

Backgrounder for the Advisory Committee for Pharmaceutical Science and Clinical
Pharmacology Meeting, March 18-19, 2008

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DRAFT

Food and Drug Administration
Center for Drug Evaluation and Research
ADVISORY COMMITTEE FOR PHARMACEUTICAL SCIENCE & CLINICAL PHARMACOLOGY
(ACPS-CP)
March 18-19, 2008
Advisory & Consultant Staff, Conference Room, Room 1066
5630 Fishers Lane, Rockville, MD 20857

AGENDA
2/22/2008 2:51 PM

Day 1: Tuesday, March 18, 2008

8:30	Call to Order	Jürgen Venitz, M.D., Ph.D. Acting Chair, ACPS-CP
	Conflict of Interest Statement	Mimi Phan, Pharm.D., R.Ph. Designated Federal Officer, ACPS-CP
8:45	Introduction to the meeting Topics	Lawrence Lesko, Ph.D. Director, Office of Clinical Pharmacology (OCP), CDER, FDA

Topic 1: New Clinical Pharmacogenomics (PGx) concept paper

09:15	Key issues in the concept paper	Felix Frueh, Ph.D. Associate Director, Pharmacogenomics OCP, CDER, FDA
09:35	An industry survey on collection of PGx samples	Lisa Shipley, Ph.D. Eli Lilly
09:55	Use of pharmacogenetic information in clinical studies	Eric Lai, Ph.D. Glaxo-Smith Kline
10:15	Break	
10:30	Open Public Hearing	
11:00	Committee Discussion and Questions	
12:00	Lunch	

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Day 1: Tuesday, March 18, 2008, 2006 (continued)

Topic 2: *Quantitative Clinical Pharmacology: Critical Path Opportunities*

13:00	Leveraging Prior Knowledge to Guide Drug Development Decisions	Joga Gobburu, Ph.D. Director, Pharmacometrics OCP, CDER, FDA
13:20	An example of disease model -Non Small Cell Lung Cancer (NSCLC)	Yaning Wang, Ph.D., Team Leader, Pharmacometrics OCP, CDER, FDA
13:40	Application of FDA's NSCLC model	Rene Bruno, Ph.D. Pharsight
14:00	Committee Discussions	
14:30	Break	
15:00	FDAAA: Implications on Pediatric Studies	Lisa Mathis, M.D. Maternal Health, Office of New Drugs (OND) CDER, FDA
15:10	Pediatric Studies in Cardiovascular area: Experience & Opportunities	Norman Stockbridge, M.D. Director, Division of Cardiovascular and Renal Drug Products (DCRDP), OND, CDER, FDA
15:25	Leveraging Prior Knowledge to Design a Pediatric Study	Pravin Jadhav, Ph.D., Reviewer, Pharmacometrics OCP, CDER, FDA
15:45	Committee Discussion	
16:45	Wrap for Day 1	Lawrence Lesko, Ph.D. Director, OCP, CDER, FDA
17:00	Adjourn	

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2/22/2008 2:51 PM

Day 2: Wednesday, March 19, 2008

08:30 Call to order

Jürgen Venitz, M.D., Ph.D.
Acting Chair, ACPS-CP

Conflict of Interest Statement

Mimi Phan, Pharm.D., R.Ph.
Designated Federal Officer, ACPS-CP

Topic 3: Renal Impairment Concept Paper

08:45 When to Conduct a Study in Renal Impairment?

Shiew-Mei Huang, Ph.D.
Deputy Director, OCP
CDER, FDA

09:05 Effect of Renal Impairment on CYP/transporter

Vincent Pichette, M.D., Ph.D.
University of Montreal

09:25 Methods of Evaluation of Renal Function

Shen Xiao, M.D.
Senior Medical Officer, DCRDP,
OND, CDER, FDA

09:45 The need to Evaluate Hemodialysis Patients

William Smoyer, M.D.
The Research Institute at Nationwide Children's
Hospital

10:00 Break

10:15 PhRMA Perspectives

John A Wagner, M.D., Ph.D.
Department of Clinical Pharmacology
Merck Research Laboratories

10:35 Open Public Hearing

11:00 Advisory Committee Discussion & Recommendations

Jürgen Venitz, M.D., Ph.D.
Acting Chair, ACPS-CP

12:00 Summary of recommendations

Lawrence Lesko, Ph.D.
Director, OCP, CDER, FDA

12:30 Adjourn

Questions for the Advisory Committee Members (March 18-19, 2008 CPAC)

Topic 1: Clinical Pharmacogenomics Preliminary Draft Concept Paper

The use of genetic information from study subjects in clinical trials can increase the safety and efficacy information derived from these trials. The preliminary draft concept paper for clinical pharmacogenomics clarifies FDA's current thinking about the collection and use of DNA samples in clinical trials. In particular, the concept paper describes the use of DNA samples in early stages of new drug development and provides recommendations for decision making for subsequent trials using data derived from genetic analysis of study subjects.

1. Does the committee agree with the recommendation to collect DNA samples from all participants in clinical trials? If not, what barriers, obstacles or issues would have to be addressed to facilitate routine collection of DNA samples?
2. What comments and/or recommendations does the committee have on the scientific rationale and thought process embodied in the decision tree in the concept paper?
3. What comments and/or recommendations does the committee have on the design of clinical pharmacogenetic studies and their proposed impact on subsequent clinical trials?

Topic 2: Quantitative Clinical Pharmacology (Critical Path Initiatives)

Disease Models

Drug disease models are recommended in the FDA critical path document as a potentially valuable tool to improve the predictability and productivity of the drug development process. As an example, the NSCLC disease model presented here represents an exploratory tool under development for the purpose of improving oncology drug development in the future. Such models are intended to optimize dose selection, improve the design of clinical trials, and explore associations between biomarkers and clinical outcomes. The following are the questions for the committee on this topic:

1. What comments or suggestions does the committee have for improving the mathematical, statistical or clinical concepts in the model?
2. How does the committee envision such a model can be best utilized to improve drug development?
3. Does the committee have any general recommendations for further exploratory research into drug disease models?

Designing Pediatric Trials

About 50% of pediatric effectiveness trials lead to uninterpretable results. The availability of patient demographic, disease progression, placebo effects, drop-out and drug effect data from previous adult and pediatric trials for the same molecule and/or similar molecules provide a rich database. This information can be leveraged to develop drug/disease models that can be applied to design more efficient and informative pediatric drug development programs. The latest pediatric legislation and the potential benefit of employing modeling/simulation methods during development of protocols for written requests will be presented along with a case study. The following are the questions for the committee on this topic:

1. Do you think that such an approach will render pediatric trials more informative with respect to better dosing and study designs given the difficulties in conducting pediatric clinical trials?
2. Given limited resources, please advise us on how to prioritize pediatrics programs for applying model-based trial design?
3. Do you have any suggestions on how to improve the approach with respect to closing our knowledge gaps in pediatric pharmacotherapy?

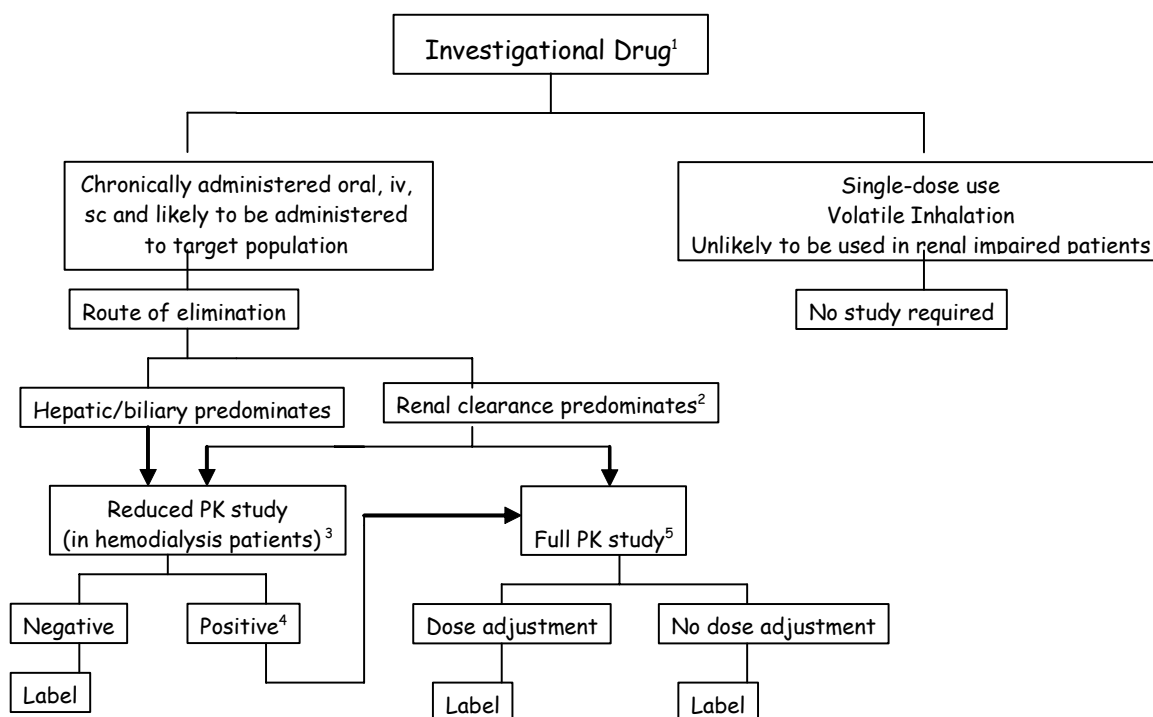
Topic 3- Concept Paper on PK Studies in Patients with Renal Impairment

The safety and efficacy of a drug generally are established for a particular dosage regimen (or range of dosage regimens) in late phase clinical trials involving relatively typical representatives from the target patient population, which frequently excluded individuals with significantly impaired renal function. The preliminary concept paper updates the previously published guidance in 1998 (The Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis and Impact on Dosing and Labeling”, <http://www.fda.gov/cder/guidance/1449fnl.pdf>, May 1998) and highlights major changes with regard to when and what PK studies should be conducted in patients with renal impairment.

1. Does the committee agree that renal impairment can affect metabolism or transport of drugs that are substrates of metabolizing enzymes and transporters?
2. Does the committee agree with the recommended methods of determining renal function and the proposed stratification of patients based on renal function?

3. What comments or recommendations does the committee have on applying the following decision tree (Figure 1) to the determination of when a renal impairment study is needed for an investigational drug?
4. What studies in hemodialysis patients does the committee recommend for drugs intended for chronic administration?

Figure 1. Decision tree to determine when a renal impairment study is recommended



1. Metabolites (active/toxic) follow the same decision tree.
2. The sponsor has the option of conducting a reduced study in patients undergoing hemodialysis (HD) between dialysis or a full study.
3. To be conducted between dialysis (to be initiated and completed within 24 hours prior to scheduled dialysis)
4. The magnitude of PK change based on the reduced PK study, risk-benefit (exposure-response) relationships, and the target patient populations may warrant a follow-up full PK study.
5. To include both “between dialysis” (within 24 hours prior to the scheduled dialysis) and “during dialysis” (if there is low volume of distribution of the NME and high dialytic clearance)

Advisory Committee for Pharmaceutical Science and Clinical Pharmacology

March 18-19, 2008

Quantitative Clinical Pharmacology: Critical Path Opportunities

Executive Summary

The cost of developing a new drug is more than \$800 million and typically takes well over a decade. The clinical trial failure rate in late stage development is unacceptably high at around 50% and the public has been surprised by the recent number of drugs previously regarded as safe, but which have been found to cause unacceptable toxicity once on the market. The FDA has publicly stated its desire to participate in improving drug development productivity and quality in providing safe and effective medicines to American patients. One of the major criticisms against drug development is its negligence to leverage prior knowledge to drive drug development decisions such as trial design and analysis. The value of quantitative thinking in drug development and regulatory review is increasingly being appreciated [Bhattaram et al, AAPS J, 2005; Bhattaram et al, CPT, 2007; Wang et al, JCP, 2008]. Modeling and simulation of data pertaining to pharmacokinetic, pharmacodynamic and disease progression is often referred to as the *pharmacometrics analyses*. Extracting prior knowledge within the FDA on disease change or placebo effect was required to solve some of these case problems. Sponsors also valued this information that was not proprietary. This led to the idea that developing a mechanism to share disease, placebo and dropout models would be a valuable service for FDA to offer the scientific community to improve drug and regulatory development decisions.

This session will entail two topics focused on leveraging prior quantitative knowledge: a) Disease Models and b) Designing pediatric trials.

Disease Models

Disease models for the purpose of this discussion are defined as the collection of sub-models that describe the distribution of exclusion/inclusion criteria (e.g.: baseline disease severity distribution and its relation with other risk factors); disease progression and its relationship to relevant biomarkers (e.g.: the contribution of changes in HbA1c to the risk of MI over time); drug effects (e.g.: concentration-HbA1c relationship) and drop-out model (e.g.: characteristics of

patients who drop-out). The main objective of this initiative is to advance the utility and application of models to account for patient, disease, and drug effects on effectiveness and toxicity targeted to facilitate drug development decisions (e.g.: molecule screening, dose selection, trial design). Specifically our progress on the non-small cell lung cancer (NSCLC) model will be presented.

Lung cancer remains the leading cause of cancer-related deaths in the United States in both men and women. While recent advances in treatment of NSCLC have been demonstrated with improved outcomes for molecularly targeted therapies such as erlotinib, there remains a relatively low success rate (5%) for oncology products in general.

Drug disease models are recommended in the FDA critical path document as a potentially valuable tool to improve the predictability and productivity of the drug development process. The NSCLC disease model presented here represents an exploratory tool under development for the purpose of improving oncology drug development in the future. The model is intended to optimize dose selection, improve the design of clinical trials, and explore associations between biomarkers and clinical outcomes. A detailed report on this disease model is provided in the subsequent section of this document.

Designing Pediatric Trials

About 50% of pediatric effectiveness trials lead to uninterpretable results. The availability of patient demographic, disease progression, placebo effects, drop-out and drug effect data from previous adult and pediatric trials for the same molecule and/or similar molecules provide a rich database. This information can be leveraged to develop drug/disease models that can be applied to design more efficient and informative pediatric drug development programs. The latest pediatric legislation and the potential benefit of employing modeling/simulation methods during development of protocols for written requests will be presented along with a case study. A detailed description of this topic is provided in the subsequent section of this document

NON-SMALL CELL LUNG CANCER (NSCLC) DISEASE MODEL

INTRODUCTION

The success rate of new molecules in oncology is 5%, lowest compared to other therapeutic areas. Yet, cancer is one of the leading causes of deaths in US, and non-small cell lung cancer (NSCLC) being the top cause within cancer deaths. Given the urgent need for more effective NSCLC treatments and the low yield drug development, we elected to understand risk factors for death in patients with non-small cell lung cancer (NSCLC) patients and whether anticancer drug activity can be characterized more precisely early in clinical development based on predictive biomarker, such as tumor size. This knowledge might then aid drug developers to better screen drug molecules, design trials and select doses.

Four registration trials for NSCLC provided nine different regimens that are either first-line or second-line treatments for locally advanced or metastatic NSCLC. Various risk factors for survival were screened based on Cox proportional hazard model. Tumor size dynamic data were described with a disease model that incorporates both the tumor growth property and the regimen's anti-tumor activity. Patient survival times were described with a parametric survival model that includes various risk factors and tumor size change as predictors. The survival model was evaluated across nine regimens.

Among 11 potential risk factors for survival, ECOG score and baseline tumor size were found to be significantly related to survival in almost all regimens. The disease model describes the longitudinal tumor size data fairly well, especially for early weeks after treatment initiation. Parametric survival model includes ECOG score, baseline tumor size and week 8 tumor size change as predictors for patient survival time. The survival model based on one regimen predicted the survival outcomes for the other eight regimens reasonably well despite that these regimens have different mechanism of actions and were studied in different trials.

ECOG score and baseline tumor size are consistent prognostic factors for survival. The survival model and the tumor dynamic model can be applied to screen compounds, simulate NSCLC clinical trials and optimize trial designs

1 Methods

The analysis database included four randomized clinical studies of NSCLC treatment (A, B, C, and D). Together the four trials enrolled and followed a total of 3398 patients. Trial selection was driven predominantly by availability of electronic datasets containing tumor size measurements over time, as well as survival data. Eight active and one placebo treatment arms were tested in these

studies (A1, A2, B1, B2, B3, C1, C2, D1 and D2). Patients received either first- or second- line treatments for locally advanced or metastatic NSCLC (Stages IIIA/B or IV). Following identification of baseline risk factors for NSCLC survival, a tumor model was developed to describe tumor size change over time under various treatments. Subsequently a quantitative relationship between tumor size change and time to death (survival model) was developed. All data were used to screen baseline risk factors. Patients without post-baseline tumor size data were excluded from development of the tumor model. During the development of survival model, more data were excluded so that a consistent model can be developed across the nine treatments.

Baseline Risk Factors for Survival

Brundage et al described potential risk factors for advanced NSCLC.¹ Table 1 shows the risk factors considered in our analysis based on the stratification factors used in the four trials and those identified by *Brundage et al*. Factors such as disease stage, weight loss, patient performance status were reported as important. A Cox regression model (SAS[®] version 9.1) was used to screen for consistent significant factors across the nine arms in the four trials. Step wise selection method was used with inclusion significance at 0.1 and exclusion significance at 0.05. Risk factors identified by this method were used in the tumor-survival model to adjust patient baseline heterogeneity so that the results for the nine arms can be compared.

Table 1. Potential risk factors for death of NSCLC patients

No.	Factors
1	Six-month weight loss (< 5% vs. ≥ 5%)
2	ECOG performance status (0 + 1 vs 2 + 3 or 0 vs 1)
3	Prior surgery (Yes or No)
4	Prior radiation (Yes or No)
5	Stage (III or V)
6	Best response to prior therapy (complete response [CR]; partial response [PR]; stable disease [SD]; progressive disease [PD])
7	Sex (Male or Female)
8	Age (Continuous)
9	Baseline tumor size (sum of longest dimensions)
10	Number of prior chemotherapy treatments
11	Lactate dehydrogenase (whether higher than ULN or not)

Tumor Model

Tumor size from available datasets was recorded as the sum of longest dimensions. As shown in Table 2, most tumors were measured by computed

tomography (CT) scan and only a small percentage were measured using plain radiography, physical exam, or some other methods.

Table 2. Methods (%) for tumor size measurement

Method	A	B	C	D
CT Scan	97.9	75.7	93.5	95.5
Physical Exam	1.1	5.2	3.7	2.3
X-Ray	0.8	13	2.5	1.3
Other	0.2	6.1	0.3	0.9

The longitudinal tumor size data were analyzed using nonlinear mixed effect models (NONMEM® V, Globomax). A model with mixed exponential decay (shrinkage) and linear growth (progression) components described the time course of tumor change (Equation 1).

$$TS_i(t) = BASE_i \cdot e^{-SR_i \cdot t} + PR_i \cdot t \text{ (Equation 1)}$$

where $TS_i(t)$ is the tumor size at time t for i^{th} individual, $BASE_i$ is the baseline tumor size, SR_i is the exponential tumor shrinkage rate constant and PR_i is the linear tumor progression rate.

Random variability was attributed to two sources: a) between-patient variability and b) residual variability. Every patient was allowed to have unique shrinkage and progression rates (i.e., between-patient variability) and the population was assumed to follow a log-normal distribution as illustrated in Equation 2.

$$BASE_i = M_BASE \cdot \exp(\eta_i) \text{ (Equation 2)}$$

where M_BASE is the population median baseline tumor size and η_i is the difference between the individual and population median baseline values on a log-scale, which is assumed to follow a normal distribution with mean of zero and variance of ω_{BASE}^2 (between patient variability, BPV_{BASE}). The individual SR and PR parameters were also described using similar equations. An exponential error model (Equation 3) was used for residual variability (RV)

$$TSO_i(t) = TS_i(t) \cdot \exp(\varepsilon_i) \text{ (Equation 3)}$$

where $TSO_i(t)$ is the observed tumor size at time t for i^{th} individual, $TS_i(t)$ is the expected tumor size at time t for i^{th} individual, and ε_i is the difference between the observed and expected values on a log-scale. ε_i is assumed to follow a normal distribution with mean of zero and variance of σ^2 .

The main purpose of the tumor model was to predict (interpolate) tumor sizes where observations were not available. Therefore, the main model diagnostic criterion was how well the individual predicted values matched the observed data. If necessary, a mixture model was used to statistically separate the patient population into subgroups to have a better individual prediction.

Survival Model

Survival Modeling comprised two steps: a) model building and b) model evaluation. To build a relationship between tumor size change and time to death, the individual tumor size model was used to predict tumor size change at some early time points, e.g. 4, 6 and 8 weeks. Predicted tumor size changes were used to develop a tumor-survival model, taking the identified baseline patient risk factors into consideration. The main purpose of the current research is to establish a quantitative link between risk factors including tumor size and survival for designing future trials. Hence, a parametric survival model was used to relate risk factors and tumor size change to time to death. Several widely used survival functions including exponential, log-normal, Weibull, and gamma were tested. Likelihood ratio tests and diagnostic plots were applied for selection of an appropriate survival function. This model was fitted to each treatment arm separately. SAS[®] version 9.1 was used for this analysis.

Evaluation of the tumor-survival model involved two steps: a) quantifying uncertainty in the relationship and b) quantifying prediction quality of the relationship. Uncertainty in the estimated tumor-survival model was estimated by randomly sampling 1000 bootstrap datasets from A1 data with replacement. Each replicate of A1 arm data provided one set of tumor-survival model parameter estimates. Median survival curves and 95% confidence intervals (CI) were constructed across the 1000 replicates.

The tumor-survival relationship built employing each of the 1000 replicates of the A1 arm data was used to predict the survival time for each of the patients receiving the other eight treatments. The net result was that each patient receiving the other eight treatments will have 1000 predictions. The predicted survival curves (median and 95% CI across the 1000 replicates) were compared to the observed survival curves (mean and 95% CI).

Parameters for the tumor-survival model were estimated for each treatment. Final parameters were updated with a pooled analysis across the nine treatments.

2 Results

Dataset

All data were used for screening significant baseline risk factors. However, during development of tumor and survival models, three levels of data exclusion were applied, as described in Table 3. Overall, 20-33% data were excluded for trials A, B and D, while 50% were excluded for trial C. Distributions of baseline tumor size, ECOG status, percentage of censored patients, and median survival times are listed in Table 4 (included data) and Table 5 (excluded data). Since the median survival times for those excluded patients are consistently shorter than those included patients even if ECOG status and baseline tumor size are comparable, the excluded patients represent a poorly responding population in terms of survival time. Therefore, clinical trial simulation should include these excluded patients as a different population in addition to the included patients.

Table 3. Reasons for three levels of exclusion

Reason	Percent
Lack of post-baseline tumor data	20% - 30%
No ECOG 2/3 patients in trials A and B	7% - 20% (trials C and D only)
Patients with survival time shorter than 8 weeks	0.2% - 4%

Table 4. The Distribution of log-transformed baseline tumor size (cm, Mean and SD), percentage censored, and median survival time (day) stratified by ECOG in each treatment group (included for final survival model)

Treatment	ECOG	N	Percent	Mean	SD	Censor%	MedianT(day)
A1	0	134	40	2.04	0.66	29	510
	1	201	60	1.91	0.72	17	360
A2	0	144	43	1.81	0.68	23	420
	1	191	57	1.92	0.72	17	330
B1	0	192	64	2.01	0.58	28	380
	1	110	36	2.02	0.68	25	310
B2	0	163	57	1.93	0.62	29	350
	1	122	43	2.16	0.66	19	300
B3	0	166	59	1.95	0.56	31	430
	1	115	41	2.02	0.6	10	270
C1	0	26	22	1.78	0.7	35	370
	1	90	78	1.95	0.64	18	210
C2	0	45	20	1.82	0.62	40	490
	1	176	80	1.95	0.66	27	280

D1	0	38	20	1.69	0.64	53	440
	1	154	80	1.93	0.64	34	280
D2	0	47	24	1.55	0.58	49	390
	1	152	76	1.95	0.62	26	280

Table 5. The Distribution of log-transformed baseline tumor size (cm, Mean and SD), percentage censored, and median survival time (day) stratified by ECOG in each treatment group (excluded for final survival model)

Treatment	ECOG	N	Percent	Mean	SD	Censor%	MedianT(day)
A1	0	37	37	2.16	0.84	35	360
	1	59	60	1.9	0.72	17	200
	unknown	3	3	2.8	-	67	-
A2	0	31	28	2.16	0.64	26	360
	1	77	71	2.11	0.74	10	120
	unknown	1	1	-	-	0	240
B1	0	44	42	1.87	0.58	27	360
	1	62	58	1.97	0.86	13	190
B2	0	73	60	2.32	0.58	19	250
	1	48	40	2.31	0.4	6	100
B3	0	69	56	1.99	0.68	16	190
	1	54	44	1.84	0.66	13	170
C1	0	8	6	2.19	0.46	25	300
	1	42	33	2.13	0.82	5	100
	2	56	44	1.99	0.52	9	100
	3	21	17	2.37	0.62	0	100
C2	0	19	7	1.25	-	58	-
	1	80	30	1.96	0.86	18	90
	2	126	47	2.11	0.64	14	130
	3	42	16	2.22	0.74	2	60
D1	0	10	10	1.53	0.36	10	200
	1	38	40	2.31	0.56	8	60
	2	34	35	2.12	0.68	3	70
	unknown	14	15	1.88	0.78	50	80
D2	0	5	6	2.26	0.88	40	280
	1	30	36	2.02	0.76	23	100
	2	30	36	2.01	0.72	3	110
	unknown	19	23	2.4		21	70

Baseline Risk Factors for Survival

Among the eleven potential risk factors, ECOG performance score and baseline tumor size were found to be consistent significant predictors for time to death across the nine treatments in the four trials (Table 6). These two risk factors were retained for the tumor-survival model development. Although LDH was found significant in all treatments when LDH data were available, LDH was not selected because trials C and D did not have LDH information. This finding, however, suggests that LDH should be collected in future trials and it may serve as a stratification factor.

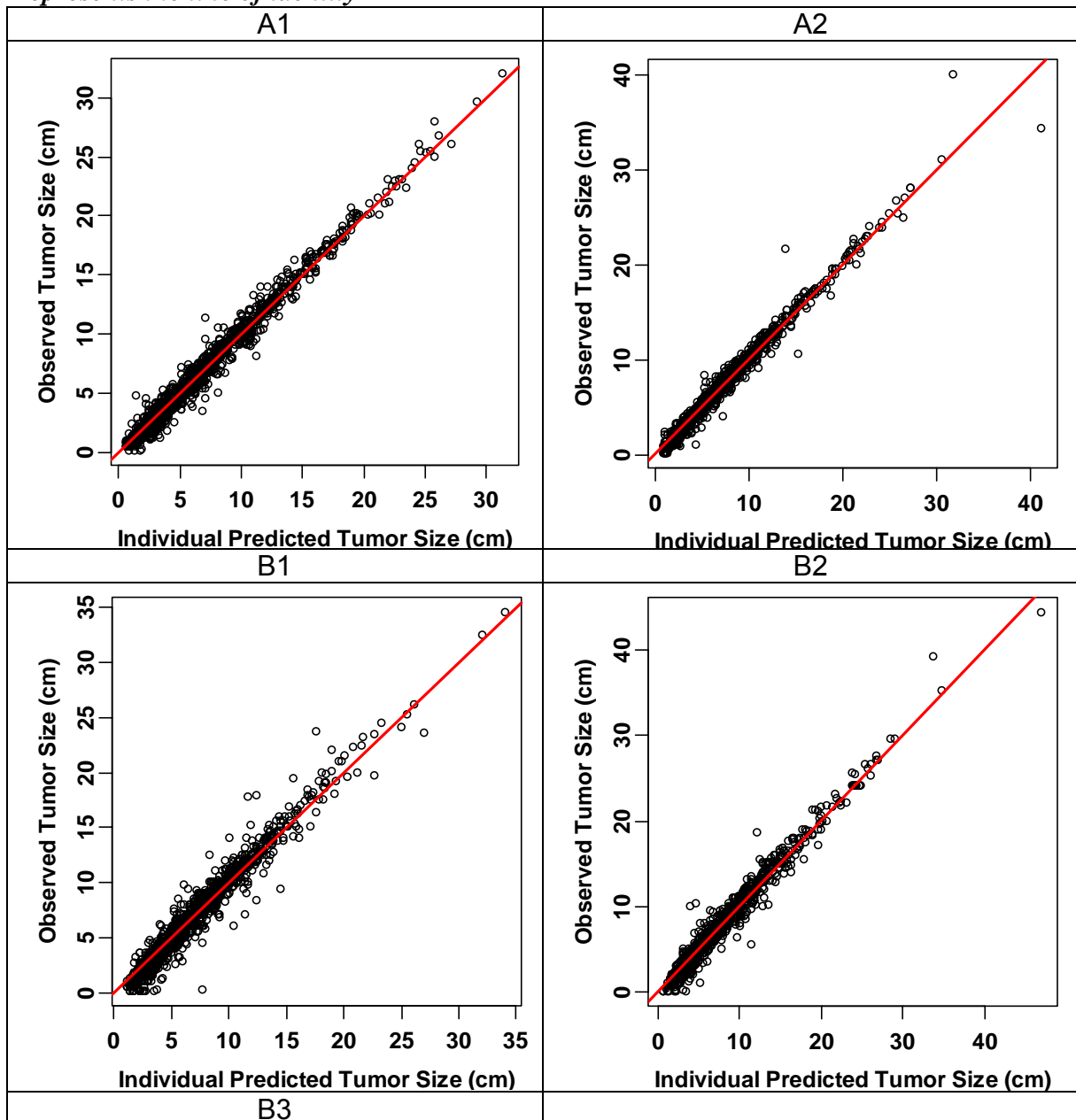
Table 6. Significance of risk factors (●: significant; ○: not significant)

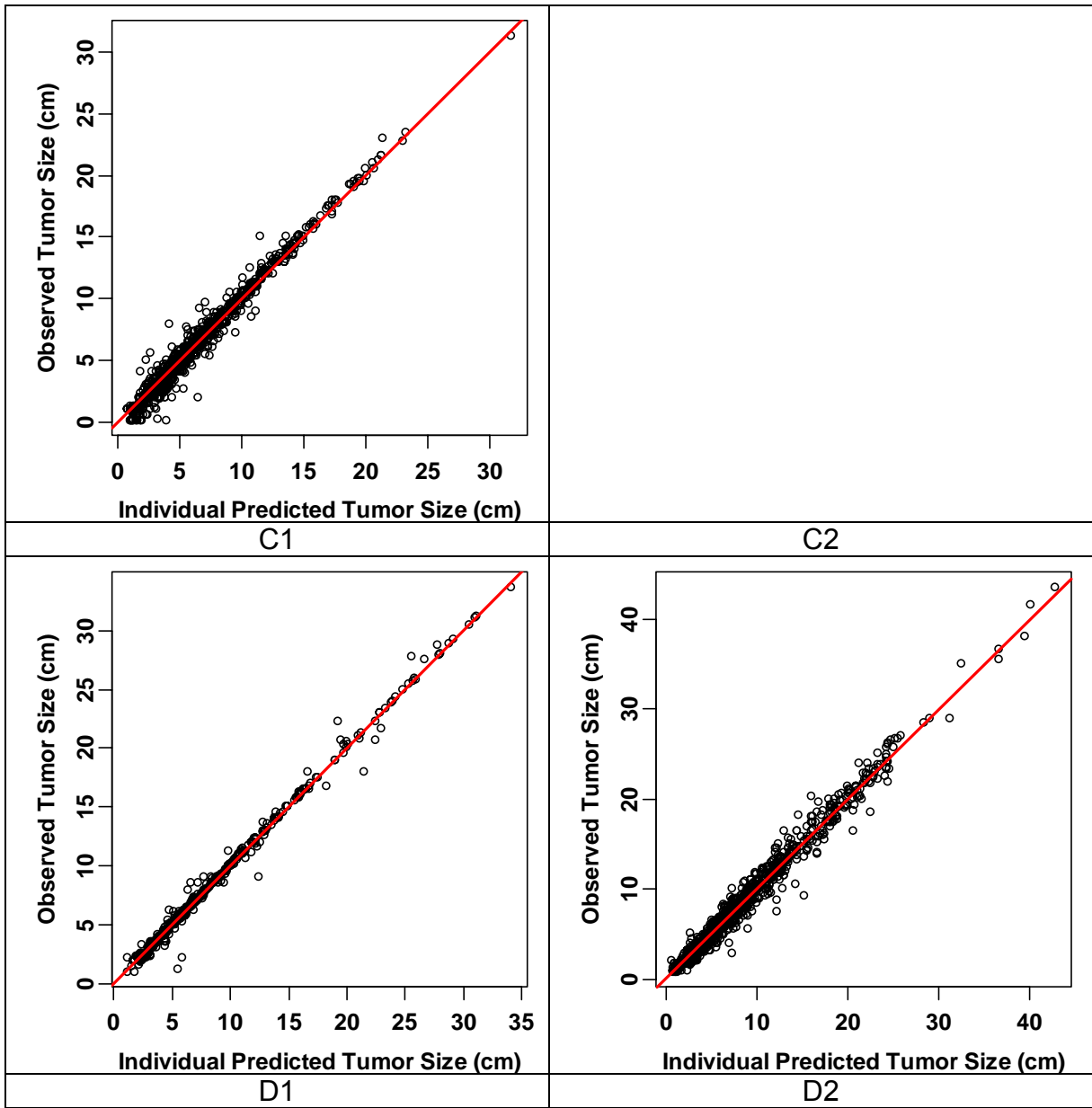
Factors	A1	A2	B1	B2	B3	C1	C2	D1	D2
ECOG	●	●	●	●	●	●	●	●	●
Baseline tumor size	●	○	●	●	●	●	●	●	●
LDH	●	●	●	●	●				
Weight loss	○	●	○	○	○	●	●		
Sex	●	●	○	○	○	○	○	○	○
Prior radiation	○	○	○	○	○	○	○	●	●
Prior surgery	○	●	○	○	○	○	○	○	○
Stage	○	○	○	○	○	○	○	○	○
Age	○	○	○	○	○	○	○	○	○
Number of Prior chemotherapy treatments						○	○	○	○
Best response to prior therapy						○	○	●	○

Tumor Model

The mixed exponential decay ('shrinkage') and linear growth ('progression') model fitted the tumor size data fairly well for all nine treatments (Figure 1). The observations are uniformly and closely distributed around the line of identity. The line of identity represents the perfect model. Figure 2 shows the flexibility of this model to describe various types of individual profiles. Nonetheless the population mean profile suggests the average tumor dynamics shows an initial tumor shrinkage followed by tumor progression. Table 7 and Table 8 list the parameter estimates and their estimation precision. Two distinct sub-populations, based on the rate of tumor shrinkage, for trial C data were identified during model diagnosis. It is estimated that the proportion of patients with fast shrinkage rate is 12% for C1 and 20% for C2. The other patients in trial C had slower shrinkage rates.

Figure 1. Diagnostic plots for tumor size model for each of the treatment arms. The symbols represent the observed individual tumor size measurements and the solid line represents the line of identity





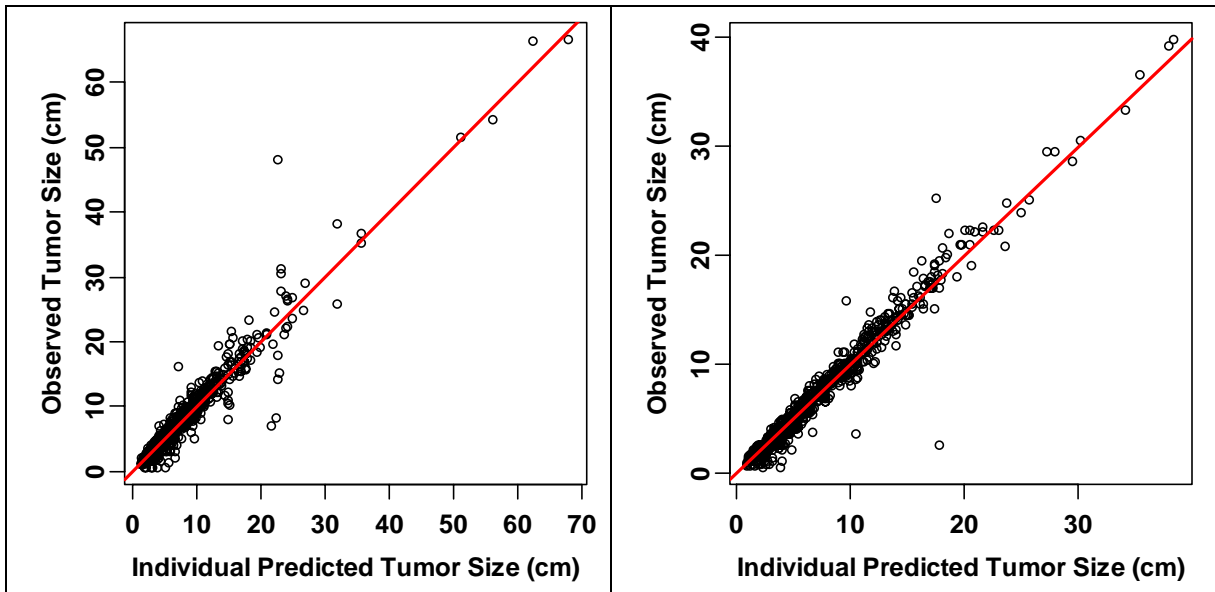


Figure 2. The time-course of tumor change for representative individual patients. The symbols represent the observed tumor sizes, the solid line represents the overall population mean tumor size and the broken line represents the individual predicted tumor size

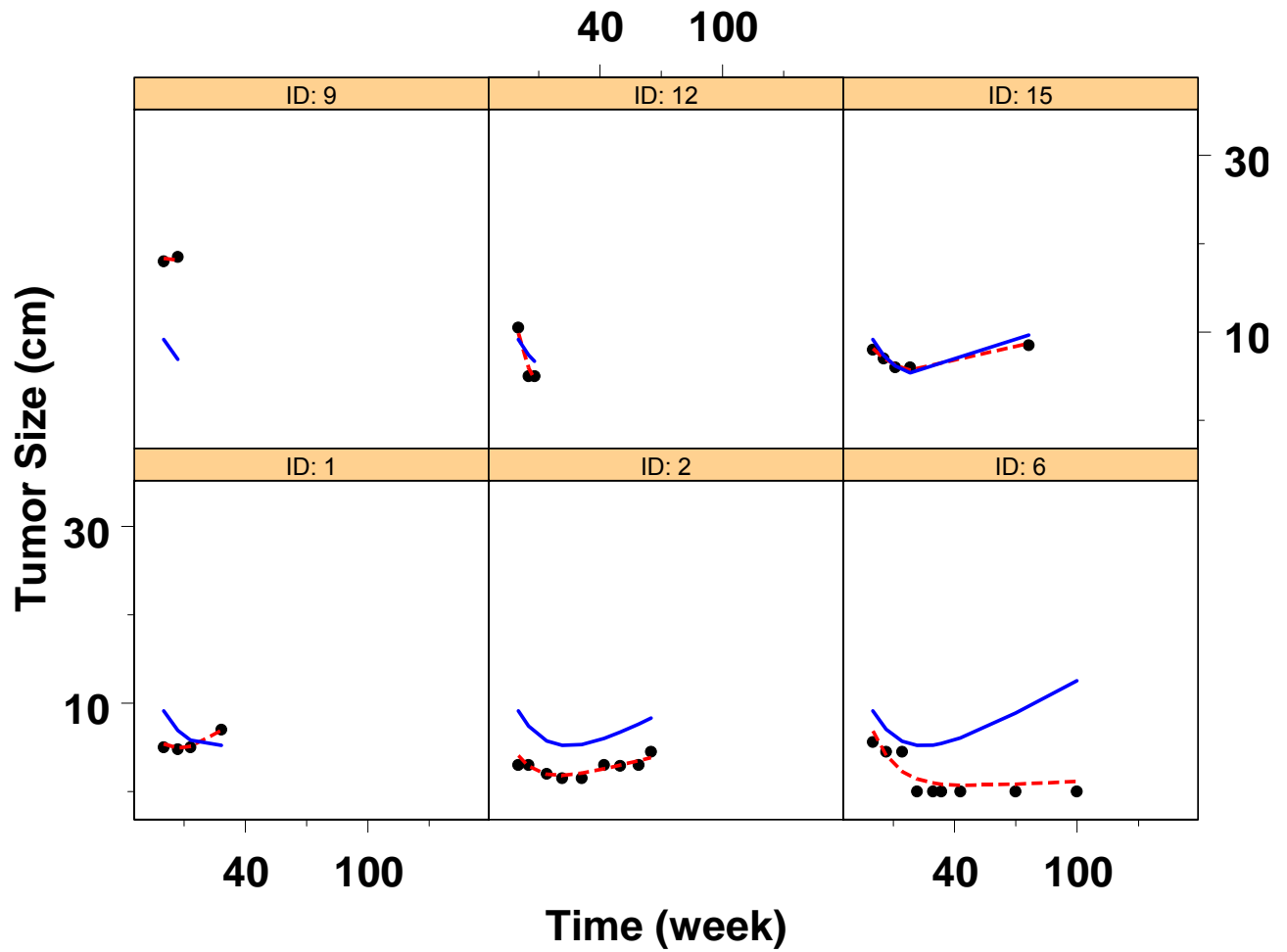


Table 7. *Parameter estimates and their precisions (SE) for the tumor progression model for Trials A, B and D (between and within patient variability is expressed as a percentage)*

Treatment	M_BASE (cm)	M_SR (1/week)	M_PR (cm/week)	ω_{BASE}	ω_{SR}	ω_{PR}	σ
A1	9.1 (0.33)	0.06 (0.004)	0.13 (0.02)	59% (0.04)	73% (0.11)	110% (0.39)	15% (0.01)
A2	8 (0.3)	0.038 (0.01)	0.14 (0.04)	63% (0.06)	98% (0.47)	74% (0.18)	16% (0.03)
B1	8.7 (0.31)	0.052 (0.01)	0.16 (0.02)	57% (0.07)	74% (0.17)	74% (0.14)	20% (0.02)
B2	9.2 (0.38)	0.047 (0.005)	0.16 (0.02)	64% (0.09)	77% (0.19)	67% (0.12)	18% (0.02)
B3	8.5 (0.28)	0.063 (0.01)	0.17 (0.02)	50% (0.04)	75% (0.18)	92% (0.34)	16% (0.02)
D1	8.5	0.033	0.13	77%	190%	14%	26%

	(0.82)	(0.01)	(0.02)	(0.23)	(1.79)	(1.02)	(0.06)
D2	7.4	0.023	0.25	70%	270%	49%	14%
	(0.47)	(0.01)	(0.05)	(0.11)	(1.46)	(0.18)	(0.02)

Table 8. *Parameter estimates and their precisions (SE) for the tumor progression model for Trial C(between and within patient variability is expressed as a percentage)*

Treatment	M_BASE (cm)	M_SR (slow) (1/week)	M_SR (fast) (1/week)	Proportion of patients with fast SR	M_PR (cm/week)	ω_{BASE}	ω_{SR}	ω_{PR}	σ
C1	8.6	0.0047	0.13	0.12	0.2	66%	430%	60%	9%
	(0.44)	(0.001)	(0.004)	(0.03)	(0.02)	(0.08)	(1.63)	(0.56)	(0.02)
C2	8.4	0.0045	0.11	0.2	0.058	67%	280%	80%	15%
	(0.32)	(0.001)	(0.05)	(0.02)	(0.02)	(0.09)	(0.53)	(0.34)	(0.02)

Survival model

Baseline tumor size (centered at 8.5 cm), ECOG status (0/1) and percent tumor reduction from baseline at week 8 (PTR_{wk8}) were found to be the best predictors for time to death (T) as in Equation 4.

$$\log(T) = \alpha_0 + \alpha_1 \cdot ECOG + \alpha_2 \cdot (Baseline - 8.5) + \alpha_3 \cdot PTR_{wk8} + \varepsilon \text{ (Equation 4)}$$

where T is the time to death (day), α_0 is the intercept, α_{1-3} are the slopes for ECOG, centered baseline and tumor size percentage reduction from baseline at week 8, and ε is the residual variability following a normal distribution with mean of zero and variance of σ^2 .

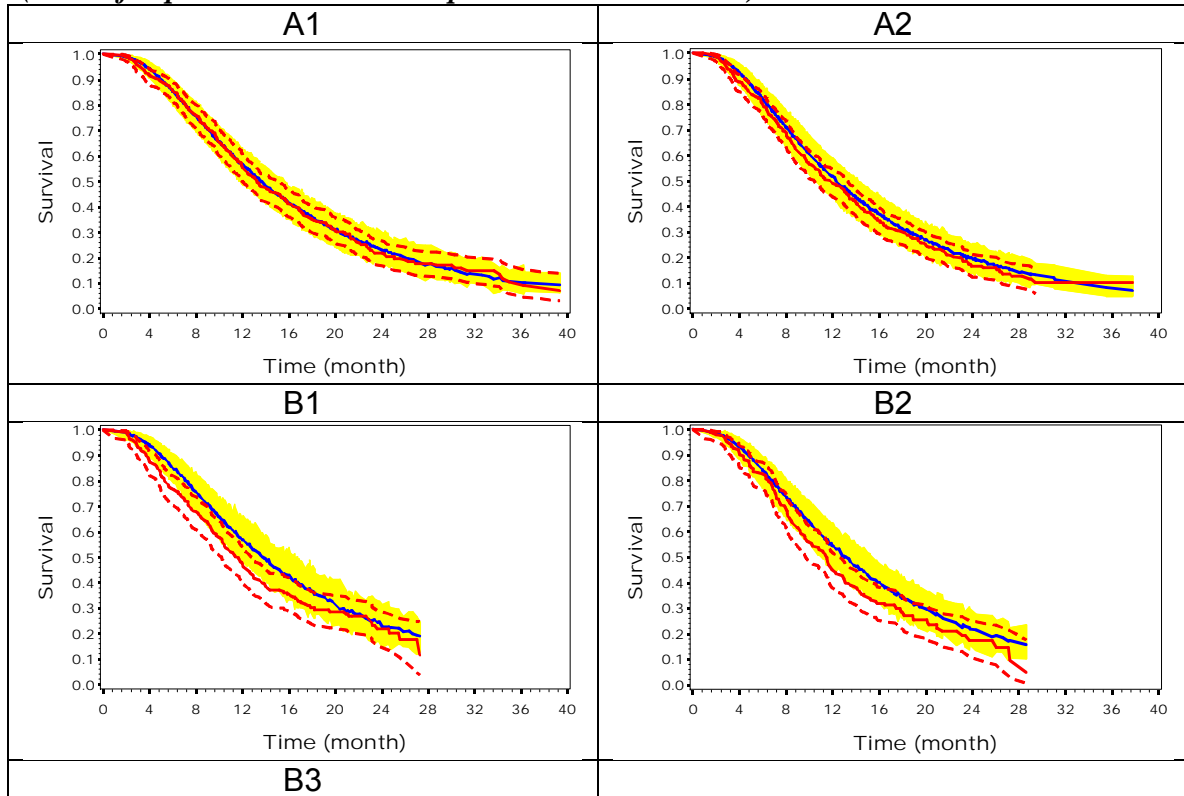
Log-normal distribution was selected for the tumor-survival model based on likelihood ratio tests (Table 9). And diagnostic plots (Figure 3) also support the log-normal distribution. The model developed based on A1 arm data was used to predict the survival curves for the other 8 treatments. The predicted survival curves (mean and 95% CI of 1000 replicates) match the observed survival curves and their 95% CI reasonably well (Figure 3). This observation is notable given that the treatments studied have different mechanisms of action and were studied in different trials. Parameter estimates and their estimation precision are listed in Table 10. An exploratory pooled analysis of all the 4 trials showed that first-line and second-line treatments had significantly different slopes for tumor size percentage change at week 8 and marginally different slopes for ECOG and intercept (Table 11).

Table 9. *-2loglikelihood for each group under various distributions (Exponential is nested within Weibull (df=1), Weibull is nested within Gamma (df=1), and log-normal is nested within Gamma (df=1))*

Distribution	A1	A2	B1	B2	B3	C1	C2	D1	D2
Exponential	807.3	821.6	726.3	673.2	647.2	273.4	536.2	407.5	427.2
Weibull	728.2*	750.9*	664.6*	596.3*	543.6*	241.5*	502.8*	349.4*	346.1*
Gamma	697.2*	715.8*	636.4*	562.8*	532.9*	233.8*	479.3*	344.3*	337.1*
Log-normal	697.6	717.2	637.5	564.8	535	233.9	482.2	344.3	337.1

*: Reduction in -2loglikelihood is >3.8, corresponding to $p \leq 0.05$ for chi-square test with degree of freedom (df) of 1. The significance for Gamma is relative to Weibull. Relative to log-normal, Gamma is not significant for any group. Therefore, log-normal was selected.

Figure 3. *Predicted survival curves versus observed survival curves. The blue solide line and yellow shaded area represent the predicted survival curve and its 95% CI and the red solid and dashed lines represent the observed survival curve and its 95% CI. (model for prediction was developed based on A1 alone)*



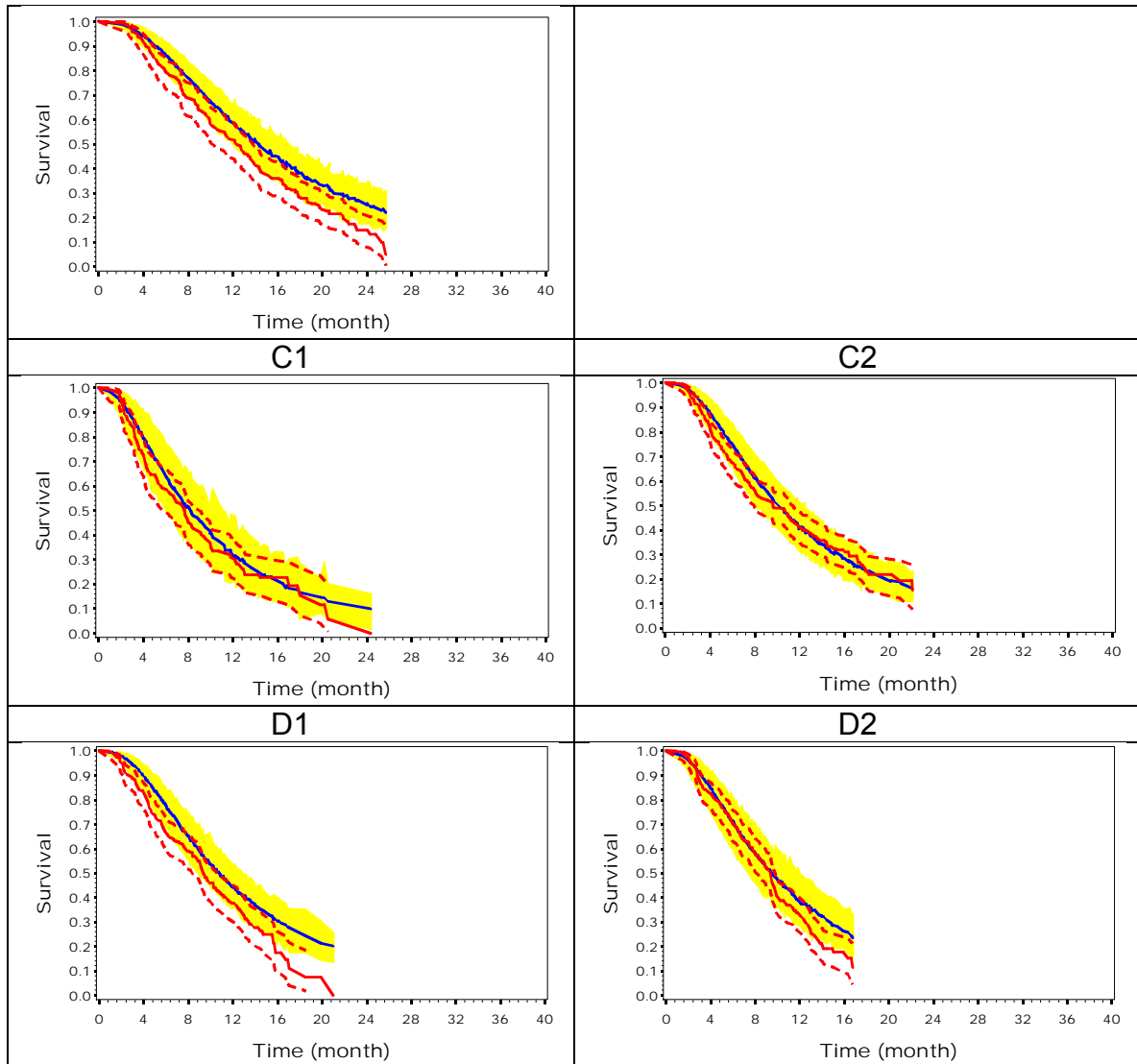


Table 10. Parameter estimates and the precision (SE) for tumor-survival model

Parameter	Treatments								
	A1	A2	B1	B2	B3	C1	C2	D1	D2
α_0	5.9 (0.093)	5.8 (0.071)	5.6 (0.072)	5.6 (0.067)	5.8 (0.067)	6 (0.15)	5.9 (0.13)	6 (0.13)	5.9 (0.11)
α_1	-0.31 (0.084)	-0.2 (0.084)	-0.18 (0.092)	-0.092 (0.085)	-0.37 (0.082)	-0.52 (0.16)	-0.26 (0.14)	-0.43 (0.14)	-0.34 (0.12)
α_2	-0.029 (0.0073)	-0.028 (0.0079)	-0.03 (0.0092)	-0.022 (0.007)	-0.037 (0.009)	-0.047 (0.012)	-0.035 (0.01)	-0.02 (0.0084)	-0.035 (0.0097)
α_3	0.94 (0.21)	0.8 (0.17)	1.4 (0.2)	1.3 (0.19)	0.96 (0.15)	0.48 (0.2)	0.58 (0.23)	0.25 (0.1)	0.53 (0.14)
σ	0.72	0.74	0.74	0.67	0.65	0.69	0.8	0.68	0.6

(0.033) (0.033) (0.038) (0.034) (0.032) (0.053) (0.048) (0.046) (0.038)

Table 11. Parameter estimates and the precision (SE) for pooled analysis

Parameter	First-line	Second-line
α_0	5.7 (0.033)	5.8 (0.052)
α_1	-0.22 (0.039)	-0.33 (0.039)
α_2	-0.030 (0.0036)	-0.036 (0.0046)
α_3	1.1 (0.081)	0.39 (0.062)
σ	0.74 (0.016)	0.79 (0.022)

Since certain fractions of data were excluded during the survival model development, efforts were made to develop separate survival models for the excluded data based on only baseline risk factors. Due to the smaller sample size within each treatment, baseline tumor size and ECOG status could not be simultaneously identified as significant predictors for survival time across all nine treatments. Therefore, a simplified survival model (Equation 5) was fitted to each ECOG level within each treatment.

$$\log(T) = \alpha_0 + \varepsilon \text{ (Equation 5)}$$

The parameter estimates are presented in Table 12. The larger residual variability (σ) is partially due to the lack of any predictors in the model.

Table 12. Parameter estimates and the precision (SE) for excluded data

Treatment	α_0				σ			
	ECOG0	ECOG1	ECOG2	ECOG3	ECOG0	ECOG1	ECOG2	ECOG3
A1	5.8 (0.33)	5.2 (0.21)	- -	- -	1.8 (0.28)	1.6 (0.17)	- -	- -
A2	5.7 (0.3)	4.9 (0.13)	- -	- -	1.6 (0.24)	1.2 (0.1)	- -	- -
B1	5.7 (0.22)	5 (0.18)	- -	- -	1.4 (0.18)	1.4 (0.14)	- -	- -
B2	5.3 (0.16)	4.4 (0.18)	- -	- -	1.3 (0.13)	1.3 (0.13)	- -	- -
B3	5.1 (0.15)	5 (0.2)	- -	- -	1.2 (0.12)	1.5 (0.16)	- -	- -
C1	5.4 (0.53)	4.6 (0.16)	4.6 (0.15)	4.2 (0.17)	1.4 (0.43)	1 (0.11)	1.1 (0.11)	0.8 (0.12)
C2	6.4	4.7	4.9	4.2	1.5	1.4	1.3	1.2

	(0.47)	(0.16)	(0.12)	(0.19)	(0.43)	(0.13)	(0.09)	(0.14)
D1	5.3	4.4	4.2	-	0.7	1	1	-
	(0.21)	(0.17)	(0.16)	-	(0.16)	(0.12)	(0.12)	-
D2	5.4	4.7	4.7	-	1.1	1.1	0.7	-
	(0.57)	(0.22)	(0.13)	-	(0.51)	(0.17)	(0.1)	-

3 Discussion

Two earlier reports from the FDA describe the regulatory basis and experience in using tumor change based endpoints for accelerated approvals.^{2 3} In contrast, the focus of the current scientific research is to understand the time course of tumor progression and relate that to the probability of survival. The ultimate goal of our research is to provide a tool for rendering oncologic drug development more efficient. Specifically, by quantifying the various aspects of patient risk factors and tumor growth, we have developed models that can be incorporated into clinical trial simulations to aid early drug development decisions such as molecule screening, mortality trial design and dose selection.

Three sub-models are required for these simulations. First, the distributions of the key baseline risk factors are required to simulate the patient population. Second, the time course of the tumor shrinkage/progression is needed to quantify the effects of therapy on tumor size. Third, the relationship between the tumor size and time to death should be known to allow the impact of therapy on patient survival to be predicted. These models should ultimately allow clinical trial simulation for survival trials.

In agreement with the publication by Brundage, *et al.*, we found that ECOG performance status is by itself an important risk factor in NSCLC patients. Our analysis further provides a quantitative model to recreate an ECOG status distribution for simulating future trial populations.

Previously Mery *et al*⁴ and Port *et al*⁵ reported the hazard ratios for overall survival reflecting the relationship between the tumor size category (1-1.9 cm, 2-2.9 cm, 3-3.9 cm, 4-4.9 cm, 5-6 cm) and time to death in stage 1 or 1A NSCLC patients. According to Mery *et al*, the hazard ratio gradually increased from 1.27 to 1.95 with increasing baseline tumor size for these Stage 1 tumor size categories, respectively, relative to the 1-1.9 cm group in a total of 9191 patients. Port *et al* found that the hazard ratio was about 1.5 for the group having tumors larger than 2 cm compared to those with smaller tumors among 244 Stage 1A patients. By contrast, Patz *et al*⁶ found no correlation between tumor size as a continuous variable or as a categorical variable and overall survival in 510 Stage 1A NSCLC patients. Black⁷ subsequently described multiple reasons why the

findings of Patz, *et al* might not reflect current understanding of this disease. The identification of baseline tumor size as a significant predictor for overall survival in our analysis supports the conclusions of Mery, *et al.* and Port, *et al.* even though patients in our database had more advanced (Stage IIIA/B or IV) NSCLC. This finding in patients with more advanced cancer strengthens the observed relationship between baseline tumor size and prognosis for survival. The distributions of the ECOG status and tumor size at baseline for our database were described in the current article and can be used to simulate the baseline disease status for a patient population.

The time course of tumor growth can be described using several different approaches. The Gompertz model ⁸ is widely applied and considered as a classic approach to model tumor growth. Swan's book ⁹ describes numerous mathematical models involving differential equations that deal with the dynamic, or time course, variation of cancer. A more recent model by Barbolosi and Iliadis ¹⁰ incorporated a cell-loss component into Gompertz-type growth equation in order to quantify the effect of drug exposure on the cell death. These models were explored. However, most of the data could not be described with stable models. By contrast, a mixed exponential and linear model was developed to describe the time course of tumor size. This relatively simple model is much more stable than other more complicated models for the database we studied. The exponential tumor shrinkage component characterizes the treatment effect on tumor shrinkage over time, which will reduce the tumor size asymptotically towards zero. The rate constant for the shrinkage is restricted to be non-negative. The linear growth component is an approximation of the tumor's growth under a specific treatment. Therefore, the slope for the linear growth is also treatment dependent in our model. This parameter is also restricted to be non-negative. Patients with a good response to treatment have large shrinkage rate constants and small slopes for linear growth, while patients with a poor treatment response have small shrinkage rate constants and a larger slope for linear growth. Given the sparse measurements of tumor size in the database and the single dose regimen in each treatment, this model is flexible enough to describe individual tumor observations well (Figure 1 and Figure 2). If the relevant information is available, the tumor size model can be expanded to include dose or drug exposure effect, which could influence both the shrinkage and linear growth rate constants. In addition, other more complicated models can be applied to quantify the tumor size change over time.

Table 7 and Table 8 present the tumor model parameter estimates. Each treatment arm was modeled separately to obtain the best individual prediction (Figure 1). For trial C, a mixture model is necessary to separate this population into two subgroups, one with fast shrinkage (~12-20%) and the other with slow shrinkage (~80-88%), to achieve the desired individual prediction. Interestingly,

some treatment effects are on the shrinkage rate (trial A), some on the growth rate (trial C), and some on both (trial D). Given the lack of different treatment effects on either shrinkage rate or growth rate in trial B, one can surmise that no difference would be expected in the survival outcome.

Figure 3 shows the model-predicted and observed proportions of patients surviving on study for all treatment arms. For treatment A1, the model predicted and observed surviving proportions are superimposed signifying that a log-normal survival function is appropriate. The shaded confidence interval for these predictions is tight. Also shown in Figure 3 is the ability for the survival model built using A1 data to predict the surviving proportions for all other treatments. Considering the diversity of treatment regimens and follow-up schedules, the overall predictions are impressive. The predictions are best (by graphical inspection) for A2 compared to the other arms, suggesting the model may be further improved by including more predictors, *e.g.* additional trial-specific factors that were missed during initial identification of risk factors.

Among the different times when tumor size was evaluated, week 8 tumor size change was selected because it was consistently identified as a significant predictor across all nine treatments. Importantly, it is also still early enough to serve as an “early” biomarker for survival prediction. The large difference among the coefficients for percent tumor reduction at 8 weeks for the different treatments (0.25 to 1.4) was mainly explained by the fact that treatments in trials A and B were first-line treatments while those in trials C and D were second-line treatments. The significantly smaller slope for PTR_{wk8} for second-line treatment indicated that the survival times for patients under second-line treatment were significantly less sensitive to tumor percentage reduction at week 8 compared to those under first-line treatment when the reference point is no change of tumor size at week 8. The marginally larger intercept for second-line treatment suggests that patients who started second-line treatment with ECOG status of 0 and achieved zero tumor growth by week 8 tend to survive longer than those patients who started first-line treatment with ECOG status of 0 and achieved zero tumor growth by week 8. However, the median percentage reduction of tumor size at week 8 ranged from 15% to 29% for patients under first-line treatments while it ranged from -14% (tumor size increase) to 12% for patients under second-line treatments. This observation suggests that achieving a median zero tumor growth within 8 weeks is not good enough for a first-line treatment.

Even though a Bayesian method can be applied for a meta-analysis to quantify the between-treatment difference in parameter estimates as random effect after incorporating the fixed effects we identified, we felt that reporting the parameter estimates for each treatment would allow the readers to apply non-parametric sampling method to generate parameter set with the appropriate correlation

among these parameters maintained. A weighting scheme can be applied based on the sample size and residual variability in each treatment during sampling. The number of treatment is not large enough to derive a reliable parametric distribution for between-treatment variability without any prior information. It is recommended to use results from trials A and B for first-line treatments and results from trials C and D for second-line treatments. A full clinical trial simulation should include both the included and excluded patients. Therefore, both Equation 4 and Equation 5 should be used to simulate two different patient populations and the results should be combined to form a full population.

Since survival is an integrated endpoint of a drug's efficacy and toxicity, an ideal survival model should also take the drug's toxicity into account. In fact, the parameter estimates in Equation 4 and Equation 5 should be influenced by each treatment's inherent toxicity even though we only included efficacy related biomarkers in the model. The influence, however, could be minimal since the death rate due to toxicity is trivial (0.3% - 3%) compared to the death rate due to the disease (86% - 94%). It is possible that a drug's toxicity may indirectly influence the efficacy outcome by affecting the patients' compliance, e.g. a more toxic treatment may lead to more frequent treatment holidays. However, the net effect is expected to be captured in the efficacy related biomarker, such as tumor size. Unless an oncology drug's toxicity is severe enough to compete with the disease as a significant factor for death, the influence of drug toxicity on overall survival may not be so significant relative to the disease itself.

To the best of our knowledge, our work utilizes one of the world's largest databases of NSCLC trials to develop a quantitative model of survival benefit using patient risk factors and tumor size data. We show that tumor percentage reduction at week 8 can be useful for predicting survival outcome. Therefore, a scheduled visit at week 8 with CT imaging for tumor size measurements can provide an early signal for drug effect. Such information can be then utilized to decide whether to develop that molecule further or not. In addition, if a molecule is selected for further development, pivotal trial design can be optimized using clinical trial simulations. Mortality trials in oncology are costly and patients are challenging to recruit due to availability. Utilizing this model to test various scenarios by computer simulation is perhaps the most cost-effective approach to increasing the trial success rate. Similarly, factors that affect the tumor size such as dose or dosing regimen can be optimized using tumor size changes. Optimizing dose or dosing regimen in mortality trials is impractical given the typical nominal effect size and sample size needs.

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Pediatric Written Requests for Antihypertensive Drugs

Introduction

Pediatric drug research is essential to providing children with safe and effective therapies, but until about 10 years ago drug studies in children were uncommon. Several factors contributed to the lack of pediatric studies, but one of the major factors was the limited financial incentive to do the research. Without pediatric-specific information, doctors and parents were forced to base their decisions about what drugs to give children, and what doses to administer, on results from studies in adults. Differences in the physiology of adults and children can, however, produce significant differences in the way adults and children respond to therapies.

With the growing realization that pediatric treatment decisions based on adult data could put the health of children at risk, Congress added section 505A to the Food, Drug, and Cosmetic Act in 1997, creating a program to encourage drug manufacturers to conduct studies in children. This program allowed a company to receive a six-month extension of marketing exclusivities and patent protections for an active ingredient if they conducted pediatric studies requested by the FDA in a “Written Request.” This incentive is commonly referred to as “pediatric exclusivity.” The exclusivity program has been successful and was reauthorized as the Best Pharmaceuticals for Children Act of 2003, and again under the Food and Drug Administration Amendments Act of 2007. Since the beginning of the exclusivity program, over 830 studies have been requested in 356 Written Requests for pediatric studies. Over 140 medication labels have been updated with pediatric use data from these studies.

Several products studied under the exclusivity program were oral antihypertensive medications that had demonstrated efficacy in clinical trials with adults. Antihypertensive drug products are managed by the Division of Cardiovascular and Renal Products (DCaRP), one of 15 review divisions of the Office of New Drugs in CDER. As of January 2008, DCaRP has authored more than 35 Pediatric Written Requests, 24 of which were in antihypertensives. Based on analysis of data from studies of antihypertensive products studied in the pediatric population, the FDA has had to make adjustments in study design. One of the major changes to the design of the pediatric antihypertensive studies involved modeling of the exposure-response data to optimize the study design including dose selection, sample size, and endpoint selection. A case example illustrating how modeling and simulation was used to design a pediatric antihypertensive study is described below.

Some aspects of the Pediatric Written Request for an antihypertensive drug have evolved over time, based partly upon the experience with various programs. The general features of a modern Written Request include the following:

1. Development of an age-appropriate formulation, the properties of which may need investigation in adults.

2. A study to investigate pharmacokinetics in pediatric patients in the same age range as those investigated for effectiveness, but not necessarily in the same study or even in the target population. Ideally, such an investigation occurs early enough to inform dose selection in the effectiveness trial. The power requirements for the pharmacokinetic study are based upon the advice of the clinical pharmacologists, usually based upon their experience in other settings.
3. A study to investigate effectiveness. A single study with target $\alpha=0.05$ is considered sufficient, because all of these products have already been approved in adults, and the nature of hypertension is considered to be close enough in adults and children so that the adult data are considered supportive. Generally, the first member of a class of antihypertensive agents will study children age 6 to 16 years, and a subsequent member of a class will be asked to study younger children¹. Sponsors are given a choice of several trial designs, but the most common choice is a parallel design with several dose arms chosen to produce exposure in children at least as wide as the range of effective exposures in adults. Typically, the main part of the study has no placebo group², in which case there is a withdrawal phase at the end of the study in which patients are randomized to remain on their assigned dose or withdrawn to placebo. The primary end point can be either systolic or diastolic pressure, measured at the inter-dosing interval ("trough").
4. Many sponsors are openly more interested in obtaining Pediatric Exclusivity than they are in marketing their drug for use in pediatric patients. It is, then, perhaps somewhat surprising that the Written Request does not specify a sample size per se for the effectiveness study. It does, however, specify a minimally clinically relevant effect size. The sponsor is expected to use its estimates of variability to derive a sample size sufficient to detect, with 90% power, the specified effect size. The protocol also must provide for an interim analysis to look at observed variability late in the study. This can be done without unblinding and, consequently, without paying a statistical penalty for the interim analysis. If this interim analysis shows that the originally projected variability was overly optimistic, the sample size must be adjusted appropriately. In this way, the sponsor bears all of the responsibility for designing and conducting a trial optimized for detecting the effect of interest, and the result is likely to yield definitive labeling that the drug either is or is not effective in children.
5. A very optimistic sponsor can conduct a study substantially smaller than the above considerations would require, if they are confident that their product will be effective. A Written Request "escape clause" allows a sponsor to present to FDA a technically incomplete study report showing effectiveness and to petition the Division to amend the Written Request to be compatible with the study they did. The same process would be followed if the study had to be stopped because of

¹ After the second member of a class has been issued a Written Request, it is very difficult for a sponsor to develop a suitable population and end point for a study for which DCaRP will issue a Written Request.

² This has more to do with making parents and investigators comfortable than with any medical rationale. There are no established clinical benefits associated with treatment of hypertension in children.

some safety concern. Either of these results is clearly valuable and would lead to labeling.

6. Because several classes of antihypertensives work less well in adult Blacks than in Caucasians, the Written Requests usually call for 40 to 60% enrollment in each, thus optimizing studies for exploring this phenomenon in children.

Exposure-Response Modeling and Simulation to Design Pediatric Study³

Clinical trial simulations were conducted to support dosing regimens and trial design, as well as to estimate sample size for the pediatric study. Data from adult patients for drug X, placebo data from Corlopan study and experience in developing anti-hypertensive for immediate blood pressure (BP) control in pediatric population were used. The simulation experiment allowed us to design a powerful and informative study for pediatric patients, more specifically, it allowed us to

1. Study the effect on sample size, if the pediatric patients were less responsive and less sensitive compared to adult patients.
2. Study the impact of missing data and guide the choice of powerful statistical method for primary analysis.
3. Study the factors affecting the success of a given study

We reviewed clinical trial simulations and study design for drug X submitted by the sponsor. The objectives were to support dosing regimens and trial design, as well as to estimate sample size for the pediatric study. The proposed study was aimed to study the BP lowering effects of drug X administered I.V. in pediatric subjects (age 2-16 years) with asymptomatic stage 2 hypertension. The simulation experiment submitted by the sponsor was extended to include in-house data and experience in developing anti-hypertensive for immediate BP control in pediatric population.

Simulation was performed using a population pharmacokinetic (PK) and pharmacodynamic (PD) model derived using drug X data from adult patients. The placebo response rate from the PK-PD model appeared to be lower than the observed rate for Corlopan⁴, an approved treatment for identical indication. The placebo data for Corlopan were also included.

The following study design aspects were reevaluated:

1. dose regimen
2. trial duration
3. sample size
4. primary analysis

³ Wang Y et al. Leveraging prior quantitative knowledge to guide drug development decisions and regulatory science recommendations: impact of FDA pharmacometrics during 2004-2006. J Clin pharmacol. 2008; 48(2):146-56.

⁴ http://www.fda.gov/cder/foi/label/2004/19922se5-005_colopan_lbl.pdf

5. follow up trial design
6. sampling scheme

Simulation Experiment

Methods

Data

The simulation was based on population PK and PD models derived using data from a previous clinical study in adult patients and in-house pediatric placebo data from short term studies. These models were used to simulate plasma drug X concentrations and BP effects in children assuming that the PK and PD parameters would be similar in pediatric and adult populations. Subsequently, an alternate trial design scenarios were explored, assuming low sensitivity and response in pediatrics compared to that of adults.

Treatment

A total of five doses including placebo were selected for simulation. These doses were selected to cover adult dosing recommendations and possibly study higher doses. For the given indication, it was generally believed that the dose range in pediatrics should cover 50% of the lowest dose up until two fold of the highest dose in adults. Such dose selection was especially important, if the pediatric patients were to be less responsive and less sensitive compared to adult patients.

PK Model

An appropriate PK model implementing weight normalized parameters was used.

Placebo Model

The placebo model used by the sponsor assumed no systematic placebo effect over time, which could be reasonable. The placebo effect was handled via the residual error. However, in-house data from similar studies suggest that the mean placebo effect was variable over time and the response rate on placebo was higher than predicted by the model. Therefore, placebo data were simulated assuming a multivariate normal distribution to maintain correlation among observations.

PD Model

The PD model submitted by the sponsor was used to simulate effect of drug X on systolic BP (SBP) and diastolic BP (DBP). The final model assumed an E_{\max} relationship between response and plasma drug X concentration. The residual variability reported with the original model was ignored as for the most part the placebo model accounts the residual variability. However, the current approach ignored contribution of model misspecification. Also, the E_{\max} estimates were lowered (empirically) by 3% to accommodate placebo effect as the PD model development did not include placebo data.

Dropout Model

Dropout rates were approximated as the fraction of patients experiencing a $\geq 25\%$ reduction of DBP rather than a $\geq 25\%$ reduction of either SBP or DBP, because DBP percent reductions were greater on average than SBP percent reductions, and the correlation between DBP and SBP was not modeled. Thus the dropout rate was slightly underestimated, but would be substantially overestimated if both DBP and SBP were used.

Simulation Scenarios

The study design was a randomized, placebo-controlled, parallel group, dose-ranging study of drug X. For each of the five dose groups, five sample size levels per group were simulated (10, 20, 30, 40, 50 subjects per group). The simulation method was Monte Carlo (using random draws). The PK data were simulated in Pharsight Trial Simulator Version 2.2 using the weight-normalized PK model. Different scenarios (Table 1) governing PK-PD relationship in the pediatric population were simulated in S-Plus Version 7.0.

Table 1: List of scenarios

	Scenarios
1	Pediatrics EQ Adults ⁵ (Base design)
2	Pediatrics NE Adults (E_{\max} 0.75x : EC_{50} 1.5x)
3	Pediatrics NE Adults (E_{\max} 0.5x : EC_{50} 2x)
4	Pediatrics NE Adults (Null data)

For each scenario a total of 300 trials were simulated. NE=Not equal to

Data Analysis

Data were analyzed by the following methods to assess power and type-1 error.

Method⁶	Null hypothesis
Slope of dose response curve (β)	$\beta = 0$
Analysis of variance (pooled treatment data)	$\mu_{\text{pooled treatment : 30}} = \mu_{\text{placebo : 30}}$
Proportions test ⁷ (pooled treatment data)	$\text{Prop}_{\text{pooled treatment : 30}} = \text{Prop}_{\text{placebo : 30}}$
Mixed model repeated measures	$\mu_{\text{treatment : 30}} = \mu_{\text{placebo : 30}}$

β is a slope of linear regression, μ represents mean of the response variable (SBP), Prop represents the proportion of responders (as defined). The subscript represents the treatment identifier and the number represents the time in minutes at which the comparison is made.

In addition to above, sequential testing from the highest dose to lowest dose using analysis of variance (ANOVA) and simultaneous testing of all doses by the Dunnett's method using ANOVA were also evaluated. However, these methods did not perform better than the mixed model repeated measures in terms of power.

Slope of dose response curve (Dose response)

⁵ EQ means 'equal to' and NE means 'not equal to'

⁶ Missing data imputation- last observation carried forward (LOCF)

⁷ Criteria: subjects in each active dose group who achieve $\geq 10\%$ reduction in SBP from baseline

The primary endpoint for this test was significant dose-response (differs from zero at $\alpha=0.05$) at the end of double blind phase (ITT evaluation). A linear regression line was fitted to % change from baseline in SBP as a dependent variable and dose as an independent variable at 30 minute. The missing data were imputed using LOCF.

Analysis of variance on pooled treatment data (Pooled)

The primary endpoint for this test was % change from baseline in SBP at the end of double blind phase (ITT evaluation) on pooled treatment compared to that of on placebo ($\alpha=0.05$). The missing data were imputed using LOCF.

Proportions test on pooled treatment data (Chisq)

The primary endpoint for this test was proportion of subjects who experience reduction in SBP of at least 10% from baseline at the end of double blind phase on pooled treatment compared to that of on placebo (ITT evaluation) ($\alpha=0.05$). A chi-square test for proportions was used. The missing data were imputed using LOCF.

Mixed Model Repeated Measures (MMRM)

The primary endpoint for this test was % change from baseline in SBP at the end of double blind phase (ITT evaluation) on all treatments compared to that of placebo ($\alpha=0.05$). The MMRM analysis was implemented via PROC MIXED in SAS 9.1 by fitting all the data collected during the double blind phase (no imputation). The model was fitted to % change from baseline in SBP as a dependent variable and treatment, time and treatment-by-time interaction. A treatment-by-time contrast was constructed to estimate difference between treatments in mean % change from baseline as an endpoint. An unstructured (co)variance matrix was used to model the within subject errors. Parameters were estimated using restricted maximum likelihood method. Holm's procedure was applied to adjust for the multiple comparisons among doses.

Power and type-1 error

For each scenario the proportion of positive (as defined above) trials out of 300 for each endpoint were calculated at each sample size levels. The power is defined as the probability of rejecting the null hypothesis. The type-1 error is defined as the probability of rejecting the null hypothesis for the null data scenario.

Results

The proportion of subjects with greater than 10% reduction in DBP increased with drug X dose groups. Under the placebo model assumptions, the simulated data overestimated % patients with greater than 10% reduction in DBP on placebo compared to that of observed data. For example, at 5 minute sampling event, the simulated ~20% patients with greater than 10% reduction in DBP on placebo did not match well with the observed 13% response rate (internal data). Also, the cumulative dropout rate of ~20% at 30 minute did not match well with the observed 7 % dropout rate (internal data).

For the base design the MMRM was superior to all the methods of analysis. However, with 25 subjects per arm, all the methods have ~80% or more power to reject the null hypothesis. On the other hand, the power decreased drastically if pediatric population is less sensitive and less responsive. The MMRM was still superior compared to other

methods. The MMRM method exhibited ~80% power at 40 subjects per group, whereas, other methods had very low power (>50%) under the scenarios of low sensitivity and low response. A potential extreme case of non-responsive pediatric population (E_{\max} 0.5x : EC_{50} 2x) required a sample size of 45 subjects per group and a moderate case of non-responsive pediatric population (E_{\max} 0.75x : EC_{50} 1.5x) required a sample size of 25 subjects per group. For completeness, the dose response was also analyzed for the simulated data without enforcing dropout assumption (Dose response- no dropout). The power was comparable to that of MMRM. However, the power was high compared to dose response analysis with dropout assumption. In other words, the use of LOCF as an imputation technique made the dose response shallower than it actually is.

The type-1 error for MMRM at 40 subjects per arm was 6.33%.

Discussion

Pediatrics NE Adults (E_{\max} 0.5x : EC_{50} 2x) scenario was considered a potential extreme case scenario in this setting. The pediatric population has been found to be less sensitive and less responsive compared to that of adults consistently across antihypertensives.⁸ The following are some of the recommendations incorporated to improve the proposed design:

1. A total of five dose groups including placebo should be studied.

Given the approved dose range in adults, it was recommended that the dose range in pediatrics should cover 50% of the lowest dose up until two fold of the highest dose in adults. Such dose selection was especially important, if the pediatric patients were less responsive and less sensitive compared to adult patients.

2. A total of 40 subjects per group (200 in a study) should be evaluated to establish safety and effectiveness of drug X.

As explained earlier, under the placebo model assumptions, the simulated data overestimated % patients with greater than 10% reduction in DBP and the cumulative dropout rate. This is due to normality assumption that does seem to hold at the tails of the distribution. Such bias was believed to guard against unusually high placebo response that could have negative impact on trial results; therefore, no attempt was made to truncate the distribution. Needless to say, absence of such high placebo response rate and/or dropout rate further improves the possibility of a successful study. In addition, the number of subjects in a study was also driven by requirement of safety data.

3. A Mixed Model Repeated Measures analysis (MMRM) comparing % change from baseline in SBP on drug X treatment versus placebo should be used for the primary statistical analysis.

The sample size of 15 per group offered 80% power to reject the null hypothesis, if the effect in pediatrics were comparable to that of adults. A potential extreme case of non-responsive pediatric population (E_{\max} 0.5x : EC_{50} 2x) required a sample size of

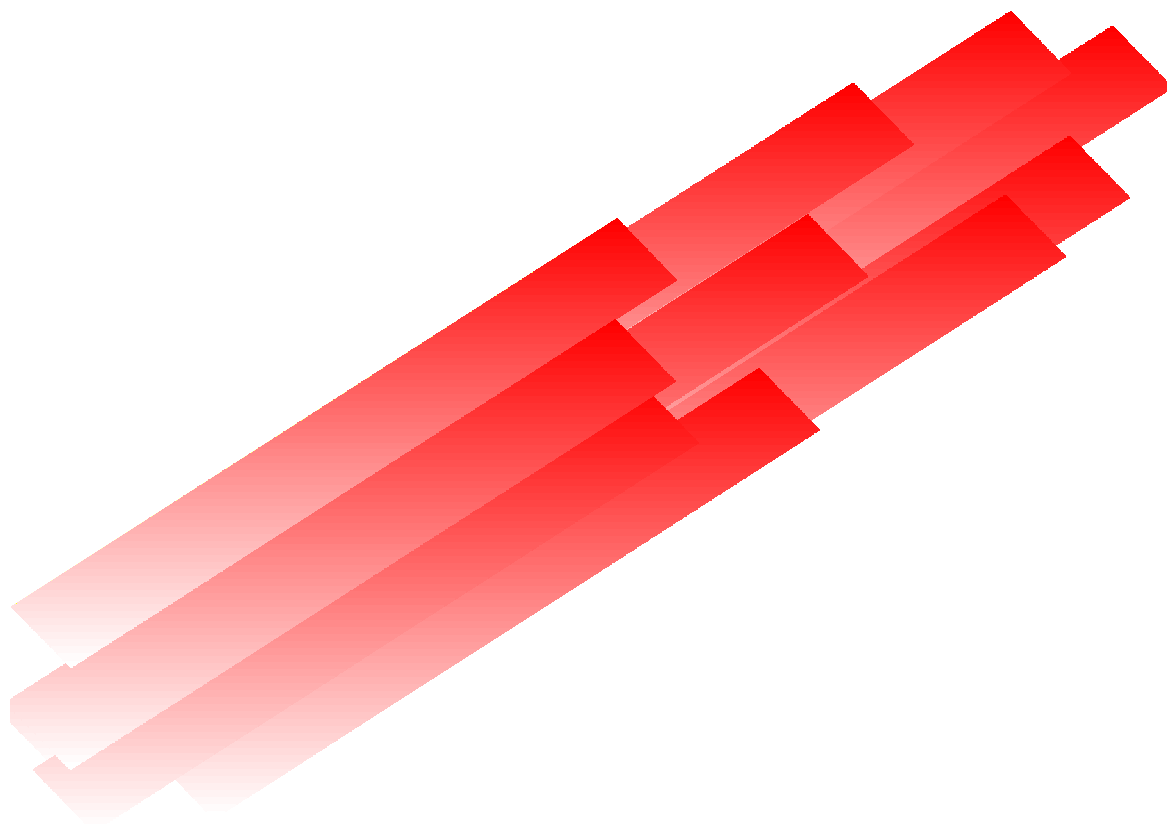
⁸ http://www.fda.gov/cder/foi/label/2004/19922se5-005_colopam_lbl.pdf

45 subjects per group and a moderate case of non-responsive pediatric population (E_{\max} 0.75x : EC_{50} 1.5x) required a sample size of 25 subjects per group.

The power of MMRM test was not unexpected. The major dropout reason considered in this study was dependent on patient's response. Meaning, the reason for dropout was dependent on the patient's last observed response. In statistical literature, such dropouts are termed Missing at Random (MAR). Under the MAR assumption, the likelihood based methods, such as MMRM are expected to be powerful and less biased. Therefore, an MMRM analysis with unstructured covariance matrix was recommended as the primary analysis method. The analysis will use SBP data measured at every five-minute time point during the 30-minute infusion (5 minutes, 10 minutes, up to 30 minutes). The covariates in the model included treatment, time and treatment-by-time interaction. The treatment-by-time interaction was the only interaction term in the model. REML estimation and Holm's procedure or sequential testing of doses for multiple comparison adjustment was recommended.

Guidance for Industry

Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling



**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
May 1998
BP 3**

Guidance for Industry

Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling

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GUIDANCE FOR INDUSTRY¹

Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling

I. INTRODUCTION

This guidance is intended for sponsors who, during the investigational phase of drug development, plan to conduct studies to assess the influence of renal impairment on the pharmacokinetics of an investigational drug.

II. BACKGROUND

After entering the body, a drug is eliminated either by excretion or by metabolism. Although elimination can occur via any of several routes, most drugs are cleared by elimination of unchanged drug by the kidney and/or by metabolism in the liver. For a drug eliminated primarily via renal excretory mechanisms, impaired renal function may alter its pharmacokinetics (PK) and pharmacodynamics (PD) to an extent that the dosage regimen needs to be changed from that used in patients with normal renal function. Although the most obvious type of change arising from renal impairment is a decrease in renal excretion, or possibly renal metabolism, of a drug or its metabolites, renal impairment has also been associated with other changes, such as changes in absorption, hepatic metabolism, plasma protein binding, and drug distribution. These changes may be particularly prominent in patients with severely impaired renal function and have been observed even when the renal route is not the primary route of elimination of a drug. Thus, for most drugs that are likely to be administered to patients with renal impairment, PK characterization should be assessed in patients with renal impairment to provide rational dosing recommendations.

¹ This guidance has been prepared by the Renal Impairment Working Group in the Clinical Pharmacology Section of the Medical Policy Coordinating Committee in the Center for Drug Evaluation and Research (CDER), with input from the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration. This guidance document represents the Agency's current thinking on this subject. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

This guidance makes recommendations regarding:

- When studies of PK in patients with impaired renal function should be performed—and conversely, when they may be unnecessary;
- The design and conduct of PK studies in patients with impaired renal function;
- The design and conduct of PK studies in end-stage renal disease (ESRD) patients treated with dialysis (hemodialysis or peritoneal dialysis);
- The analysis and reporting of the results of such studies;
- Representation of these results in approved product labeling.

III. DECIDING WHETHER TO CONDUCT A STUDY IN PATIENTS WITH IMPAIRED RENAL FUNCTION

A. When Studies May Be Important

A PK study in patients with impaired renal function is recommended when the drug is likely to be used in these patients and (1) renal impairment is likely to significantly alter the PK of a drug and/or its active/toxic metabolites and (2) a dosage adjustment is likely to be necessary for safe and effective use in such patients. In particular, a study in patients with impaired renal function is recommended when the drug or its active metabolites exhibit a narrow therapeutic index² and when excretion and/or metabolism occurs primarily via renal mechanisms (excretion or metabolism). A study also should be considered when a drug or an active metabolite exhibits a combination of high hepatic clearance (relative to hepatic blood flow) and significant plasma protein binding. In this setting, renal impairment could induce a significant increase in the unbound concentrations after parenteral administration due to a decreased plasma protein binding coupled with little or no change in the total clearance (decrease in unbound clearance).

B. When Studies May Not Be Important

For some drugs, renal impairment is not likely to alter PK enough to justify dosage adjustment. In such cases, a study to confirm that prediction may be helpful but is not necessary. If a study is not conducted, the labeling should indicate that the impact of renal

² The therapeutic index may be derived from the concentration- or dose-response data existing in the safety/efficacy database.

impairment was not studied, but that an effect requiring dosage adjustment is unlikely to be present. Current knowledge suggests that the following drug properties may justify this approach:

- Drug and active metabolites with a relatively wide therapeutic index and that are primarily eliminated via hepatic metabolism or biliary excretion;
- Gaseous or volatile drug and active metabolites that are primarily eliminated via the lungs;
- Drugs intended only for single-dose administration unless clinical concerns dictate otherwise.

Controversy exists regarding the impact of severe renal impairment on hepatic metabolism. For this reason, a renal impairment study is still considered desirable for a drug eliminated primarily via hepatic metabolism unless it also has a relatively wide therapeutic index.

Even when renal impairment is likely to have little or no effect on a drug's PK, the impact of dialysis on the PK of a drug should be considered. Patients on dialysis may require greater doses of certain drugs than patients with normal renal function. This is discussed further in the following section.

IV. STUDY DESIGN

The safety and efficacy of a drug generally are established for a particular dosage regimen (or range of dosage regimens) in late phase (phase 3) clinical trials involving relatively typical representatives from the target patient population. More often than not, individuals with significantly impaired renal function are explicitly ***excluded*** from participation in these studies, although there may be a sufficient range of function to obtain an initial estimate of the effects of decreased renal function. The primary goal of the recommended study in patients with impaired renal function is to determine if the PK is altered to such an extent that the dosage should be adjusted from that established in the phase 3 trials.

Thus, the study should reasonably focus on comparing patients with renal impairment to patients with renal function that is typical of the usual patient population — ***not necessarily to normal healthy young volunteers***.

The strategy used in this section describes the basic “full” study design that could be applied to most drugs whose pharmacodynamics (i.e., concentration-response relationship) are known to be unaffected by renal impairment or whose therapeutic indices are sufficiently large to preclude safety concerns. Then, cases are identified for which some elements of the full study design may

be simplified or excluded depending on the properties of the drug and its anticipated use in the target patient population.

A. Basic “Full” Study Design

1. Study Participants

The control renal function group in this study should optimally be representative of a typical patient population for the drug to be studied. In particular, it should not consist of normal healthy young male volunteers if the typical patient population is made up of older people, including women. However, enrollment of enough individuals with varying degrees of renal impairment who are also patients with the condition for which the drug is indicated may be difficult. An acceptable alternative would be to use volunteers who are comparable to the typical patient population with respect to renal function and other factors such as age, gender, and weight. For example, an acceptable control group for a drug intended for treatment of Alzheimer’s disease would be otherwise healthy elderly male and female patients whose baseline renal function would clearly not be comparable to young healthy male volunteers.

The study could also include a group of subjects with greater renal function than the control renal function group (e.g., a group of healthy young volunteers). The resulting wider range of renal function enhances the ability to detect and characterize the effect of renal function on PK. It also allows for the possibility that the actual patient population may include some people with greater renal function than the control group. However, recommendations about dosage adjustments should be based on comparison to the patients with renal function that is typical of the usual patient population — not necessarily to normal healthy young volunteers.

To ensure adequate representation of patients with various degrees of renal impairment, recruitment of approximately equal numbers of patients from each of the following groups is suggested:

Group	Description	Estimated Creatinine Clearance (milliliters/minutes)
1	Normal renal function	> 80 mL/min
2	Mild renal impairment	50-80 mL/min
3	Moderate renal impairment	30-50 mL/min
4	Severe renal impairment	<30 mL/min
5	ESRD	Requiring dialysis

The renal function groups should be comparable to each other with respect to age, gender, and weight. Other factors with significant potential to affect the PK of a drug to be studied (e.g., diet, smoking, alcohol intake, concomitant medications, ethnicity) should be considered depending on the drug.

The number of patients enrolled in the study should be sufficient to detect PK differences large enough to warrant dosage adjustments. The PK variability of the drug as well as the PK/PD relationships for both therapeutic and adverse responses (therapeutic index) will affect this decision.

2. Drug Administration

A single-dose study is satisfactory for cases where there is clear prior evidence that the multiple-dose PK is accurately predictable from single-dose data for all chemical species of interest (drug and potentially active metabolites). A multiple-dose PK is predictable from a single-dose PK when the drug and active metabolites exhibit linear and time-independent PK at the concentrations anticipated in the patients to be studied. A multiple-dose study is desirable when the drug or an active metabolite is known to exhibit nonlinear or time-dependent PK.

In single-dose studies, the same dose can usually be administered to all patients in the study regardless of renal function because the peak concentration generally is not greatly affected by renal function. For multiple-dose studies, lower or less frequent doses as renal function decreases may be important to prevent accumulation of drug and

metabolites to unsafe levels. The dosage regimen may be adjusted based on the best available prestudy estimates of the PK of the drug and its active metabolites in patients with impaired renal function. Alternatively, a concentration-controlled study design could be employed. Specifically, the study could be conducted to achieve a specific target concentration using therapeutic drug monitoring procedures. In multiple-dose studies, the dosing should usually be continued for a sufficiently long duration to achieve steady state. A loading dose strategy may be desirable to facilitate this, particularly if the elimination half-life is greatly prolonged in patients with renal impairment.

3. Sample Collection and Analysis

Plasma or whole blood, if appropriate, (and optionally urine) samples should be analyzed for parent drug and any metabolites with known or suspected activity (therapeutic or adverse). This is particularly important in patients with impaired renal function since renally excreted metabolites can accumulate to a much higher degree in such patients. The frequency and duration of plasma sampling and urine collection should be sufficient to accurately estimate the relevant pharmacokinetic parameters for the parent drug and its active metabolites (see section V. on Data Analysis).

Plasma protein binding is often altered in patients with impaired renal function. For systemically active drugs and metabolites, the unbound concentrations are generally believed to determine the rate and extent of delivery to the sites of action. This leads to the recommendation that the PK should be described and analyzed with respect to the unbound concentrations of the drug and active metabolites. Although unbound concentrations should be measured in each plasma sample, if the binding is concentration-independent and is unaffected by metabolites or other time-varying factors, the fraction unbound may be determined using a limited number of samples or even a single sample from each patient. The unbound concentration in each sample is then estimated by multiplying the total concentration by the fraction unbound for the individual patient. For drugs and metabolites with a relatively low extent of plasma protein binding (e.g., extent of binding less than 80%), alterations in binding due to impaired renal function are small in relative terms. In such cases, description and analysis of the PK in terms of total concentrations should be sufficient.

4. Measures of Renal Function

Currently, creatinine clearance is used widely in patient care settings as a measure of renal function. Consequently, it is more practical than most other alternatives as a criterion for adjusting dosage in outpatient and inpatient settings. The Cockcroft-Gault formula is one way of estimating creatinine clearance based on serum creatinine levels.

Using other measures of renal function that can characterize differentially glomerular filtration or renal tubular secretion may provide an additional mechanistic understanding of the effect of renal impairment on PK. Such methods are encouraged as useful additions, but not as alternatives to methods that are more readily available in patient care settings, such as using creatinine clearance or serum creatinine concentration.

The basic full study design should be structured to characterize comprehensively the effect of renal impairment on PK. This approach presumes that the drug's PK is likely to change as renal function decreases. The full study then provides the information needed to rationally adjust doses for patients with impaired renal function.

B. Reduced/Staged Study Design

If there is good reason to believe that renal impairment does not affect PK to a degree sufficient to warrant dosage adjustment, then a full study may be larger and more complex than necessary. An acceptable alternative is an adaptive two-stage approach. Stage 1 consists of studying only patients at the extremes of renal function (i.e., patients with normal [Group 1] and severely impaired [Group 4] renal function). If the results confirm that renal impairment does not alter PK to an extent that warrants dosage adjustment, no further study is warranted. If the results do not strongly support such a conclusion, in stage 2, the intermediate renal function groups (mild and moderate renal impairment) should also be studied. The results of both stages should be combined for all subsequent data analyses.

C. Population PK Studies³

A population PK screen of patients participating in phase 2/phase 3 clinical trials may be used to assess the impact of various covariates on the PK of a drug. Typically, each patient is only sparsely sampled to obtain plasma drug concentration data.

Techniques such as nonlinear mixed effects modeling may be used to model the relationship between the various covariates and PK parameters. A measure of renal function such as creatinine clearance may be one of the covariates. Therefore, it may be possible to model the relationship between creatinine clearance and PK parameters, such as the apparent clearance of the drug (CL/F). In principle, such a population PK study design and analysis can be an acceptable alternative if it retains some of the critical components of the more conventional studies described in previous sections:

³ A draft guidance for industry, "Population Pharmacokinetics," (September 1997) is available on the internet (<http://www.fda.gov/cder/guidance/index.htm>)

- A sufficient number of patients and a sufficient representation of a range of renal function that the study could detect PK differences large enough to warrant dosage adjustment;
- Measurement of unbound concentrations when appropriate;
- Measurement of parent drug and potentially active metabolites.

Such features are particularly critical if the sponsor intends to use the results to support a claim that no dosage adjustment is required for patients with impaired renal function.

Patients with severe renal impairment often are excluded or poorly represented in population PK studies. When that occurs for a drug that is likely to be administered to such patients, a separate study should be conducted to assess PK in patients with severe renal impairment (i.e., a study such as the reduced/staged study design described in the previous section). The data from both sources should be combined to construct an overall assessment of the effect of renal impairment.

D. Effect of Dialysis on Pharmacokinetics

Dialysis may significantly affect the PK of a drug to an extent that dosage adjustment is appropriate. The need for dosage adjustment results when a significant fraction of the drug or active metabolites in the body is removed by the dialysis process. In such cases, a change in the dosage regimen, such as a supplemental dose following the dialysis procedure, may be required.

For drugs that are likely to be administered to end stage renal disease (ESRD) patients treated with dialysis, PK should be studied in such patients under both dialysis and nondialysis conditions to determine the extent to which dialysis contributes to the elimination of the drug and potentially active metabolites. Primary questions to be addressed are whether the dosage should be adjusted as a consequence of dialysis and, if so, by how much. The results of the study also provide valuable insight regarding the value of dialysis for treatment of overdose. The assessment of PK in dialysis may be integrated with the PK in renal impairment study, as described above, or it may be conducted as a separate study.

As it is most commonly used in ESRD patients, intermittent hemodialysis is usually the most important method to be evaluated. PK studies in patients treated with peritoneal dialysis may also be desirable (e.g., CAPD, continuous ambulatory peritoneal dialysis, which is the next most common form of dialysis). A study in CAPD patients is recommended if the drug is likely to be used in such patients and CAPD is likely to significantly affect PK.

In general, a study of the effect of dialysis on PK may be omitted if the dialysis procedure is unlikely to result in significant elimination of drug or active metabolites. This is arguable for drugs and active metabolites that have a large unbound volume of distribution (V_u) or a large unbound nonrenal clearance ($CL_{NR,u}$).

If the drug and metabolites have a large unbound volume of distribution (V_u), only a small fraction of the amounts in the body will be removed by dialysis. For example, if V_u were greater than 360 L, less than 10 percent of the amount initially in the body could be removed by 3 hours of high flux hemodialysis with an unbound dialysis clearance of 200 mL/min.

If the drug and metabolites have a large unbound nonrenal clearance ($CL_{NR,u}$), dialysis contributes a relatively small amount to the overall unbound clearance. For example, if $CL_{NR,u}$ were greater than 125 mL/min, 3 hours of high-flux hemodialysis with an unbound dialysis clearance of 200 mL/min administered every 2 days would contribute less than 10 percent to the overall clearance.

E. Pharmacodynamic Assessments

Whenever appropriate, pharmacodynamic assessment should be included in the studies of renal impairment. The selection of the pharmacodynamic endpoints should be discussed with the appropriate FDA review staff and should be based on the pharmacological characteristics of the drug and metabolites (e.g., extent of protein binding, therapeutic index, and the behavior of other drugs in the same class in patients with renal impairment).

V. DATA ANALYSIS

The primary intent of the data analysis is to assess whether dosage adjustment is required for patients with impaired renal function, and, if so, to develop dosing recommendations for such patients based on measures of renal function. The data analysis typically consists of the following steps:

- Estimation of PK parameters;
- Mathematical modeling of the relationship between measures of renal function and the PK parameters;
- Development of dosing recommendations including an assessment of whether dosage adjustment is warranted in patients with impaired renal function.

A. Parameter Estimation

Plasma concentration data (and urinary excretion data if collected) should be analyzed to estimate various parameters describing the PK of the drug and its active metabolites. The PK parameters of a drug can include the area under the plasma concentration curve (AUC), peak concentration (C_{\max}), apparent clearance (CL/F), renal clearance (CL_R), apparent volume of distribution (V_z/F or V_{ss}/F), terminal half-life ($t_{1/2}$). The PK parameters of active metabolites can include the area under the plasma concentration curve (AUC), peak concentration (C_{\max}), renal clearance (CL_R), terminal half-life ($t_{1/2}$). If possible, parameters are preferably expressed in terms of unbound concentrations; for example, apparent clearance relative to the unbound drug concentrations ($CL_u/F = D/AUC_u$) where the subscript 'u' indicates unbound drug. Noncompartmental and/or compartmental modeling approaches to parameter estimation can be employed.

B. Modeling the Relationship Between Renal Function and PK

The objective of this step is to construct mathematical models for the relationships between the RF, the measures of renal function, particularly creatinine clearance (CL_{cr}) and relevant PK parameters. The PK parameters of greatest interest are usually the apparent unbound clearance (CL_u/F), or the dose-normalized area under the unbound concentration curve (AUC_u/D), and the dose-normalized peak unbound concentration ($C_{\max,u}/D$) for the drug and active metabolites. The intended result is a model that can successfully predict PK behavior given information about renal function. Generally, this involves a regression approach in which RF and the PK parameters are treated as continuous variables. This is usually preferred to an analysis in which RF is treated as a categorical variable corresponding to the normal, mild, moderate, and severe renal impairment groups. One commonly used model is a linear relationship between CL_{cr} and the total or renal clearance of the drug. Other models can be used if adequately supported by the data and/or mechanistic arguments.

The intent of the modeling exercise is to provide a rational quantitative basis for dosage recommendations in the drug's labeling. The model itself may be described in the clinical pharmacology section of the labeling.

The reported modeling results should include estimates of the parameters of the chosen model as well as measures of their precision (standard errors or confidence intervals). Prediction error estimates are also desirable (e.g., confidence bounds for prediction of AUC_u/D for the drug and its active metabolites over a range of RF).

C. Development of Dosing Recommendations

Specific dosing recommendations should be constructed based on the study results using the aforementioned model for the relationships between RF and relevant PK parameters. Typically the dose is adjusted to produce a comparable range of unbound plasma concentrations of drug or active metabolites in both normal patients and patients with

impaired renal function. Simulations are encouraged as a means to identify doses and dosing intervals that achieve that goal for patients with different levels of renal function.

For some drugs, even severe renal impairment may not alter PK sufficiently to warrant dosage adjustment. A sponsor could make this claim by providing an analysis of the study data to show that the PK measurements most relevant to therapeutic outcome in patients with severe renal impairment are similar, or equivalent, to those in patients with normal renal function.

One approach would be for the sponsor to recommend, prior to the conduct of the studies, specific "no effect" boundaries for the ratio of a PK measurement from patients with severe and normal renal functions respectively, such as $(AUC_{Cu,severe} / AUC_{Cu,normal})$ (D_{normal}/D_{severe}). If the 90% confidence interval for the ratio of PK measurements fell within these boundaries, the sponsor could claim "no effect" of severe renal impairment on PK, and it would be reasonable to conclude that no dosage adjustment is required for renal impairment. The sponsor could determine "no effect" boundaries from population (or individual) PK-PD relationships, dose-finding studies and/or dose-response studies which are conducted as part of drug development.

Another approach would be for the sponsor to assume, a priori, "no effect" boundaries of 70-143% for C_{max} and 80-125% for AUC without further justification, recognizing that the limitation for small clinical sample sizes in renal impairment studies coupled with high inter-subject variability may preclude meeting these "no-effect" boundaries.

VI. LABELING

The labeling should reflect the data pertaining to the effect of renal function on the pharmacokinetics and pharmacodynamics (if known) obtained from studies conducted. The various permutations of intrinsic drug characteristics and the effect of renal impairment on drug performance preclude precise specification of how such drugs should be labeled. The following comments offer general suggestions on which sections of the labeling should include standardized information and how such information should be structured.

A. Clinical Pharmacology

1. The pharmacokinetics subsection should include information on the:
 - Mechanism of renal elimination (e.g., filtration, secretion, active reabsorption)
 - Percentage of drug that is eliminated by renal excretion and whether it is eliminated unchanged or as metabolites;
 - Disposition of metabolites in patients with impaired renal function (if applicable);
 - Effects of renal impairment on protein binding of parent drug and metabolites (if applicable);
 - Effects of changes in urinary pH or other special situations that should be mentioned (e.g., tubular secretion inhibited by probenecid);
 - If applicable, the effects of impaired renal function on stereospecific disposition of enantiomers of a racemic drug product should be described if there is evidence of differential stereoisomeric activity or toxicity
2. Special Populations Subsection

This section should recapitulate, in brief, the pharmacokinetic changes found in various degrees of renal impairment and, if necessary, dosing adjustments for patients with varying degrees of renal impairment. This information should be based on the studies performed as described in this guidance. Reference should be made to the PRECAUTIONS/WARNINGS and the DOSAGE AND ADMINISTRATION sections. The following text provides examples of appropriate wording for these sections.

The simplest situation involves drugs for which impaired renal function has little or no effect on PK:

Impaired renal function has little or no influence on _____ pharmacokinetics and no dosing adjustment is required.

Similarly, for drugs whose PK is influenced by renal impairment, the following statement may be modified as appropriate and in accordance with what is known about the drug (e.g., racemate with different activity of stereoisomers, active or toxic metabolite) and from the studies performed in accordance with this guidance:

The disposition of _____ was studied in patients with varying degrees of renal function. Elimination of the drug (and metabolite, if applicable) is significantly correlated with the creatinine clearance. Total body clearance of (unbound, if applicable) _____/metabolite was reduced in patients with impaired renal function by --- % in mild (CLcr = ___-___ mL/min), --- % in moderate (CLcr = ___-___ mL/min) and --- % in severe renal impairment (CLcr = ___-___ mL/min), and --- % in patients under dialysis compared to normal subjects (CLcr > ___mL/min). The terminal half-life of _____/metabolite is prolonged by ---, ---, and --- fold in mild, moderate, and severe renal impairment, respectively. [Alternatively, the relationship between renal function and the PK parameters may be described in terms of equations, e.g., a linear equation relating unbound clearance and CLcr.] Protein binding of _____/metabolite is/is not affected by decreasing renal function. The drug/metabolite accumulates in patients with impaired renal function on chronic administration. The pharmacologic response is/is not affected by renal function. Approximately --- % of the drug/metabolite in the body was cleared from the body during a standard 4-hour hemodialysis procedure. The dosage should be reduced in patients with impaired renal function receiving _____ and supplemental doses should/should not be given to patients after dialysis. (See DOSAGE AND ADMINISTRATION).

B. Precautions/Warnings

Use in Patients with Impaired Renal Function: If the effects of renal impairment result in clinically important changes in drug pharmacokinetics, this should be included in the PRECAUTIONS/WARNINGS section with reference to DOSAGE AND ADMINISTRATION section.

C. Dosage and Administration

As appropriate, the following statement may be considered:

The influence of impaired renal function on _____ pharmacokinetics is sufficiently small that no dosing adjustment is required.

However, for many drugs, impaired renal function may require dosing adjustments. In such cases, the following information should be included:

1. A statement describing the relationship between _____ clearance and endogenous creatinine clearance.
2. If there is a need for dosage adjustment, the following statement may be adapted as appropriate:

_____ dosing must be individualized according to the patient's renal function status. Refer to the following table for recommended doses and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CL_{cr}) in mL/min is required. CL_{cr} in mL/min may be estimated from a spot serum creatinine (mg/dL) determination using the following formula:

$$CL_{cr} \approx \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \{ \times 0.85 \text{ for female patients} \}$$

The serum creatinine should represent a steady-state of renal function. The following formulas are preferable for children (to be included if the drug has a pediatric indication):

Infants less than one year:

$$CL_{cr} \approx \frac{0.45 \times \text{length (cm)}}{\text{serum creatinine (mg/dL)}}$$

Children 1–12 years:

$$CL_{cr} \approx \frac{0.55 \times \text{length (cm)}}{\text{serum creatinine (mg/dL)}}$$

3. The dosing adjustment regimen should be represented in tabular format (see example below).

Group	Creatinine Clearance (mL/min)	Dosage (mg)	Frequency
Normal	> __	x	Every x hours
Mild	__-__		
Moderate	__-__		
Severe	< __		
ESRD patients using dialysis			Supplemental dose should be given after dialysis.

4. Special consideration should be given to combination drug products.

Dosing adjustment should be recommended according to the degree of renal impairment, provided there is sufficient information to indicate that the pharmacokinetics/pharmacodynamics of the individual components of the combination product are comparably affected by impaired renal function. In situations in which this does not apply, the following statement should be adapted:

Because the doses of this fixed combination product cannot be individually titrated and impaired renal function results in a reduced clearance of component A to a much greater extent than component B, combination drug should generally be avoided in patients with suspected or documented renal impairment (see PRECAUTIONS/WARNINGS).

D. Overdosage

Although the primary objective of a hemodialysis study is to evaluate the need for dosing adjustments in ESRD, additional information regarding the value of hemodialysis in overdose situations may reasonably be garnered from such studies (if performed). In situations in which this information is known, the following wording may be adapted as appropriate:

_____ is not eliminated to a therapeutically significant degree by hemodialysis.

or

Standard hemodialysis procedures result in significant clearance of _____ and should be considered in cases of life-threatening overdose.

Preliminary Concept Paper

Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling

For Discussion Purposes Only

Clinical Pharmacology Advisory Committee Presentation
March 19, 2008

Send comments to Shiewmei.huang@fda.hhs.gov

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Preliminary Concept Paper

Pharmacokinetics in Patients with Impaired Renal Function — Study Design, Data Analysis, and Impact on Dosing and Labeling

I. INTRODUCTION

This concept paper is intended for sponsors who, during the investigational phase of drug development, plan to conduct studies to assess the influence of renal impairment on the pharmacokinetics of an investigational drug.

II. BACKGROUND

After entering the body, a drug is eliminated either by excretion or by metabolism. Although elimination can occur via any of several routes, most drugs are cleared by elimination of unchanged drug by the kidney and/or by metabolism in the liver and/or small intestine. For a drug eliminated primarily via renal excretory mechanisms, impaired renal function usually alters its pharmacokinetics (PK) and pharmacodynamics (PD) to an extent that the dosage regimen needs to be changed from that used in patients with normal renal function. The most obvious type of change arising from renal impairment is a decrease in renal excretion, or possibly renal metabolism, of a drug or its metabolites. Renal impairment also adversely affects some pathways of hepatic/gut drug metabolism to a significant extent and has also been associated with other changes, such as changes in absorption, plasma protein binding, transporter, and tissue distribution. These changes may be particularly prominent in patients with severely impaired renal function and have been observed even when the renal route is not the primary route of elimination of a drug. Thus, for most drugs that are likely to be administered to patients with renal impairment, PK and/or PD characterization should be assessed in patients with renal impairment to provide rational dosing recommendations.

This concept paper makes recommendations regarding:

- When studies of PK in patients with impaired renal function should be performed—and conversely, when they may be unnecessary;
- The design and conduct of PK studies in patients with impaired renal function;
- The design and conduct of PK studies in end-stage renal disease (ESRD) patients treated with dialysis (hemodialysis);
- The analysis and reporting of the results of such studies;
- Representation of these results in approved product labeling.

III. DECIDING WHETHER TO CONDUCT A STUDY IN PATIENTS WITH IMPAIRED RENAL FUNCTION

A. When Studies May Be Important

A PK study in patients with impaired renal function is recommended when the drug is likely to be used in these patients and (1) renal impairment is likely to significantly alter the PK of a drug and/or its active/toxic metabolites and (2) a dosage adjustment is likely to be necessary for safe and effective use in such patients. In particular, a study in patients with impaired renal function is recommended when the drug or its active metabolites exhibit a narrow therapeutic range² and when excretory and/or metabolic pathways are likely to be adversely affected by impaired renal function.

B. When Studies May Not Be Important or Practicable

For some drugs, renal impairment is not likely to alter PK enough to justify dosage adjustment. In such cases, a study to confirm that prediction may be helpful but is not necessary. If a study is not conducted, the labeling should indicate that the impact of renal impairment was not studied, but that an effect requiring dosage adjustment is unlikely to be present. Current knowledge suggests that the following drug properties may justify this approach:

- Drug and active metabolites with a relatively wide therapeutic index;
- Gaseous or volatile drug and active metabolites that are primarily eliminated via the lungs;
- Drugs intended only for single-dose administration unless clinical concerns dictate otherwise.
- Oncologic drugs which are usually withheld from patients with severely impaired renal function or ESRD. In this case a population PK study (see below) may provide sufficient information for appropriate dose regimen design in patients with some degree of renal impairment.

² The therapeutic range may be derived from the concentration- or dose-response data existing in the safety/efficacy database.
(refer to the Drug Interaction Guidance)

Even when renal impairment is likely to have little or no effect on a drug's PK, the impact of dialysis on the PK of a drug should be considered. Patients on dialysis may require greater doses of certain drugs than patients with normal renal function. This is discussed further in the following section.

IV. STUDY DESIGN

The safety and efficacy of a drug generally are established for a particular dosage regimen (or range of dosage regimens) in late phase (phase 3) clinical trials involving relatively typical representatives from the target patient population. Frequently, individuals with significantly impaired renal function are explicitly **excluded** from participation in these studies. However, there may be a sufficient range of function in enough patients to estimate of the effects of decreased renal function from population PK analysis. The primary goal of the recommended study in patients with impaired renal function is to determine if the PK is altered to such an extent that the dosage should be adjusted from that established in the phase 3 trials.

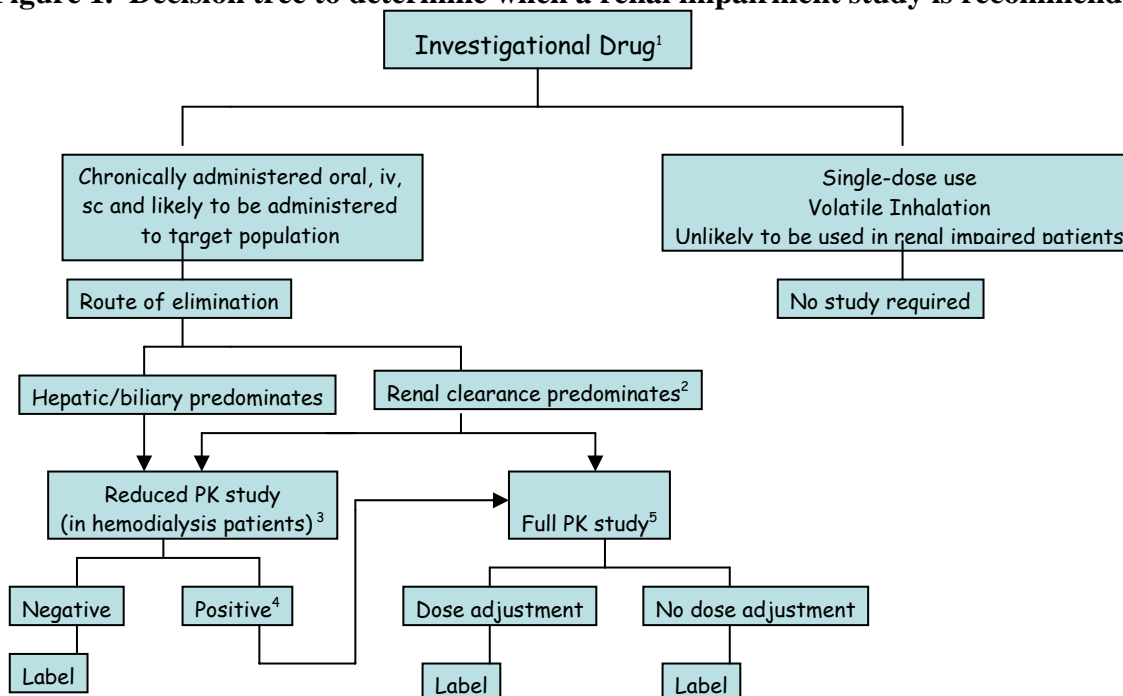
In many cases the effects of impaired renal function on drug PK can be evaluated initially with a "Reduced PK Study" design (see IV.A below). This would apply to drugs that are predominantly renally cleared or drugs that are predominantly metabolized or biliary secreted. Figure 1 illustrates a possible model to determine when a renal impairment study is recommended. The "Reduced PK Study" design consists of studying only patients at the extremes of renal function (i.e., patients with normal renal function and dialysis-dependent patients with ESRD). If a drug is predominantly eliminated by the renal pathway, the sponsor, in addition to using the "Reduced PK Study" design, may also evaluate PK in patients with all levels of renal functional impairment ("Full Study Design", see IV.B below).

A. "Reduced PK Study" Design

1. Patient Selection

The strategy used in this section describes an initial PK study to compare the PK parameters in hemodialysis-dependent (ESRD) patients within 24 hours prior to the scheduled hemodialysis (pre-dialysis) and the PK parameters in subjects with normal renal function. This strategy allows the estimation of the "worst case scenario" PK changes due to renal impairment. When a drug is also administered via an intravenous route, the data may provide information on whether the nonrenal clearance (metabolic or biliary clearance) is modified by renal disease. The number of patients enrolled in the study should be sufficient to detect PK differences large enough to warrant dosage adjustments. The PK variability of the patients as well as the PK/PD relationships for both therapeutic and adverse responses (therapeutic range) will affect this decision.

Figure 1. Decision tree to determine when a renal impairment study is recommended



1. Metabolites (active/toxic) follow the same decision tree.
2. The sponsor has the option of conducting a reduced study in patients undergoing hemodialysis (HD) between dialysis or a full study.
3. To be conducted between dialysis (to be initiated and completed within 24 hours prior to scheduled dialysis)
4. The magnitude of PK change based on the reduced PK study, risk-benefit (exposure-response) relationships, and the target patient populations may warrant a follow-up full PK study.
5. To include both "between dialysis" (within 24 hours prior to the scheduled dialysis) and "during dialysis" (if there is low volume of distribution of the NME and high dialytic clearance)

2. Drug Administration

A single-dose study is satisfactory for cases where there is clear prior evidence that the multiple-dose PK is accurately predictable from single-dose data for all chemical species of interest (drug and potentially active metabolites). A multiple-dose PK is predictable from a single-dose PK when the drug and active metabolites exhibit linear and time-independent PK at the concentrations anticipated in the patients to be studied. A multiple-dose study is desirable when the drug or an active metabolite is known to exhibit nonlinear or time-dependent PK.

In single-dose studies, the same dose can usually be administered to all patients in the study regardless of renal function because the peak concentration generally is not greatly affected by renal function. For multiple-dose studies, lower or less frequent doses as renal function decreases may be important to prevent accumulation of drug and metabolites to unsafe levels. The dosage regimen may be adjusted based on the best available prestudy estimates of the PK of the drug and its active metabolites in patients with impaired renal function. Alternatively, a concentration-controlled study design could be employed. Specifically, the study could be conducted to achieve a specific target concentration using therapeutic drug monitoring procedures. In multiple-dose studies, the dosing should usually be continued for a sufficiently long duration to achieve steady state. A loading dose strategy may be desirable to facilitate this, particularly if the elimination half-life is greatly prolonged in patients with renal impairment.

3. Sample Collection and Analysis

Plasma or whole blood, if appropriate, (and optionally urine) samples should be analyzed for parent drug and any metabolites with known or suspected activity (therapeutic or adverse). The frequency and duration of plasma sampling and urine collection should be sufficient to accurately estimate the relevant pharmacokinetic parameters for the parent drug and its active metabolites (see section on Data Analysis).

Plasma protein binding is often altered in patients with impaired renal function. For systemically active drugs and metabolites, the unbound concentrations are generally believed to determine the rate and extent of delivery to the sites of action. Unbound concentrations should be measured in each plasma sample only if the binding is concentration-dependent and/or is affected by metabolites or other time-varying factors. Otherwise, the fraction unbound may be determined using a limited number of samples or even a single sample from each patient. For drugs and metabolites with a relatively low extent of plasma protein binding (e.g., extent of binding less than 80%), alterations in binding due to impaired renal function are small in relative terms. In such cases, description and analysis of the PK in terms of total concentrations should be sufficient.

4. Additional Studies

If results from the initial study in dialysis-dependent patients are positive (that is, clinical significant PK changes were observed), a full study can be carried out (see IV. B below) or additional studies can be conducted including a population PK evaluation in patients participating in phase 2/phase 3 clinical trials to assess the impact of a decrease in creatinine clearance on the PK of a drug. Typically, each patient is only sparsely sampled to obtain plasma drug concentration data. Techniques such as nonlinear mixed effects modeling may be used to model the relationship between the various covariates such as creatinine clearance and PK parameters. Therefore, it may be possible to model the relationship between creatinine clearance and PK parameters, such as the apparent clearance of the drug (CL/F). In principle, such a population PK study design and analysis can be acceptable if it retains some of the critical components of the more conventional studies described in the following section on Full Study Design. Important considerations are:

- Inclusion of a sufficient number of patients and a sufficient representation of a range of renal function that the study can detect PK differences large enough to warrant dosage adjustment;
- Measurement of unbound concentrations when appropriate;
- Measurement of potentially active metabolites as well as parent drug.

B. “Full PK Study” Design

1. Study Participants

The control renal function group in this study is the same as that used in the initial study. Since enrollment of enough individuals with varying degrees of renal impairment who are also patients with the condition

for which the drug is indicated may be difficult, an acceptable alternative would be to use volunteers who are comparable to the typical patient population with respect to renal function and other factors such as age, gender, race, and weight. For example, an acceptable control group for a drug intended for treatment of Alzheimer's disease would be otherwise healthy elderly male and female patients whose baseline renal function would clearly not be comparable to young healthy male volunteers.

To ensure adequate representation of patients with various degrees of renal impairment, recruitment of approximately equal numbers of patients from each of the following stages is suggested:

Stage	Description	GFR (ml/min/1.73m ²)
1	Control (normal) GFR	≥ 90
2	Mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-30
5	Kidney failure (ESRD)	<15 or Requiring dialysis

(Stages of renal impairment are based on K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease (CKD) from National Kidney Foundation in 2002); GFR: glomerular filtration rate; ESRD: end stage renal disease.

It is not certain whether individuals with chronically decreased GFR in the range of 60 to 89 mL/min/1.73 m² without kidney damage are at increased risk for adverse outcomes, such as toxicity from drugs excreted by the kidney. Therefore, for drugs that are NOT narrow therapeutic index drugs, patients may be stratified based on ≥ 60 (relative normal), 15-59 (moderate to severe renal damage) and ≤ 15 mL/min/1.73 m² (end stage) with or without dialysis.

To ensure adequate representation of patients with various degrees of renal impairment, equal numbers of patients with intermediate levels of impaired renal function should be enrolled in Groups 2-4. The patients in these groups should be comparable to each other with respect to age, gender, race, and weight. Other factors with significant potential to affect the PK of the drug to be studied (e.g., diet, smoking, alcohol intake, concomitant medications, race/ethnicity) should be considered depending on the drug. The number of patients enrolled in each group should be sufficient to detect the level of renal impairment at which the hypothesis of the initial study breaks down (e.g. nonrenal elimination becomes impaired). The PK variability within the patient group as well as the PK/PD relationships for both therapeutic and adverse responses (therapeutic range) will affect this decision.

2. Measures of Renal Function

Although the exogenous markers such as inulin, iothalamate, EDTA, diethylene triamine pentaacetic acid, and iohexol provide accurate estimation of glomerular filtration rate (GFR), these methods are complicated, expensive, and difficult to do in routine clinical practice. Currently, creatinine clearance is used widely in patient care settings as a measure of GFR to represent the renal function. Consequently, it is more practical than most other alternatives as a criterion for adjusting dosage in outpatient and inpatient settings. Currently, the Cockcroft-Gault and MDRD study equations are the most commonly used formulas to estimate the GFR based on serum creatinine levels. MDRD seems to provide a more accurate estimate of GFR than the Cockcroft-Gault equation and should be recommended for the PK study in patients with

impaired renal function. However, since the Cockcroft-Gault equation has been widely used in previous PK studies and in the guidance of drug dosing, and the GFR estimates from the MDRD study and the Cockcroft-Gault equations fall within the same interval for dose adjustment in most cases, the sponsor should be encouraged to provide the data based on the Cockcroft-Gault equation as the reference in addition to the original data from the MDRD study.

Using other measures of renal function that can characterize differentially glomerular filtration or renal tubular secretion may provide an additional mechanistic understanding of the effect of renal impairment on PK. Such methods are encouraged as useful additions, but not as alternatives to creatinine clearance estimates.

3. Drug Administration

Considerations regarding drug administration are the same as in the initial study.

4. Sample Collection and Analysis

Plasma or whole blood, if appropriate, and urine samples should be analyzed for parent drug and any metabolites with known or suspected activity (therapeutic or adverse). The frequency and duration of plasma sampling and urine collection should be sufficient to accurately estimate the relevant pharmacokinetic parameters for the parent drug and its active metabolites (see the “Reduced PK Study” Section on Sample Collection and Analysis).

C. Effect of Dialysis on Pharmacokinetics

Dialysis may significantly affect the PK of a drug to an extent that dosage adjustment is appropriate. The need for dosage adjustment results when a significant fraction of the drug or active metabolites in the body is removed by the dialysis process. In such cases, a change in the dosage regimen, such as a supplemental dose following the dialysis procedure, may be required.

For drugs that are likely to be administered to end stage renal disease (ESRD) patients treated with dialysis, PK should be studied in such patients under both dialysis and nondialysis conditions to determine the extent to which dialysis contributes to the elimination of the drug and potentially active metabolites. The assessment of PK in dialysis may be integrated with the pre-dialysis PK study in hemodialysis dependent patients, as described above, or it may be conducted as a separate study. Primary questions to be addressed are whether the dosage should be adjusted as a consequence of dialysis and, if so, by how much. The results of the study also provide valuable insight regarding the value of dialysis for treatment of overdose.

In general, a study of the effect of dialysis on PK may be omitted if the dialysis procedure is unlikely to result in significant elimination of drug or active metabolites. This is particularly true for drugs that have a high molecular weight or which have tight binding to plasma proteins that is not affected by impaired renal function. It also is arguable for drugs and active metabolites that have a large volume of distribution or primarily nonrenal clearance. If the drug and metabolites have a large volume of distribution, only a small fraction of the amount in the body will be removed by dialysis. For example, if the volume of distribution

were greater than 360 L, less than 10 percent of the amount initially in the body could be removed by 3 hours of high flux hemodialysis with an unbound dialysis clearance of 200 mL/min. If the drug and metabolites have primarily nonrenal clearance, dialysis contributes a relatively small amount to the overall clearance. For example, if nonrenal? clearance were greater than 125 mL/min, 3 hours of high-flux hemodialysis with a dialysis clearance of 200 mL/min administered every 2 days would contribute less than 10 percent to the overall clearance.

1. Study Design

As it is most commonly used in ESRD patients, intermittent hemodialysis (HD) is usually the most important method to be evaluated. Since most dialysis centers in US are currently using a high-flux dialyzer during the intermittent HD, PK studies are recommended in patients treated with high-flux HD. The blood flow, dialysate flow, and the make and model of the dialyzer should be recorded. The dialysis study should cover both the non-dialysis and dialysis sessions.

PK studies should also be considered in other dialysis situations such as continuous ambulatory peritoneal dialysis (CAPD) if the drug is likely to be used in these patients and these dialysis modalities are likely to significantly affect the drug PK.

Seriously ill patients with acute renal failure are often treated with continuous renal replacement therapy (CRRT) rather than intermittent HD. It may be difficult to directly extrapolate the effect of intermittent HD on the PK of drugs to CRRT. The in vitro data and/or the filter clearance rate (calculating from the drug concentrations of both arterial side and venous side between the filter) plus the available data from intermittent HD should attempt to provide appropriate dosing recommendations in these patients.

2. Sample Collection and Data Analysis

Blood samples should be collected pre-dialysis and from blood flowing from the patient to the dialysis cartridge and from the dialysis cartridge to the patient at appropriate intervals during the dialysis period. The entire dialysate should be collected, its volume recorded, and a sample retained for drug concentration analysis. Blood flow through the dialysis cartridge and the make and model of the cartridge should be recorded.

Plasma (or blood if more suitable) concentrations of the drug and its active metabolites (if any) should be measured in both blood and dialysate samples and dialysis clearance (CL_D) calculated based on the amount of drug recovered in the dialysate:

$$CL_D = \frac{\text{Amount Recovered}}{AUC_{t_0-t_1}}$$

where t_0 marks the start time and t_1 the termination of the hemodialysis session.

Pre-dialysis and end of dialysis blood samples should also be used to measure drug binding to plasma

proteins. The fraction of the administered dose that is recovered in the dialysate should be calculated in order to assess the need for administering supplemental drug doses to hemodialysis patients.

D. Pharmacodynamic Assessments

Whenever appropriate, pharmacodynamic assessment should be included in the studies of renal impairment. The selection of the pharmacodynamic endpoints should be discussed with the appropriate FDA review staff and should be based on the pharmacological characteristics of the drug and metabolites (e.g., extent of protein binding, therapeutic index, and the behavior of other drugs in the same class in patients with renal impairment).

V. DATA ANALYSIS

The primary intent of the data analysis is to assess whether dosage adjustment is required for patients with impaired renal function, and, if so, to develop dosing recommendations for such patients based on measures of renal function. The data analysis typically consists of the following steps:

- Estimation of PK parameters;
- Mathematical modeling of the relationship between measures of renal function and the PK parameters;
- Development of dosing recommendations including an assessment of whether dosage adjustment is warranted in patients with impaired renal function.

A. Parameter Estimation

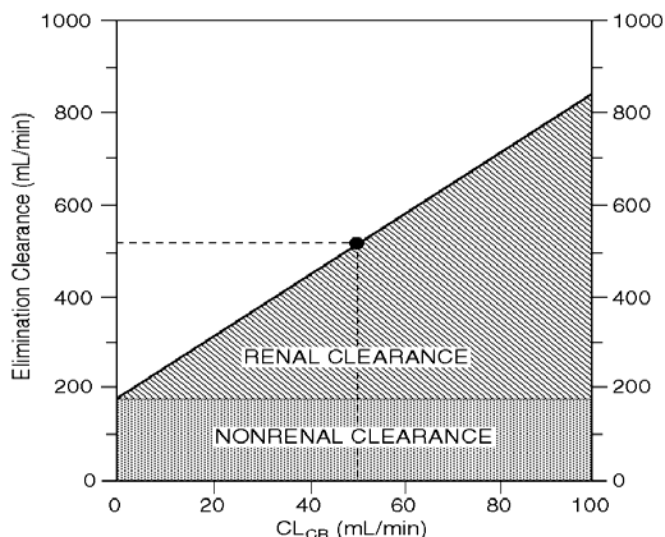
Plasma concentration data and urinary excretion data should be analyzed to estimate various parameters describing the PK of the drug and its active metabolites. The PK parameters of a drug can include the area under the plasma concentration curve (AUC), peak concentration (C_{max}), apparent clearance (CL/F), renal clearance (CL_R), apparent nonrenal clearance (CL_{NR}/F), apparent volume of distribution (V_d/F), and terminal half-life ($t_{1/2}$). If CL and CL_{NR} are not estimated directly, indirect estimates can be made from absolute bioavailability studies. The PK parameters of active metabolites can include the area under the plasma concentration curve (AUC), peak concentration (C_{max}), renal clearance (CL_R), terminal half-life ($t_{1/2}$). Noncompartmental and/or compartmental modeling approaches to parameter estimation can be employed.

B. Modeling the Relationship Between Renal Function and PK

The objective of this step is to construct mathematical models for the relationships between the RF, the measures of renal function, particularly creatinine clearance (CL_{cr}) and relevant PK parameters. The intended result is a model that can successfully predict PK behavior given information about renal function. Generally, this involves a regression approach in which RF and the PK parameters are treated as continuous variables. This is usually preferred to an analysis in which RF is treated as a categorical variable corresponding to the normal, mild, moderate, and severe renal impairment groups. One commonly

used model is that proposed by Lucien Dettli (Med Clin North Am 1974;58:977-85). In this model, there is a linear relationship between CL_{cr} and renal clearance of the drug but nonrenal clearance (CL_{NR}) remains constant:

$$CL = \alpha CL_{CR} + CL_{NR}$$



The assumption that the CL_{NR} remains constant should be supported by the Full Study Data. However, other models can be used if adequately supported by the data and/or mechanistic arguments.

The intent of the modeling procedure is to provide a rational quantitative basis for dosage recommendations in the drug's labeling. The model itself may be described in the clinical pharmacology section of the labeling.

The reported modeling results should include estimates of the parameters of the chosen model as well as measures of their precision (standard errors or confidence intervals). Prediction error estimates are also desirable (e.g., confidence bounds for prediction of clearance for the drug and its active metabolites over a range of RF).

C. Development of Dosing Recommendations

Specific dosing recommendations should be constructed based on the study results using the aforementioned model for the relationships between creatinine clearance and relevant PK parameters. Typically the dose and dosing interval are adjusted to produce a comparable range of plasma concentrations of drug or active metabolites in both normal patients and patients with impaired renal function. Simulations are encouraged as a means to identify doses and dosing intervals that achieve that goal for patients with different levels of renal function. Nomograms will help in providing dose recommendations and can lead to more precise dosing for drugs with a narrow therapeutic index.

For some drugs, even severe renal impairment may not alter PK sufficiently to warrant dosage adjustment. A sponsor could make this claim by providing an analysis of the study data to show that the PK

measurements most relevant to therapeutic outcome in patients with severe renal impairment are similar, or equivalent, to those in patients with normal renal function.

One approach would be for the sponsor to recommend, prior to the conduct of the studies, specific "no effect" boundaries for the ratio of a PK measurement from patients with severe and normal renal functions respectively. If the 90% confidence interval for the ratio of PK measurements fell within these boundaries, the sponsor could claim "no effect" of severe renal impairment on PK, and it would be reasonable to conclude that no dosage adjustment is required for renal impairment. The sponsor could determine "no effect" boundaries from population (or individual) PK-PD relationships, dose-finding studies and/or dose-response studies which are conducted as part of drug development.

Another approach would be for the sponsor to assume, a priori, "no effect" boundaries of 70-143% for C_{max} and 80-125% for AUC without further justification, recognizing that the limitation for small clinical sample sizes in renal impairment studies coupled with high inter-subject variability may preclude meeting these "no-effect" boundaries.

VI. LABELING

The labeling should reflect the data pertaining to the effect of renal function on the pharmacokinetics and pharmacodynamics (if known) obtained from studies conducted. The various permutations of intrinsic drug characteristics and the effect of renal impairment on drug performance preclude precise specification of how such drugs should be labeled. The following comments offer general suggestions on which sections of the labeling should include standardized information and how such information should be structured.

A. Clinical Pharmacology

1. The pharmacokinetics subsection should include information on the:

- Mechanism of renal elimination (e.g., filtration, secretion, active reabsorption)
- Percentage of drug that is eliminated by renal excretion and whether it is eliminated unchanged or as metabolites;
- Disposition of metabolites in patients with impaired renal function (if applicable);
- Effects of renal impairment on protein binding of parent drug and metabolites (if applicable);
- Effects of changes in urinary pH or other special situations that should be mentioned (e.g., tubular secretion inhibited by probenecid);
- If applicable, the effects of impaired renal function on stereospecific disposition of enantiomers of a racemic drug product should be described if there is evidence of differential stereoisomeric activity or toxicity

2. Special Populations Subsection

This section should recapitulate, in brief, the pharmacokinetic changes found in various degrees of renal impairment and, if necessary, dosing adjustments for patients with varying degrees of renal impairment. This information should be based on the studies performed as described in this guidance. Reference should be made to the PRECAUTIONS/WARNINGS and the DOSAGE AND ADMINISTRATION sections. The following text provides examples of appropriate wording for these sections.

The simplest situation involves drugs for which impaired renal function has little or no effect on PK:

*Impaired renal function has little or no influence on _____
pharmacokinetics and no dosing adjustment is required.*

A clinically significant relationship between renal function and the PK parameters may be described in terms of the nomogram shown above or equations, e.g., a linear equation relating clearance and CL_{Cr}.

Protein binding of _____/metabolite is/is not affected by decreasing renal function. The drug/metabolite accumulates in patients with impaired renal function on chronic administration. The pharmacologic response is/is not affected by renal function. Approximately --- % of the drug/metabolite in the body was cleared from the body during a standard 4-hour hemodialysis procedure. The dosage should be reduced in patients with impaired renal function receiving _____ and supplemental doses should/should not be given to patients after dialysis. (See DOSAGE AND ADMINISTRATION).

Alternatively, for drugs whose PK is influenced by renal impairment, the following statement may be modified as appropriate and in accordance with what is known about the drug (e.g., racemate with different activity of stereoisomers, active or toxic metabolite) and from the studies performed in accordance with this guidance:

The disposition of _____ was studied in patients with varying degrees of renal function. Elimination of the drug (and metabolite, if applicable) is significantly correlated with the creatinine clearance. Total body clearance of (unbound, if applicable) _____/metabolite was reduced in patients with impaired renal function by --- % in mild (CL_{Cr} = __-__ mL/min), --- % in moderate (CL_{Cr} = ____ mL/min) and --- % in severe renal impairment (CL_{Cr} = __-__ mL/min), and --% in patients under dialysis compared to normal subjects (CL_{Cr} > ____ mL/min). The terminal half-life of _____/metabolite is prolonged by ---, ---, and --- fold in mild, moderate, and severe renal impairment, respectively.

B. Precautions/Warnings

Use in Patients with Impaired Renal Function: If the effect of renal impairment results in clinically important changes in drug pharmacokinetics, this should be included in the PRECAUTIONS/WARNINGS section with reference to DOSAGE AND ADMINISTRATION section.

C. Dosage and Administration

As appropriate, the following statement may be considered:

The influence of impaired renal function on _____ pharmacokinetics is sufficiently small that no dosing adjustment is required.

However, for many drugs, impaired renal function may require dosing adjustments. In such cases, the following information should be included:

1 A statement describing the relationship between _____ clearance and endogenous creatinine clearance AS ESTIMATED BY COCKCROFT-GAULT IN ADULTS?.

2 If there is a need for dosage adjustment, either a nomogram such as that shown above or the following statement may be adapted as appropriate:

_____ dosing must be individualized according to the patient's renal function status. Refer to the following table for recommended doses and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in mL/min is required. CLcr in mL/min may be estimated from a spot serum creatinine (mg/dL) determination using the following formula:

$$CLcr = \frac{[140 \times \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \{ \times 0.85 \text{ for female patients} \}$$

The serum creatinine should represent a steady-state of renal function. The following formulas are preferable for children (to be included if the drug has a pediatric indication):

Infants less than one year: CLcr. $\frac{0.45 \times \text{length (cm)}}{\text{serum creatinine (mg/dL)}}$

”

Children 1–12 years: CLcr. $\frac{0.55 \times \text{length (cm)}}{\text{serum creatinine (mg/dL)}}$

If also indicated for pediatric patients, the full study should be conducted in pediatrics.

The dosing adjustment regimen should be represented in tabular format (see example below).

Special consideration should be given to combination drug products.

485

Group	Creatinine Clearance (mL/min)	Dosage (mg)	Frequency
Normal	> __	x	Every x hours
Mild	__-__		
Moderate	__-__		
Severe	< __		
ESRD patients using dialysis			Supplemental dose should be given after dialysis.

486

487 Dosing adjustment should be recommended according to the degree of renal impairment, provided there is
488 sufficient information to indicate that the pharmacokinetics/pharmacodynamics of the individual
489 components of the combination product are comparably affected by impaired renal function. In situations
490 in which this does not apply, the following statement should be adapted:

491 *Because the doses of this fixed combination product cannot be individually titrated and impaired renal*
492 *function results in a reduced clearance of component A to a much greater extent than component B,*
493 *combination drug should generally be avoided in patients with suspected or documented renal impairment*
494 *(see PRECAUTIONS/WARNINGS).*

495 **D. Overdosage**

496 Although the primary objective of a hemodialysis study is to evaluate the need for dosing adjustments in
497 ESRD, additional information regarding the value of hemodialysis in overdose situations may reasonably
498 be garnered from such studies (if performed). In situations in which this information is known, the
499 following wording may be adapted as appropriate:

500 _____ is not eliminated to a therapeutically significant degree by
501 hemodialysis.
502 or

503 *Standard hemodialysis procedures result in significant clearance of _____ and should be*
504 *considered in cases of life-threatening overdose.*
505