oxcarbazepine), better trial design where the previous trials failed (nesiritide, case study 6), and minimizing risk (zoledronic acid). For example, in the case of nesiritide, the exposure-response model suggested that the blood pressure effect always lags behind the PCWP. Hence, titration based on this undesired effect is unlikely, an important insight that highlighted the need for a bolus dose. Also, the VMAC trial results matched well with those simulated (Figure 5). Retrospectively, it seems likely that an early interaction between the sponsor and the FDA to discuss the selection of doses based on pharmacometric analysis could have saved 3 years of drug development time and 1 clinical trial. The time and money needed to perform the pharmacometric analysis is negligible compared with the costs of unsuccessful trials (in terms of obtaining approval). The OCPB team ranked the pharmacometric analysis (conducted by the sponsor on the recommendation of the FDA) to be pivotal for approval and labeling. Whereas quantitative thinking identified the need to optimize the dosing, such thinking led to the success of the VMAC trial and avoided the need for additional trials. A similar case was presented at the clinical pharmacology advisory committee meeting.[18] Satisfying the prespecified primary analysis may not ensure approval, and risk-benefit assessment is important. Quantitative methods can effectively aid in these evaluations.

The pharmacometric analysis played a different role in developing dosing guidelines for busulfan. The benefit-to-risk ratio in this case indicated the need for individualization of the treatment. Exploring several dosing strategies in clinical trials, especially in pediatrics, can be impractical, costly, and, perhaps, unethical. Based on a well-conducted study, the sponsor and the FDA performed simulations to explore competing dosing strategies and select the optimal dose. The inability of any dosing scheme to ensure target exposures and the need for therapeutic drug monitoring could only be realized via modeling. The population PK analysis indicated that the within-patient variability is negligible and that controlling for between-patient variability would result in target exposures. The analysis also aided in recommending sampling times to perform therapeutic drug monitoring. It is always challenging to approve dosing strategies that are not directly studied in the clinical trials. Also, the FDA and sponsor interacted effectively on scientific matters, which ultimately resulted in meaningful labeling. The OCPB team ranked the pharmacometric analysis (conducted by the sponsor and refined by the FDA) to be pivotal for approval and labeling.

It is critical to note that the pharmacometric analysis could impact the 42 NDAs only because the required data (such as concentrations and responses) were collected in these trials. For example, if concentration measurements for nesiritide and oxcarbazepine and biomarker measurements for case study 6 in the registration trials were not collected, such informative quantitative analysis could not have been possible.

Pharmacometric analyses, we believe, are valuable to gain insights into the data across drugs and to plan future development. The modeling and simulation approaches should not be viewed as substitutes to conducting clinical trials in all instances. Also, such quantitative analyses should not be primarily used to "rescue" failed trials for seeking regulatory approval. Where appropriate, the FDA accepted simulation results (eg, oxcarbazepine, busulfan, sotalol, and zoledronic acid).

Future Perspective

The rate of attrition is alarmingly high in drug development, including at the late clinical and regulatory review stages. For example, 59% of cancer drugs and 42% of drugs for women's health are reported to be failures in the registration trials or during regulatory review.[19] Although it is recognized that the failure rate is high in drug development, the root causes are unidentified. The cases presented in this report indicate that poor dose finding led to an increase in the development time and review cycles (5 of the 14 NDAs). Alleviation of the burden of additional trials by use of pharmacometric analysis, in 6 of the 14 NDAs, was possible only because effectiveness and safety assessments were performed over a reasonable exposure range (doses or concentrations). Also, relevant concentration information was collected.

To efficiently address the late-phase attrition, the FDA has recently proposed End-of-Phase IIA meetings.[20] The FDA expects that the End-of-Phase IIA meetings will provide a more rational basis of dose selection for registration trials, reduce the number of cycles involved in a NDA review, and improve the efficiency of drug development. Also, the FDA published the Critical Path Initiative, which emphasizes the need for advanced quantitative methods to enhance drug development efficiency.[21]

CONCLUSIONS

The following are key inferences from the survey conducted across the 42 NDAs: (1) review of NDAs involves independent quantitative evaluation of the exposure-response data by FDA pharmacometricians; (2) pharmacometric analyses were pivotal in regulatory decision making in more than half of the 42 NDAs; (3) of the 14 reviews that were pivotal to approval-related decisions, 5 identified the need for additional trials, whereas 6 reduced the burden of conducting additional trials; a prerequisite for this impact is the availability of relevant exposure-response data; (4) of the 32 reviews that influenced the labeling decisions, 15 contributed to statements in the Dosage and Administration section, 12 to the Precautions or Warnings sections, and 20 to Clinical Pharmacology section; (5) successful incorporation of the pharmacometric analyses into regulatory decision making involved collaboration among the FDA disciplines, as well as with the sponsors; and (6) the survey and the case studies emphasized the need for engaging quantitative tools early in the development. Also, early FDA-sponsor dialogue may help the sponsor in planning the development more efficiently, by better appreciating the regulatory expectations.

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