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# Guidance for Industry

## Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications

### *DRAFT GUIDANCE*

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**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)  
March 2002  
CP**

# Guidance for Industry

## Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications

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Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)  
March 2002**

# TABLE OF CONTENTS

<b>I.</b>	<b>INTRODUCTION.....</b>	<b>1</b>
<b>II.</b>	<b>BACKGROUND.....</b>	<b>2</b>
<b>III.</b>	<b>REGULATORY APPLICATIONS .....</b>	<b>2</b>
	A. INFORMATION TO SUPPORT THE DRUG DISCOVERY AND DEVELOPMENT PROCESSES.....	3
	B. INFORMATION TO SUPPORT A DETERMINATION OF SAFETY AND EFFICACY .....	3
<b>IV.</b>	<b>DOSE-CONCENTRATION-RESPONSE RELATIONSHIPS AND EFFECTS OVER TIME.....</b>	<b>8</b>
	A. DOSE AND CONCENTRATION-TIME RELATIONSHIPS .....	8
	B. CONCENTRATION-RESPONSE RELATIONSHIPS: TWO APPROACHES.....	9
<b>V.</b>	<b>DESIGNS OF EXPOSURE-RESPONSE STUDIES .....</b>	<b>9</b>
	A. POPULATION VS. INDIVIDUAL EXPOSURE-RESPONSE .....	10
	B. EXPOSURE-RESPONSE STUDY DESIGN .....	10
	C. MEASURING SYSTEMIC EXPOSURE .....	12
	D. MEASURING RESPONSE .....	15
<b>VI.</b>	<b>MODELING OF EXPOSURE-RESPONSE RELATIONSHIPS.....</b>	<b>17</b>
	A. GENERAL CONSIDERATIONS .....	17
	B. MODELING STRATEGY .....	18
<b>VII.</b>	<b>SUBMISSION INFORMATION: EXPOSURE-RESPONSE STUDY REPORT.....</b>	<b>20</b>
	<b>REFERENCES .....</b>	<b>22</b>
	<b>APPENDIX A C RELATED GUIDANCES .....</b>	<b>23</b>
	<b>APPENDIX B.....</b>	<b>26</b>

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**Guidance for Industry<sup>1</sup>**

**Exposure-Response Relationships: Study Design, Data Analysis,  
and Regulatory Applications**

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*If you plan to submit comments on this draft guidance, to expedite FDA Review of your comments, please:*

- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale/justification for the proposed change.*
- *Identify specific comments by line number(s); use the PDF version of the document, whenever possible.*

**I. INTRODUCTION**

This document provides recommendations for sponsors of investigational new drugs (INDs) and applicants submitting new drug applications (NDAs) or biologics license applications (BLAs) on the use of exposure-response information in the development of drugs, including therapeutic biologics. It should be considered along with the International Conference on Harmonization (ICH) E4 guidance on *Dose-Response Information to Support Drug Registration* and other pertinent guidances (see Appendix A).

This guidance describes (1) the uses of exposure-response studies in regulatory decision-making, (2) the important considerations in exposure-response study designs to ensure valid information, (3) the strategy for prospective planning and data analyses in the exposure-response modeling process, (4) the integration of assessment of exposure-response relationships into all phases of drug development, and (5) the format and content for reports of exposure-response studies.

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<sup>1</sup> This guidance has been prepared by the Exposure-Response Working Group under the Medical Policy Coordinating Committee, Center for Drug Evaluation and Research (CDER), in cooperation with the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration (FDA).

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37 This guidance is not intended to be a comprehensive listing of all of the situations where  
38 exposure-response relationships can play an important role, but it does provide a range of  
39 examples of where such information may be of value.

40  
41

### 42 **II. BACKGROUND**

43

44 Exposure-response information is at the heart of any determination of the safety and  
45 effectiveness of drugs. That is, a drug can be determined to be safe and effective only when the  
46 relationship of beneficial and adverse effects to a defined exposure is known. There are some  
47 situations, generally involving very well tolerated drugs with little dose-related toxicity, in which  
48 drugs can be used effectively and safely at a single dose well onto the plateau part of their  
49 exposure-response curve, with little adjustment for pharmacokinetic (PK) or other influences in  
50 individuals. There are other situations, generally for relatively toxic drugs, in which all clinical  
51 use is based on titration to effect or tolerance. In most cases, however, it is important to develop  
52 information on population exposure-response relationships for favorable and unfavorable effects,  
53 and information on how, and whether, exposure should be adjusted for various subsets of the  
54 population.

55

56 Historically, drug developers have been relatively successful at establishing the relationship of  
57 dose to blood levels in various populations, thus providing a basis for adjustment of dosage for  
58 PK differences among demographic subgroups or subgroups with impaired elimination (e.g.,  
59 hepatic or renal disease), assuming systemic concentration-response relationships are unaltered.  
60 Far less attention has been paid to establishing the relationship between blood levels and  
61 pharmacodynamic (PD) responses and possible differences among population subsets in these  
62 concentration-response (often called PK-PD) relationships. These can be critical, as illustrated  
63 by the different responses to angiotensin-converting enzyme (ACE) inhibitors in both  
64 effectiveness and safety between Black and Caucasian populations.

65

66 For the purposes of this guidance, we are using the broad term *exposure* to refer to dose (drug  
67 input to the body) and various measures of acute or integrated drug concentrations in plasma and  
68 other biological fluid (e.g., C<sub>max</sub>, C<sub>min</sub>, C<sub>ss</sub>, AUC). Similarly, *response* refers to a direct  
69 measure of the pharmacologic effect of the drug. Response includes a broad range of endpoints,  
70 including a nonclinical *biomarker* (e.g., receptor occupancy), a presumed mechanistic effect  
71 (e.g., ACE inhibition), a potential or accepted *surrogate* (e.g., effects on BP, lipids, cardiac  
72 output), and the full range of short-term or long-term clinical effects related to either efficacy or  
73 safety. This exposure-response guidance focuses on human studies, but exposure-response  
74 information in animal pharmacology/toxicology studies is also a highly useful component of  
75 planning the drug development process (Peck 1994; Lesko 2000).

76

77

### 78 **III. REGULATORY APPLICATIONS**

79

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80 This section describes the potential uses of exposure-response relationships in drug development  
81 and regulatory decision-making. The examples are not intended to be comprehensive, but rather  
82 to illustrate the value of a better understanding of exposure-response relationships. Sponsors  
83 should refer to other ICH and FDA guidances for a discussion of the uses of exposure-response  
84 relationships (see Appendix A).

### **A. Information to Support the Drug Discovery and Development Processes**

85  
86  
87  
88 Many drugs thought to be of potential value in treating human disease are introduced into  
89 development based on knowledge of in vitro binding properties and identified  
90 pharmacodynamic effects in animals. Apart from describing the tolerability and PK of a drug  
91 in humans, phase 1 and 2 studies that explore the relationship of exposure (whether dose or  
92 concentration) to response (e.g., biomarkers, potentially valid surrogate endpoints, or short-  
93 term clinical effects) can also (1) link animal and human findings, (2) provide *proof of*  
94 *concept* (evidence that the hypothesized mechanism is affected by the drug), (3) provide  
95 evidence that the effect on the mechanism leads to a desired short-term clinical outcome  
96 (more proof of concept), and (4) provide guidance for designing initial clinical endpoint trials  
97 that use a plausibly useful dose range. Both the magnitude of an effect and the time course of  
98 effect are important to choosing dose, dosing interval, and monitoring procedures, and even  
99 to deciding what dosage form (e.g., controlled-release dosage form) to develop. Exposure-  
100 response and PK data can also define the changes in dose and dosing regimens that account  
101 for intrinsic and extrinsic patient factors.

### **B. Information to Support a Determination of Safety and Efficacy**

102  
103  
104  
105 Apart from their role in helping design the well-controlled studies that will establish the  
106 effectiveness of a drug, exposure-response studies, depending on study design and endpoints,  
107 can:

- 108  
109 • Represent a well-controlled clinical study, in some cases a particularly persuasive one,  
110 contributing to substantial evidence of effectiveness (where clinical endpoints or accepted  
111 surrogates are studied)
- 112  
113 • Add to the weight of evidence supporting efficacy where mechanism of action is well  
114 understood (e.g., when an effect on a reasonably well-established biomarker/surrogate is  
115 used as an endpoint)
- 116  
117 • Support, or in some cases provide, primary evidence for approval of different doses,  
118 dosing regimens, or dosage forms, or use of a drug in different populations, when  
119 effectiveness is already well-established in other settings and the study demonstrates a  
120 PK-PD relationship that is similar to, or different in an interpretable way from the  
121 established setting
- 122

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123 In general, the more critical a role that exposure-response information is to play in the  
124 establishment of efficacy, the more critical it is that it be derived from an adequate and well-  
125 controlled study (see 21 CFR 314.126), whatever endpoints are studied. Thus, critical studies  
126 should (1) have prospectively defined hypotheses/objectives, (2) use an appropriate control  
127 group, (3) use randomization to ensure comparability of treatment groups and to minimize bias,  
128 and (4) use other techniques to minimize bias.  
129

130 In contrast, some of the exposure-response studies considered in this document include analyses  
131 of nonrandomized data sets where associations between volunteer or patient exposure patterns  
132 and outcomes are examined. These analyses are often primarily exploratory, but along with other  
133 clinical trial data may provide additional insights into exposure-response relationships,  
134 particularly in situations where volunteers or patients cannot be randomized to different  
135 exposures, such as in comparing effects in demographic subgroups.  
136

### *1. Contributing to Primary Evidence of Effectiveness and/or Safety*

137  
138  
139 A dose-response study is one kind of adequate and well-controlled trial that can provide  
140 primary clinical evidence of effectiveness. It is a particularly informative design,  
141 allowing observations of benefits and risks at different doses and therefore providing an  
142 ability to weigh these in choosing doses. It can help ensure that excessive doses (beyond  
143 those that add to efficacy) are not used, offering some protection against unexpected and  
144 unrecognized dose-related toxicity. Captopril, for example, was a generally well tolerated  
145 drug that caused dose and concentration-related agranulocytosis. Earlier recognition that  
146 daily doses beyond 75-150 milligrams were not necessary, and that renal impairment led  
147 to substantial accumulation, might have avoided most agranulocytosis.  
148

149 Dose-response studies can, in some cases, be particularly convincing and can include  
150 elements of internal consistency that, depending on the size of the study and outcome, can  
151 allow reliance on a single study as evidence of effectiveness. Any dose-response study  
152 includes several comparisons (e.g., each dose vs. placebo, each dose vs. lower doses). A  
153 consistent ordering of these responses (most persuasive when, for example, several doses  
154 are significantly different from placebo and in addition, show an increasing response with  
155 dose) represents at least internal (within-study) replication, reducing the possibility that  
156 an apparent effect is due to chance.  
157

158 In some cases, measurement of systemic exposure levels (e.g., plasma drug  
159 concentrations) as part of dose-response studies can provide additional useful  
160 information. Systemic exposure data are especially useful when an assigned dose is  
161 poorly correlated with plasma levels, obscuring an existing concentration-response  
162 relationship. This can occur when there is a large degree of interindividual variability in  
163 pharmacokinetics and there is a nonlinear relationship between dose and plasma drug  
164 levels. Blood levels can also be helpful when (1) both parent drug and metabolites are  
165 active, (2) different exposure measures (e.g., C<sub>max</sub>, AUC) provide different relationships  
166 between exposure and efficacy or safety, (3) the number of fixed doses in the dose-

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167 response studies is limited, and (4) responses are highly variable and it is helpful to  
168 explore the underlying causes of variability of response.

### 2. *Providing Support for Primary Efficacy Studies*

171  
172 Exposure-response information can support the primary evidence of safety and/or  
173 efficacy. In some circumstances, exposure-response information can provide important  
174 insights that can allow a better understanding of the clinical trial data (e.g., in explaining a  
175 marginal result on the basis of knowledge of systemic concentration-response  
176 relationships and achieved concentrations). Ideally, in such cases the explanation would  
177 be further tested, but in close cases this information could support approval. Even when  
178 the clinical efficacy data are convincing, there may be a safety concern that exposure-  
179 response data can resolve. For example, it might be reassuring to observe that even  
180 patients with increased plasma concentrations (e.g., metabolic outliers or patients on other  
181 drugs in a study) do not have increased toxicity. Exposure-response data thus can add to  
182 the weight of evidence of an acceptable risk/benefit relationship and support approval.  
183 The exposure-response data might also be used to understand or support evidence of  
184 subgroup differences suggested in clinical trials, and to establish covariate relationships  
185 that explain and enhance the plausibility of observed subgroup differences in response.

186  
187 Exposure-response data using short-term biomarkers or surrogate endpoints can  
188 sometimes make further exposure-response data from clinical endpoint exposure-response  
189 studies unnecessary. For example, if it can be shown that the short-term effect does not  
190 increase past a particular dose or concentration, there may be no reason to explore higher  
191 doses or concentrations in the clinical trials. Similarly, short-term exposure response  
192 studies with biomarkers might be used to evaluate early (e.g., first dose) responses seen in  
193 clinical trials.

### 3. *Supporting New Target Populations, Use in Subpopulations, Doses/Dosing Regimens, Dosage Forms, and Routes of Administration*

194  
195  
196  
197  
198  
199 Exposure-response information can sometimes be used to support use, without further  
200 clinical data, of a drug in a new target population by showing similar (or altered in a  
201 defined way) concentration-response relationships for a well-understood short-term  
202 clinical or pharmacodynamic endpoint. Similarly, this information can sometimes  
203 support the safety and effectiveness of alterations in dose or dosing interval or changes in  
204 dosage form or formulation with defined PK effects by allowing assessment of the  
205 consequences of the changes in concentration caused by these alterations. In some cases,  
206 if there is a change in the mix of parent and active metabolites from one population (e.g.,  
207 pediatric vs. adult), dosage form (e.g., because of changes in drug input rate), or route of  
208 administration, additional exposure-response data with short-term endpoints can support  
209 use in the new population, the new product, or new route without further clinical trials.  
210

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211 a. New target populations

212  
213 A PK-PD relationship or data from an exposure-response study can be used to  
214 support use of a previously approved drug in a new target patient population, such  
215 as a pediatric population, where the clinical response is expected to be similar to  
216 the adult population, based on a good understanding of the pathophysiology of the  
217 disease, but there is uncertainty as to the appropriate dose and plasma  
218 concentration. A decision tree illustrating the use of a PK-PD relationship for  
219 bridging efficacy data in an adult population to a pediatric population is shown in  
220 Appendix B. Possible use of PK-PD bridging studies assessing a well-described  
221 PD endpoint (e.g., beta-blockade, angiotension I or II inhibition) to allow  
222 extension of clinical trial information performed in one region to another region is  
223 discussed in the ICH E5 guidance on *Ethnic Factors in the Acceptability of*  
224 *Foreign Clinical Data*.

225  
226 b. Adjustment of dosages and dosing regimens in subpopulations defined on the  
227 basis of intrinsic and extrinsic factors

228  
229 Exposure-response information linking dose, concentration, and response can  
230 support dosage adjustments in patients where pharmacokinetic differences are  
231 expected or observed to occur because of one or more intrinsic (e.g., demographic,  
232 underlying or accompanying disease, genetic polymorphism) or extrinsic (e.g.,  
233 diet, smoking, drug interactions) factors. In some cases, this is straightforward,  
234 simply adjusting the dose to yield similar systemic exposure for that population.  
235 In others, it is not possible to adjust the dose to match both C<sub>max</sub> and AUC, so the  
236 implications of a different PK profile should be considered. Exposure-response  
237 information can help evaluate these implications. In other cases, exposure-  
238 response information can support an argument that PK changes in exposure would  
239 be too small to affect response and therefore, that no dose or dose regimen  
240 adjustments are appropriate.

241  
242 c. New dose regimens, dosage forms and formulations, routes of administration,  
243 and minor product changes.

244  
245 A known exposure-response relationship can be used to (1) interpolate and/or  
246 extrapolate previous clinical results to new dosages and dosing regimens not well  
247 studied in clinical trials, (2) allow marketing of new dosage forms and  
248 formulations, (3) support different routes of administration, and (4) ensure  
249 acceptable product performance in the presence of changes in components,  
250 composition, and method of manufacture that lead to PK differences. Generally,  
251 these uses of exposure-response information should be based on an understanding  
252 of the relationship between the response and concentration, and between dose and  
253 concentration.

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255 Exposure-response data can sometimes be used to support a new dose or dosing  
256 schedule (e.g., twice a day to once a day) that was not studied in safety and  
257 efficacy clinical trials. Exposure-response information can provide insight into  
258 the effect of the change in concentrations achieved with these changes and  
259 whether or not this will lead to a satisfactory therapeutic response. The new  
260 regimen would usually be within the range of total doses studied clinically, but in  
261 certain circumstances could be used to extend an approved dose range without  
262 additional clinical safety and efficacy data. For example, a once-daily dosing  
263 regimen could produce a higher C<sub>max</sub> and a lower C<sub>min</sub> than the same dose given  
264 as a twice-daily regimen. If exposure-response data were available, it might be  
265 considered reasonable to increase the recommended daily dose to maintain a  
266 similar C<sub>min</sub>, even without further studies. Exposure response data are not likely  
267 to be useful in lieu of clinical data in supporting new dosing schedules unless the  
268 relationship of the measured responses to relevant safety and efficacy outcomes  
269 are well understood.

270  
271 In some cases, exposure-response data can support the approval of a new drug  
272 delivery system (e.g., a modified-release dosage form) when the PK profile is  
273 changed intentionally relative to an approved product, generally an immediate-  
274 release dosage form. A known exposure-response relationship could be used to  
275 determine the clinical significance of the observed differences in exposure, and to  
276 determine whether additional clinical efficacy and/or safety data are necessary.

277  
278 Exposure-response data can also support a new formulation that is unintentionally  
279 pharmacokinetically different from the formulation used in the clinical trials to  
280 demonstrate efficacy and/or safety. In vitro and/or in vivo bioequivalence testing  
281 alone is usually used to show that the performance of a new formulation is  
282 equivalent to that used to generate the primary efficacy and safety data.  
283 Sometimes, however, these BE studies can fail to meet the standard  
284 bioequivalence intervals of 80-125% using a 90% confidence interval, or can  
285 demonstrate a difference in exposure that falls within the standard interval but is  
286 nonetheless real. Rather than reformulating the product or repeating the BE study,  
287 a sponsor may be able to support the view that the wider confidence interval or  
288 difference in bioavailability or exposure would not lead to a therapeutic  
289 difference. In other cases, where the altered bioavailability could be of clinical  
290 consequence, adjustment of the marketed dosage strength might be used to adjust  
291 for the PK difference. Changes in the manufacturing process of biological drugs  
292 often lead to subtle unintentional changes in the product, resulting in altered  
293 pharmacokinetics. In cases in which the change in product can be determined not  
294 to have any pharmacologic effects (e.g., no effect on unwanted immunogenicity),  
295 exposure-response information may allow appropriate use of the new product.  
296 Exposure response data are not likely to obviate the need for clinical data when  
297 formulation or manufacturing changes result in altered pharmacokinetics unless

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298 the relationships between measured responses, and relevant clinical outcomes are  
299 well understood.

300  
301 Exposure-response information could also be used to support a change in route of  
302 administration of a drug. An established exposure-response relationship would  
303 allow interpretation of the clinical significance of the difference in PK related to  
304 the different route. Such information about active metabolites could also be  
305 important in this situation.

306

### **IV. DOSE-CONCENTRATION-RESPONSE RELATIONSHIPS AND EFFECTS OVER TIME**

309

310 Depending on the purpose of the study and the measurements made, exposure-response  
311 information can be obtained at steady state without consideration of the impact of fluctuations in  
312 exposure and response over time, or can be used to examine responses at the various  
313 concentrations attained after a single dose during the dosing interval or over the course of  
314 treatment. Where effectiveness is readily measured repeatedly in the course of a dosing interval  
315 (e.g., analgesia, blood pressure, blood glucose), it is possible to relate clinical response to blood  
316 concentrations over time, which can be critical information for choosing a dose and dosing  
317 interval. This is standard practice with antihypertensives, for example, where effect at the end of  
318 the dose interval and at the time of the peak plasma concentration is routinely assessed and where  
319 24-hour automated BP measurements are often used. Controlled-release decongestants have also  
320 been assessed for their effects over the dosing interval, especially the last several hours of the  
321 dosing interval.

322

323 Often, however, the clinical measurement is delayed or persistent compared to plasma levels,  
324 resulting in an exposure-response relationship with considerable hysteresis. Even in this case,  
325 exposure-response relationships can be informative. Furthermore, safety endpoints can have a  
326 time-dependent concentration-response relationship and it could be different from that of the  
327 desired effect.

328

#### **A. Dose and Concentration-Time Relationships**

329

330  
331 As noted in the ICH E4 guidance for industry on *Dose-Response Information to Support*  
332 *Drug Registration*, dose-response information can help identify an appropriate starting dose  
333 and determine the best way (how often and by how much) to adjust dosage for a particular  
334 patient. If the time course of response and the exposure-response relationship over time is  
335 also assessed, time-variant effects on drug action (e.g., induction, tolerance,  
336 chronopharmacologic effects) can be detected. In addition, testing for concentration-response  
337 relationships within a single dosing interval for favorable and adverse events can guide the  
338 choice of dosing interval and dose and suggest benefits of controlled-release dosage forms.  
339 The information on the effects of dose, concentration, and response can be used to optimize  
340 trial design and product labeling.

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342 Although dose is the measurement of drug exposure most often used in clinical trials, it is  
343 plasma concentration measurements that are more directly related to the concentration of the  
344 drug at the target site and thus to the effect. Relationships between concentration and  
345 response can, of course, vary among individuals, but concentration-response relationships in  
346 the same individual over time are especially informative because they are not potentially  
347 confounded by dose-selection/titration phenomena and individual PK variability.  
348

### **B. Concentration-Response Relationships: Two Approaches**

349  
350  
351 There are two fundamentally different approaches to examining plasma concentration-  
352 response relationships: (1) assigning patients randomly to desired plasma concentrations,  
353 titrating dose to achieve them, and relating the concentration to observed response; and (2)  
354 observing the plasma concentrations attained in patients who have been given various doses  
355 of drug, and relating the plasma concentrations to observed response. The former is the  
356 randomized, concentration-controlled trial (Sanathanan and Peck 1991) and is a credible  
357 effectiveness study. Unlike the second approach, the first approach is not affected by  
358 potential confounding factors, such as an unrecognized relationship between  
359 pharmacokinetics and responsiveness, or by the random imbalance of influential factors in  
360 the way patients are chosen to receive higher doses. For example, if it were found that  
361 patients with better absorption, and thus higher concentrations, had greater response, this  
362 might not be related to the higher concentrations but to another factor causing both the  
363 greater absorption and the greater response. Similarly, renal failure could simultaneously  
364 lead to increased plasma concentrations and susceptibility to adverse effects, leading to an  
365 erroneous relation of concentration to adverse effects. Also, a study that titrated only  
366 nonresponders to higher doses might show a lower response with higher concentrations (i.e.,  
367 an *umbrella-shaped* concentration-response (or dose-response) curve, a misleading result).  
368 The second kind of study should be analyzed using specialized approaches (Sheiner,  
369 Hashimoto, and Beal). Because of potential confounding of concentration and response, an  
370 observed concentration-response relationship in these studies may not be credible evidence of  
371 efficacy or even of dose response (see ICH E4). Thus, although it is useful to look in data for  
372 such relationships, they usually should be subjected to further evaluation. The potential  
373 problem of interrelated factors leading to both an effect on pharmacokinetics and an effect on  
374 response and an erroneous concentration-response relationship when individuals are not  
375 randomized to concentrations generally does not occur when concentration-response  
376 relationships in the same individual are observed over time (e.g., over a dosing interval).  
377  
378

## **V. DESIGNS OF EXPOSURE-RESPONSE STUDIES**

379  
380  
381 As noted above, exposure-response studies can examine the relationships between randomly  
382 assigned dose or plasma concentration and PD response (biomarker, surrogate, or clinical  
383 endpoint) or examine the relationship between attained plasma concentration and PD response.  
384 The appropriate designs depend on the study purpose. Randomization of patients to different  
385 doses or concentrations is an essential aspect of the design of well-controlled studies to establish

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386 efficacy. Other designs can also be informative or can suggest further study. The designs of  
387 exposure-response studies discussed here thus also include nonrandomized approaches that can  
388 assume mechanistic models for relationships and that do not rely on randomization for making  
389 comparisons.

### **A. Population vs. Individual Exposure-Response**

391  
392  
393 Exposure-response relationships based on data from randomized parallel studies in which  
394 each treatment group receives only a single dose level provide only an estimate of the  
395 distribution of individual responses at that dose, but do not provide information about the  
396 distribution of individual dose-response relationships. Administration of several dose levels  
397 to each study participant (crossover study) can provide information about the distribution of  
398 individual exposure-response relationships. The individual data allow examination of the  
399 relative steepness or flatness of an individual exposure-response relationship and the  
400 distinctions between responders and nonresponders. In such crossover studies, the sequence  
401 and duration of dosing should be taken into account, as should the possibility of sequence and  
402 carryover effects.

### **B. Exposure-Response Study Design**

403  
404  
405  
406 The various exposure-response study designs and their strengths and limitations have been  
407 extensively discussed in the ICH E4 guidance on *Dose Response Information to Support*  
408 *Drug Registration*. The statistical considerations in designing dose-response studies are  
409 briefly considered in the ICH E9 guidance on *Statistical Principles for Clinical Trials*.

410  
411 In this section, important study design issues on exposure-response analyses are emphasized  
412 and summarized without repeating details already described in the ICH E4 guidance. In  
413 general, the rigor of the design for an exposure-response study should depend on the purpose  
414 of the study. During the drug discovery and development stage, the exposure-response  
415 studies can be more exploratory, because they are intended to gather information for  
416 designing later, more definitive studies. In addition, as emphasized in the ICH E4 guidance,  
417 the entire drug development database should be examined for potentially interesting  
418 exposure-response relationships. For example, gender differences in response can sometimes  
419 be explained by observed gender-related PK data obtained during trials (population PK data)  
420 or in studies obtaining blood samples for measuring plasma concentrations in patients with  
421 adverse effects. When an exposure-response study is designed for supporting regulatory  
422 decisions by providing evidence of efficacy, randomization to exposure (dose or  
423 concentration) is critical, and the study should be prospectively designed to ensure the  
424 reliability and credibility of its results.

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**Table I. Summary of Exposure-Response Study Designs for Different Regulatory Purposes**

<b>Purpose</b>	<b>Study Design Features</b>
Demonstrate effectiveness and tolerability	Randomized, controlled trial Blinded where possible Parallel or crossover Parallel fixed dose or concentration controlled; optional or forced titration vs. control Clinical endpoint or accepted surrogate
Characterize dose-response or compare regimens for group	Randomized, fixed dose, dose-response, or concentration response trial Blinded where possible Parallel or crossover Randomized withdrawal to several fixed doses Wide range of doses Clinical endpoint or accepted surrogate
Individual dose-response	Controlled trials with exposure of each patient to >1 dose; Randomized crossover or titration, forced titration vs. placebo, or optional titration with modeling
Drug discovery and development, dose-response	Use of clinical endpoints, surrogates, and biomarkers Controlled trials, including titration designs with modeling Observational designs based on response vs. blood level

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430 The strengths and limitations of various exposure-response study designs are described in the  
431 ICH E4 guidance and should be considered in selecting designs for these studies. Sources of bias  
432 in data due to study design or conduct should also be considered. These are summarized in Table  
433 I

434  
435 **Table II. Points for Consideration in Different Study Designs from the**  
436 **Exposure-Response Perspective**  
437  
438

<b>Study Design</b>	<b>Points to Consider in Study Design and Exposure-Response Analysis</b>
Crossover, fixed dose	<ul style="list-style-type: none"><li>• For immediate, acute, reversible responses</li><li>• Provide both population mean and individual exposure-response information</li><li>• Safety information obscured by time effects, tolerance, etc.</li><li>• Treatment by period interactions and carryover effects are possible; dropouts are difficult to deal with</li><li>• Changes in baseline-comparability between periods can be a problem</li></ul>
Parallel, fixed dose	<ul style="list-style-type: none"><li>• For long-term, chronic, or responses that are not quickly reversible</li><li>• Provides only population mean, no individual dose response</li><li>• Should have a relatively large number of subjects (1 dose per patient)</li><li>• Gives good information on safety</li></ul>
Titration	<ul style="list-style-type: none"><li>• Provide population mean and individual exposure-response curves, if appropriately analyzed</li><li>• Confounds time and dose effects, a particular problem for safety assessment</li></ul>
Concentration-controlled, fixed dose, parallel, or crossover	<ul style="list-style-type: none"><li>• Directly provides group concentration-response curves (and individual curves, if crossover) and handles intersubject variability in pharmacokinetics at the study design level rather than data analysis level</li><li>• Requires real-time assay availability</li></ul>

439  
440 **C. Measuring Systemic Exposure**  
441  
442 There are many important considerations in selecting one or more active moieties in plasma  
443 for measurement and in choosing specific measures of systemic exposure. Some of these  
444 considerations are summarized below.

445  
446 *1. Chemical Moieties for Measurement*  
447

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448 a. Active moieties

449  
450 To the extent possible, exposure-response studies should include measurement of the  
451 parent drug and its metabolites. Measurement of all active moieties is especially  
452 important when the route of administration of a drug is changed, as different routes of  
453 administration can result in different proportions of parent compound and metabolites  
454 in plasma. Similarly, hepatic or renal impairment or concomitant drugs can alter the  
455 relative proportions of a drug and its active metabolites in plasma.

456  
457 b. Racemates and enantiomers

458  
459 Many drugs are optically active and are usually administered as the racemate.  
460 Enantiomers sometimes differ in both their pharmacokinetic and pharmacodynamic  
461 properties. Early elucidation of the PK and PD properties of the individual  
462 enantiomers can help in designing a dosing regimen and in deciding whether it can be  
463 of value to develop one of the pure enantiomers as the final drug product. Further  
464 description on how to develop information for a drug with one or more chiral centers  
465 is provided in a FDA Policy Statement, *Development of New Stereoisomeric Drugs*.<sup>2</sup>  
466

467 c. Complex mixtures

468  
469 Complex drug substances can include drugs derived from animal or plant materials  
470 and drugs derived from traditional fermentation processes (yeast, mold, bacterium, or  
471 other microorganisms). For some of these drug substances, identification of  
472 individual active moieties and/or ingredients is difficult or impossible. In this  
473 circumstance, measurement of only one or more moieties can be appropriate as  
474 *markers* in understanding exposure-response relationships and can even be used to  
475 identify the major active moieties.

476  
477 d. Endogenous ligand measurements

478  
479 The response to a drug is often the result of its competition with an endogenous ligand  
480 for occupancy of a receptor. For example, a beta-blocker exerts its effect by  
481 competing with endogenous catecholamines for receptor sites. Taking into account  
482 endogenous catecholamine concentrations as well as drug concentrations may help  
483 explain the overall physiological response in patients with different concentrations of  
484 circulating catecholamines. Biorhythms can affect the concentrations of endogenous  
485 compounds, which can make adjustments in daily dosing schedule important, as seen  
486 in some treatment regimens for hypertension. Consideration of the endogenous  
487 ligand concentration and the drug concentration in various tissues, and of the relative  
488 affinities of the ligand to the drug can be important to explain concentration-response  
489 relationships.

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<sup>2</sup> This document is available on the Internet at <http://www.fda.gov/cder/guidance/stereo.htm>.

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e. Unbound drug and/or active metabolite (protein binding)

Most standard assays of drug concentrations in plasma measure the total concentration, consisting of both bound and unbound drug. Renal or hepatic diseases can alter the binding of drugs to plasma proteins. These changes can influence the understanding of PK and PK-PD relationships. Where feasible, studies should be performed to determine the extent of protein binding and to understand whether this binding is or is not concentration-dependent. This is particularly important when comparing responses in patient groups that can exhibit different plasma protein binding (e.g., in various stages of hepatic and renal disease). For highly protein bound drugs, PK and PK-PD modeling may be more informative using unbound drug concentrations, particularly if there is significant variation in binding among patients or in special populations of patients.

A special case of protein binding is the development of antibodies to a drug. Antibodies can alter the pharmacokinetics of a drug and can also affect PK-PD relationships by neutralizing the activity of the drug or preventing its access to the active site.

2. *Exposure Variables*

Pharmacokinetic concentration-time curves for a drug and/or its metabolites can be used to identify exposure metrics such as AUC, C<sub>max</sub>, or C<sub>min</sub>. These simple measurements of exposure ignore the time course of exposure, in contrast to the sequential measurement of concentration over time.

a. Area under the concentration-time profiles (AUC)

The area under the concentration-time full profile is a typical pharmacokinetic variable used to represent the average drug concentration over a time period. It is also a variable that can be used to compare exposure to a drug after multiple doses to single dose exposure. It is frequently useful to correlate long-term drug effects to steady-state AUC, as the effects usually reflect the daily exposure to drug following multiple dosing.

b. Peak plasma concentrations (C<sub>max</sub>)

Peak plasma concentrations of a drug can be associated with a PD response, especially adverse events. There can be large interindividual variability in the time to peak concentration, and closely spaced sampling times are often critical to determine the peak level accurately in individual patients. The sampling design for obtaining plasma levels to estimate peak concentrations should account for expected differences

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533 in PK profiles (e.g., in T<sub>max</sub>, time to C<sub>max</sub>) due to demographics, disease states, and  
534 food effects, if any.

535

536 c. Trough plasma concentrations (C<sub>min</sub>)

537

538 During chronic therapy, collection of multiple plasma samples over a dosing interval  
539 is often not practical. As a substitute, a trough plasma sample can be collected just  
540 before administration of the next dose at scheduled study visits. Trough levels are  
541 often proportional to AUC, because they do not reflect drug absorption processes, as  
542 peak levels do in most cases. For many of the drugs that act slowly relative to the  
543 rates of their absorption, distribution, and elimination, trough level and AUC can  
544 often be equally well correlated with drug effects.

545

546 d. Sparse plasma sampling

547

548 An increasingly common sampling practice in clinical trials is to obtain plasma  
549 samples at randomly selected times during the study conduct, or at prespecified but  
550 different times, to measure drug concentration and, in some cases, response. With  
551 only two or three samples per subject, the usual pharmacokinetic data analysis  
552 methods should not be used to make precise estimates of individual PK parameters.  
553 In these circumstances, a specialized technique, population PK analysis combined  
554 with Bayesian estimation method can be used to approximate population and  
555 individual PK parameters, providing an exposure variable that is more readily  
556 correlated to response than the sparse plasma levels themselves. This approach is  
557 particularly recommended when relatively complete PK information is desired, but it  
558 is difficult or unethical to sample repeatedly C for example, in pediatric and geriatric  
559 populations (see the FDA guidance for industry on *Population Pharmacokinetics*  
560 (February 1999)). Sampling times should be planned prospectively and known  
561 accurately to ensure accurate estimation of PK parameters.

562

563 e. Plasma concentration-time profiles

564

565 In traditional PK studies (not sparse sampling), the concentrations of active moieties  
566 are measured over time. This allows not only calculation of AUC but also the  
567 determination of concentration versus time profiles over a dosing interval for each  
568 individual, as well as the population. This approach yields relatively detailed  
569 exposure information that can be correlated to the observed response in individuals.  
570 The exposure-response relationship based on concentration-time profiles can provide  
571 time-dependent information that cannot be derived from AUC or C<sub>min</sub>.

572

### **D. Measuring Response**

573

574 Broadly speaking, both positive (efficacy) and negative (safety) effects of a drug can be  
575 characterized using a variety of measurements or response endpoints. These effects include  
576

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577 clearly clinically pertinent effects (clinical benefit or toxicity), effects on a well-established  
578 surrogate (blood pressure or QT interval), and effects on a more remote biomarker (ACE  
579 inhibition, bradykinin levels). All of these measurements can be expected to show exposure-  
580 response relationships that can guide therapy, suggest dose/dose intervals, or suggest further  
581 study.

582  
583 In many cases, multiple response endpoints are more informative than single endpoints for  
584 establishing exposure-response relationships. Specifically, less clinically persuasive  
585 endpoints (biomarkers, surrogates) can help in choosing doses for the larger and more difficult  
586 clinical endpoint trials and can suggest areas of special concern. In all cases, measurement of  
587 response endpoints should be standardized to conform across studies and between study sites  
588 and/or laboratories.

589  
590 *1. Biomarkers*

591  
592 *Biological marker* (biomarker) refers to a variety of physiologic, pathologic, or anatomic  
593 measurements that are thought to relate to some aspect of normal or pathological biologic  
594 processes (Temple 1995; Lesko and Atkinson 2001). These biomarkers include  
595 measurements that suggest the etiology of, the susceptibility to, or the progress of disease;  
596 measurements related to the mechanism of response to treatments; and actual clinical  
597 responses to therapeutic interventions. Biomarkers differ in their closeness to the  
598 intended therapeutic response or clinical benefit endpoints, including the following:

- 599
- 600 • Biomarkers thought to be valid surrogates for clinical benefit (e.g., blood pressure,  
601 cholesterol, viral load)
- 602 • Biomarkers thought to reflect the pathologic process and be at least candidate  
603 surrogates (e.g., brain appearance in Alzheimer's Disease, brain infarct size,  
604 various radiographic/isotopic function tests)
- 605 • Biomarkers reflecting drug action but of uncertain relation to clinical outcome  
606 (e.g., inhibition of ADP-dependent platelet aggregation, ACE inhibition)
- 607 • Biomarkers that are still more remote from the clinical benefit endpoint (e.g.,  
608 degree of binding to a receptor or inhibition of an agonist)
- 609

610 From a regulatory perspective, a biomarker is not considered an acceptable surrogate  
611 endpoint for a determination of efficacy of a new drug unless it has been empirically  
612 shown to function as a valid indicator of clinical benefit (i.e., is a valid surrogate).  
613 Theoretical justification alone does not meet the evidentiary standards for market access.  
614 Many biomarkers will never undergo the rigorous statistical evaluation that would  
615 establish their value as a surrogate endpoint to determine efficacy or safety, but they can  
616 still have use in drug development and regulatory decision making. Changes in  
617 biomarkers typically exhibit a time course that is different from changes in clinical  
618 endpoints and often are more directly related to the time course of plasma drug  
619 concentrations, possibly with a measurable delay. For this reason, exposure-response

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620 relationships based on biomarkers can help establish the dose range for clinical trials  
621 intended to establish efficacy that will then be studied more formally, indicate how soon  
622 titration should occur, examine potential pharmacodynamic interactions, and give insight  
623 into potential adverse effects. Biomarkers can also be useful during the drug discovery  
624 and development stage, where they can help link preclinical and early clinical exposure-  
625 response relationships and better establish dose ranges for clinical testing.  
626

### 2. *Surrogate Endpoint*

627  
628  
629 Surrogate endpoints are a subset of biomarkers. A surrogate endpoint is a laboratory  
630 measurement or physical sign used in therapeutic trials as a substitute for a clinically  
631 meaningful endpoint that is expected to predict the effect of the therapy (Temple 1999).  
632 A well-validated surrogate will predict the clinical benefit of an intervention both  
633 quantitatively and qualitatively (Prentice 1989), with consistent results in several settings.  
634 FDA is able to rely on less well-established surrogates for accelerated approval of drugs  
635 that provide meaningful benefit over existing therapies for serious or life-threatening  
636 illnesses (e.g. acquired immunodeficiency syndrome). In these cases, the surrogates  
637 should be reasonably likely to predict clinical benefit based on epidemiologic,  
638 therapeutic, pathophysiologic, or other scientific evidence. However, in general trials  
639 examining surrogate endpoints, even where the endpoint is well correlated with a clinical  
640 outcome, surrogates will be unable to evaluate clinically relevant effects of the drug not  
641 related to the surrogate, whether these are beneficial or adverse (Temple 1999).  
642

### 3. *Clinical Benefit or Outcome Endpoints*

643  
644  
645 Clinical benefit endpoints are variables that reflect how a patient feels, functions, or  
646 survives. Clinical endpoints reflect desired effects of a therapeutic intervention and are  
647 the most credible response measurements in clinical trials.  
648

## **VI. MODELING OF EXPOSURE-RESPONSE RELATIONSHIPS**

### **A. General Considerations**

649  
650  
651 Adequate and well-controlled clinical studies that establish a drug's effectiveness are the  
652 basis for approval of new drugs. Exposure-response data can be derived from these clinical  
653 studies, as well as from other preclinical and clinical studies, and provide a basis for  
654 integrated model-based analysis and simulation (Machado et al. 2000; Sheiner and Steimer  
655 2000). Simulation is a way of predicting expected relationships between exposure and  
656 response in situations where real data are sparse or absent. There are many different types of  
657 models for the analysis of exposure-response data (e.g., descriptive PD models (Emax model  
658 for exposure-response relationships) or empirical models that link a PK model (dose-  
659 concentration relationship) and a PD model (concentration-response relationship)).  
660 Descriptive or empirical model-based analysis does not necessarily establish causality or  
661 provide a mechanistic understanding of a drug's effect and would not ordinarily be a basis for  
662

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664 approval of a new drug. Nevertheless, dose-response or PK-PD modeling can help in  
665 understanding the nature of exposure-response relationships and can be used to analyze  
666 adequate and well-controlled trials to extract additional insights from treatment responses.  
667 Adequate and well-controlled clinical studies that investigate several fixed doses and/or  
668 measure systemic exposure levels, when analyzed using scientifically reasonable causal  
669 models, can predict exposure-response relationships for safety and/or efficacy and provide  
670 plausible hypotheses about the effects of alternative doses and dosage regimens not actually  
671 tested. This can suggest ways to optimize dosage regimens and to individualize treatment in  
672 specific patient subsets for which there are limited data. Creating a theory or rationale to  
673 explain exposure-response relationships through modeling and simulation allows  
674 interpolation and extrapolation to better doses and responses in the general population and to  
675 subpopulations defined by certain intrinsic and extrinsic factors.

### **B. Modeling Strategy**

677  
678  
679 The process of PK-PD modeling should contain the following steps:  
680

#### 681 1. *Statement of the Problem*

682  
683 The objectives of the modeling, the study design, and the available PK and PD data  
684 should be clearly identified.  
685

#### 686 2. *Statement of Assumptions*

687  
688 The assumptions of the model should be clearly laid out. The assumptions can be related  
689 to dose-response, PK, PD, and/or one of the following:  
690

- 691 ● The mechanism of the drug actions for efficacy and adverse effects
- 692 ● Immediate or cumulative clinical effects
- 693 ● Development of tolerance or absence of tolerance
- 694 ● Drug-induced inhibition or induction of PK processes
- 695 ● Disease state progression
- 696 ● Circadian variations in basal conditions
- 697 ● Influential covariates
- 698 ● Absence or presence of an *effect compartment*
- 699 ● Presence or absence of active metabolites and their contribution to clinical effects
- 700 ● The PK model of absorption and disposition and the parameters to be estimated
- 701 ● The PD model of effect and the parameters to be estimated
- 702 ● Distribution of PK and PD measures and parameters

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- 703 ● Distributions of intra- and inter-individual variability in parameters
- 704 ● Inclusion and/or exclusion of specific patient data
- 705

706 The assumptions should be justified based on previous data or from the results of the  
707 current analysis.

708

### 709 3. *Selection of the Model*

710

711 The answer to the question of what constitutes an appropriate model is complex. The  
712 model selected should be based on the assumptions made and the intended use of the  
713 model in decision making. If the assumptions do not lead to a mechanistic model, an  
714 empirical model can be selected. In this case, the validation of the model predictability  
715 becomes especially important. The available data can also govern the types of models  
716 that can be used. The model selection process can be a series of trial and error steps.  
717 Different model structures or newly added or dropped components to an existing model  
718 can be assessed by visual inspection and tested using one of several objective criteria.  
719 New assumptions can be added when emerging data indicates that this is appropriate.  
720 The final selection of the model should be the simplest possible, have reasonable  
721 goodness of fit, and provide a level of predictability appropriate for its use in decision  
722 making.

723

### 724 4. *Validation of the Model*

725

726 The issue of model validation is not totally resolved. Generally, the predictive power of a  
727 model should be dealt with during the study design as well as in the data analysis stages.  
728 The study should be designed to yield a predictive model. When plausible exposure-  
729 response models are identified based on prior knowledge of the drug before conducting  
730 an exposure-response study, the predictive power of the final models derived from the  
731 study results becomes a function of study design factors, such as number of subjects and  
732 sampling plan. The predictive power can be estimated through simulation, by considering  
733 distributions of pharmacokinetic, pharmacodynamic, and study design variables. A  
734 robust study design will provide accurate and precise model parameter estimations that  
735 are insensitive to model assumptions.

736

737 During the analysis stage of a study, models can be validated based on internal and/or  
738 external data. The ultimate test of a model is its predictive power. The common method  
739 for estimating predictability is to split the data set into two parts, build the model based  
740 on one set of data, and test the predictability of the resulting model on the second set of  
741 data. The predictability is especially important when the model is intended to (1) provide  
742 supportive evidence for primary efficacy studies, (2) address safety issues, (3) support  
743 new doses and dosing regimens in new target populations or subpopulations defined by  
744 intrinsic and extrinsic factors or when there is a change in dosage form and/or route of  
745 administration.

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### 747 **VII. SUBMISSION INFORMATION: EXPOSURE-RESPONSE STUDY REPORT**

748

749 The general format and content of a clinical study report should follow the ICH E3 guidance on  
750 the *Structure and Content of Clinical Study Reports*, but with special attention to measurements  
751 of exposure and response and planned modeling and simulation. For example, there should be a  
752 description of the assay methods used in quantifying drug concentrations (if they are components  
753 of the exposure measure). Assay performance (quality control samples), sample chromatograms,  
754 and standard curves should also be included, where applicable. The validity of the  
755 methodologies should be described. The report should contain:

756

- 757 • The response variable and all covariate information
- 758 • An explanation of how they were obtained
- 759 • A description of the sampling design used to collect the PK and PD measures
- 760 • A description of the covariates, including their distributions and, where  
761 appropriate, the accuracy and precision with which the responses were measured.
- 762 • Data quality control and editing procedures
- 763 • A detailed description of the criteria and procedures for model building and  
764 reduction, including exploratory data analysis

765

766 The following components of the data analysis method used in the study should be described: (1)  
767 the chosen dose-response or PK-PD model, (2) the assumptions and underlying rationale for  
768 model components (e.g., parameterization, error models), and (3) the chosen model-fitting  
769 method. In addition, this section should contain a description of the treatment of outliers and  
770 missing data where applicable, as well as flow diagrams, if possible, of the analysis performed  
771 and representative control/command files for each significant model building and/or reduction  
772 step. In presenting results, complete output of results obtained for the final dose-response, or  
773 PK-PD model, and important intermediate steps should be included. The report should include a  
774 comprehensive statement of the rationale for model building and reduction procedures,  
775 interpretation of the results, impact of protocol violations, and discussion and presentation of  
776 supporting graphs. The outcome of the modeling should also be discussed in terms of predictive  
777 performance.

778

779 An appendix should be provided containing the data set used in the dose-response or PK-PD  
780 analysis, the programming codes along with the printouts of the results of the final model, and  
781 any additional important plots.

782

783 Whether the analysis was performed as a result of an add-on to a clinical study or as a stand-  
784 alone exposure-response study, the original study protocol and amendments should be included  
785 in the appendix.

786

787 The FDA's Center for Drug Evaluation Research (CDER) guidance for industry on *Providing*  
788 *Regulatory Submissions in Electronic Format C NDAs* includes information on how to submit

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789 the exposure-response study report in electronic format. . Information on electronic submissions  
790 to FDA’s Center for Biologics Evaluation and Research (CBER) can be found in the guidance for  
791 industry on *Providing Regulatory Submissions to the Center for Biologics Evaluation and*  
792 *Research (CBER) in Electronic Format C Biologics Marketing Applications* (Biologics License  
793 Application (BLA), Product License Application (PLA)/Establishment License Application  
794 (ELA) and New Drug Application (NDA)). FDA is still actively working on standardizing data  
795 file formats for exposure-response and other clinical pharmacology data, and plans to provide  
796 these standards in future versions of the electronic guidance document. In the meantime,  
797 sponsors are encouraged to submit both the reports and data files with BLA or NDA submissions  
798 in electronic format. Until the details are included in an electronic BLA or NDA guidance  
799 document, sponsors should consult the clinical pharmacology and biopharmaceutics reviewer or  
800 team leader on the data sets to be provided and elements to be included in the data sets.

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### APPENDIX A C RELATED GUIDANCES

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The use of exposure-response relationships is considered in many FDA guidances for industry as well as in various ICH guidances. These guidances can be divided into those that provide general advice and those that provide specific recommendations about the use of exposure-response information to adjust a dosage regimen based on intrinsic and extrinsic factors. The ICH Common Technical Document (ICH M4, Efficacy) suggests a structure to organize the submission of exposure-response information. In addition, the statistical considerations for dose-response studies are briefly described in the ICH E9 *Guidance on Statistical Principles for Clinical Trials*.

#### **A. Guidances Providing General Statements**

The value of understanding exposure-response has been recognized in numerous domestic and international guidances. Brief abstracts of these guidances are provided below to focus on exposure-response relationships and the impact of intrinsic and extrinsic factors on these relationships.

1. *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (May 1998)

This guidance provides general information about the efficacy standard (section I) and comments further on the quantity (section II) and quality (section III) of efficacy information needed for a regulatory determination of efficacy based on both statutory and scientific considerations. The guidance focuses on (1) when efficacy for a new product can be extrapolated entirely from existing efficacy studies, (2) when one adequate and well-controlled study of a particular condition, regimen, or dose supported by information from other adequate and well-controlled studies may be appropriate, and (3) when information from a single multicenter study may be appropriate.

2. *Guideline for the Format and Content of the Clinical and Statistical Sections of an Application* (July 1988)

This guidance provides a description of the format and content of the clinical and statistical data package required as part of a new drug application under CFR 314.50. It emphasizes the importance of conducting an integrated analysis of all clinical and preclinical exposure-response data that forms the foundation for dose and dosing regimen determinations and dose adjustments for subpopulations.

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877 3. ICH E4, *Dose Response Information to Support Drug Registration* (November 1994)

878  
879 This guidance describes the purpose of exposure-response information and the uses of  
880 dose-response and/or concentration-response data in choosing doses during the drug  
881 development process. The guidance emphasizes the importance of developing exposure-  
882 response data throughout development. It further comments on the use of population and  
883 individual dose-concentration, and concentration- and/or dose-response relationships to  
884 provide dosage and administration instructions in product labeling. The guidance notes  
885 that these instructions should include information about both starting dosages and  
886 subsequent titration steps based on response to the drug, as well as information on how to  
887 adjust dose in the presence of factors that are intrinsic (age, gender, race, organ  
888 dysfunction, body size, differences in absorption, distribution, metabolism, and excretion)  
889 and extrinsic (diet, concomitant medications). The guidance emphasizes the importance  
890 of early exposure-response data to allow efficient design of later studies and the value of  
891 examining the entire database to assess exposure-response relationships. The guidance  
892 further comments on strengths and limitations of various study designs to assess  
893 exposure-response. The guidance comments briefly on the use of models to amplify  
894 understanding of exposure-response-relationships and, consistent with 21 CFR 314.126,  
895 indicates that a well-controlled dose-response study may be one type of study that  
896 supports efficacy.

897  
898 4. ICH E5, *Ethnic Factors in the Acceptability of Foreign Clinical Data* (June 1998)

899  
900 This guidance provides descriptions of PK and PD studies and expresses PD endpoints as  
901 safety and/or efficacy measures of activity thought, but not documented, to be related to  
902 clinical benefit (biomarkers), surrogate endpoints, and clinical benefit endpoints. The  
903 guidance further defines a PD study as one that describes the relationship between a  
904 pharmacological effect or clinical benefit effect in relation to dose or drug concentration.  
905 The guidance establishes a classification system of intrinsic (genetic polymorphism, age,  
906 gender, height, weight, lean body mass, body composition, and organ dysfunction) and  
907 extrinsic (medical practice, diet, use of tobacco, use of alcohol, exposure to pollution and  
908 sunshine, practices in clinical trial design and conduct, socioeconomic status, compliance  
909 with medication) ethnic factors that can affect safety, efficacy, dosage, and dosage  
910 regimen determinations. The guidance provides an additional set of factors that indicate  
911 whether a drug may be sensitive to ethnic factors (linear PK, flat PD curve, wide  
912 therapeutic range). It focuses on the bridging studies that may be critical for an  
913 application in a new region based on a clinical data package developed in another region.  
914 These bridging studies range from those that establish similarity of exposure-response  
915 relationship in the two regions for a well-established PD effect (e.g., ACE inhibition or  
916 short-term blood pressure response) to a controlled trial in the new region, preferably a  
917 dose-response study, using the pertinent clinical endpoint.

918

## *Draft C Not for Implementation*

### 919 **B. Guidances Providing Specific Statements**

920  
921 FDA has issued final or draft<sup>3</sup> guidances that focus on how to adjust dosages and dosing  
922 regimens in the presence of selected intrinsic and extrinsic factors. A general theme of these  
923 guidances is that information relating exposure to response can be used to adjust dosages and  
924 dosing regimens in the presence of influences on PK such as age, gender (demographic  
925 factors), impaired organ function (intrinsic factors), or concomitant medications and diet  
926 (extrinsic factors). In many circumstances, where the assumption can be made that the  
927 exposure-response relationships are not disturbed by these factors, PK data alone can be used  
928 to guide dosages and dosing regimens. This principle is articulated in the following FDA  
929 guidances:

- 930  
931 1. *ICH E7, Studies in Support of Special Populations: Geriatrics* (August 1994)  
932
- 933 2. *Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*  
934 *(July 1993)*
- 935  
936 3. *General Considerations for Pediatric Pharmacokinetic Studies for Drugs and*  
937 *Biological Products* (draft) (November 1998)
- 938  
939 4. *Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data*  
940 *Analysis and Impact on Dosing and Labeling* (May 1998)
- 941  
942 5. *Pharmacokinetics in Patients with Hepatic Insufficiency: Study Design, Data*  
943 *Analysis and Impact on Dosing and Labeling* (draft) (November 1999)
- 944  
945 6. *In Vivo Metabolism/Drug Interactions Studies: Study Design, Data Analysis and*  
946 *Recommendations for Dosing and Labeling* (draft) (November 1999)  
947

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<sup>3</sup> Draft guidances have been included for completeness only. As draft documents, they are not intended to be implemented until published in final form.

*Draft C Not for Implementation*

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APPENDIX B  
PEDIATRIC DECISION TREE  
ILLUSTRATING THE INTEGRATION OF PK-PD

*Pediatric Study Decision Tree*

