
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DRAFT GUIDANCE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)
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**U.S. Department of Health and Human Services
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**Exposure-Response Relationships: Study Design, Data Analysis,
and Regulatory Applications**

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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.

¹ 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

II. BACKGROUND

42

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_{max}, C_{min}, C_{ss}, 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

III. REGULATORY APPLICATIONS

78

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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_{max}, 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.
169

2. *Providing Support for Primary Efficacy Studies*

170
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.
194

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

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_{max} 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_{max} and a lower C_{min} 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_{min}, 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

390
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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425
426
427 The strengths and limitations of various exposure-response study designs are described in the
428 ICH E4 guidance and should be considered in selecting designs for these studies. Sources of bias
429 in data due to study design or conduct should also be considered. These are summarized in Table
430 I.

431
432 **Table I. Points for Consideration in Different Study Designs from the**
433 **Exposure-Response Perspective**
434
435

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

436 437 **C. Measuring Systemic Exposure** 438

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

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1. *Chemical Moieties for Measurement*

a. Active moieties

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

b. Racemates and enantiomers

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

c. Complex mixtures

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

d. Endogenous ligand measurements

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

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

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485 affinities of the ligand to the drug can be important to explain concentration-response
486 relationships.

487

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

489

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

501

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

506

507 2. *Exposure Variables*

508

509 Pharmacokinetic concentration-time curves for a drug and/or its metabolites can be used
510 to identify exposure metrics such as AUC, C_{max}, or C_{min}. These simple measurements
511 of exposure ignore the time course of exposure, in contrast to the sequential measurement
512 of concentration over time.

513

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

515

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

522

523 b. Peak plasma concentrations (C_{max})

524

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

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529 plasma levels to estimate peak concentrations should account for expected differences
530 in PK profiles (e.g., in T_{max}, time to C_{max}) due to demographics, disease states, and
531 food effects, if any.

532

533 c. Trough plasma concentrations (C_{min})

534

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

542

543 d. Sparse plasma sampling

544

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

559

560 e. Plasma concentration-time profiles

561

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

569

570 **D. Measuring Response**

571

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572 Broadly speaking, both positive (efficacy) and negative (safety) effects of a drug can be
573 characterized using a variety of measurements or response endpoints. These effects include
574 clearly clinically pertinent effects (clinical benefit or toxicity), effects on a well-established
575 surrogate (blood pressure or QT interval), and effects on a more remote biomarker (ACE
576 inhibition, bradykinin levels). All of these measurements can be expected to show exposure-
577 response relationships that can guide therapy, suggest dose/dose intervals, or suggest further
578 study.

579
580 In many cases, multiple response endpoints are more informative than single endpoints for
581 establishing exposure-response relationships. Specifically, less clinically persuasive
582 endpoints (biomarkers, surrogates) can help in choosing doses for the larger and more difficult
583 clinical endpoint trials and can suggest areas of special concern. In all cases, measurement of
584 response endpoints should be standardized to conform across studies and between study sites
585 and/or laboratories.

1. Biomarkers

586
587
588
589 *Biological marker* (biomarker) refers to a variety of physiologic, pathologic, or anatomic
590 measurements that are thought to relate to some aspect of normal or pathological biologic
591 processes (Temple 1995; Lesko and Atkinson 2001). These biomarkers include
592 measurements that suggest the etiology of, the susceptibility to, or the progress of disease;
593 measurements related to the mechanism of response to treatments; and actual clinical
594 responses to therapeutic interventions. Biomarkers differ in their closeness to the
595 intended therapeutic response or clinical benefit endpoints, including the following:

- 596
- 597 • Biomarkers thought to be valid surrogates for clinical benefit (e.g., blood pressure,
598 cholesterol, viral load)
- 599 • Biomarkers thought to reflect the pathologic process and be at least candidate
600 surrogates (e.g., brain appearance in Alzheimer's Disease, brain infarct size,
601 various radiographic/isotopic function tests)
- 602 • Biomarkers reflecting drug action but of uncertain relation to clinical outcome
603 (e.g., inhibition of ADP-dependent platelet aggregation, ACE inhibition)
- 604 • Biomarkers that are still more remote from the clinical benefit endpoint (e.g.,
605 degree of binding to a receptor or inhibition of an agonist)
- 606

607 From a regulatory perspective, a biomarker is not considered an acceptable surrogate
608 endpoint for a determination of efficacy of a new drug unless it has been empirically
609 shown to function as a valid indicator of clinical benefit (i.e., is a valid surrogate).
610 Theoretical justification alone does not meet the evidentiary standards for market access.
611 Many biomarkers will never undergo the rigorous statistical evaluation that would
612 establish their value as a surrogate endpoint to determine efficacy or safety, but they can
613 still have use in drug development and regulatory decision making. Changes in
614 biomarkers typically exhibit a time course that is different from changes in clinical

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615 endpoints and often are more directly related to the time course of plasma drug
616 concentrations, possibly with a measurable delay. For this reason, exposure-response
617 relationships based on biomarkers can help establish the dose range for clinical trials
618 intended to establish efficacy that will then be studied more formally, indicate how soon
619 titration should occur, examine potential pharmacodynamic interactions, and give insight
620 into potential adverse effects. Biomarkers can also be useful during the drug discovery
621 and development stage, where they can help link preclinical and early clinical exposure-
622 response relationships and better establish dose ranges for clinical testing.

623
624
625

2. *Surrogate Endpoint*

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

639
640
641

3. *Clinical Benefit or Outcome Endpoints*

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

645
646
647

VI. MODELING OF EXPOSURE-RESPONSE RELATIONSHIPS

A. General Considerations

648
649

650 Adequate and well-controlled clinical studies that establish a drug's effectiveness are the
651 basis for approval of new drugs. Exposure-response data can be derived from these clinical
652 studies, as well as from other preclinical and clinical studies, and provide a basis for
653 integrated model-based analysis and simulation (Machado et al. 2000; Sheiner and Steimer
654 2000). Simulation is a way of predicting expected relationships between exposure and
655 response in situations where real data are sparse or absent. There are many different types of
656 models for the analysis of exposure-response data (e.g., descriptive PD models (Emax model
657 for exposure-response relationships) or empirical models that link a PK model (dose-
658 concentration relationship) and a PD model (concentration-response relationship)).

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

673

B. Modeling Strategy

674

675 The process of PK-PD modeling should contain the following steps:

676

677

1. Statement of the Problem

678

679 The objectives of the modeling, the study design, and the available PK and PD data
680 should be clearly identified.

681

682

2. Statement of Assumptions

683

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

686

687

688

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

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- 699 ● Distribution of PK and PD measures and parameters
- 700 ● Distributions of intra- and inter-individual variability in parameters
- 701 ● Inclusion and/or exclusion of specific patient data
- 702

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

705 706 3. *Selection of the Model*

707
708 The answer to the question of what constitutes an appropriate model is complex. The
709 model selected should be based on the assumptions made and the intended use of the
710 model in decision making. If the assumptions do not lead to a mechanistic model, an
711 empirical model can be selected. In this case, the validation of the model predictability
712 becomes especially important. The available data can also govern the types of models
713 that can be used. The model selection process can be a series of trial and error steps.
714 Different model structures or newly added or dropped components to an existing model
715 can be assessed by visual inspection and tested using one of several objective criteria.
716 New assumptions can be added when emerging data indicates that this is appropriate.
717 The final selection of the model should be the simplest possible, have reasonable
718 goodness of fit, and provide a level of predictability appropriate for its use in decision
719 making.

720 721 4. *Validation of the Model*

722
723 The issue of model validation is not totally resolved. Generally, the predictive power of a
724 model should be dealt with during the study design as well as in the data analysis stages.
725 The study should be designed to yield a predictive model. When plausible exposure-
726 response models are identified based on prior knowledge of the drug before conducting
727 an exposure-response study, the predictive power of the final models derived from the
728 study results becomes a function of study design factors, such as number of subjects and
729 sampling plan. The predictive power can be estimated through simulation, by considering
730 distributions of pharmacokinetic, pharmacodynamic, and study design variables. A
731 robust study design will provide accurate and precise model parameter estimations that
732 are insensitive to model assumptions.

733
734 During the analysis stage of a study, models can be validated based on internal and/or
735 external data. The ultimate test of a model is its predictive power. The common method
736 for estimating predictability is to split the data set into two parts, build the model based
737 on one set of data, and test the predictability of the resulting model on the second set of
738 data. The predictability is especially important when the model is intended to (1) provide
739 supportive evidence for primary efficacy studies, (2) address safety issues, (3) support
740 new doses and dosing regimens in new target populations or subpopulations defined by

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741 intrinsic and extrinsic factors or when there is a change in dosage form and/or route of
742 administration.
743

744 **VII. SUBMISSION INFORMATION: EXPOSURE-RESPONSE STUDY REPORT** 745

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

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

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

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

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

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

833
834
835 The use of exposure-response relationships is considered in many FDA guidances for industry as
836 well as in various ICH guidances. These guidances can be divided into those that provide
837 general advice and those that provide specific recommendations about the use of exposure-
838 response information to adjust a dosage regimen based on intrinsic and extrinsic factors. The
839 ICH Common Technical Document (ICH M4, Efficacy) suggests a structure to organize the
840 submission of exposure-response information. In addition, the statistical considerations for dose-
841 response studies are briefly described in the ICH E9 *Guidance on Statistical Principles for*
842 *Clinical Trials*.

A. Guidances Providing General Statements

844
845
846 The value of understanding exposure-response has been recognized in numerous domestic
847 and international guidances. Brief abstracts of these guidances are provided below to focus
848 on exposure-response relationships and the impact of intrinsic and extrinsic factors on these
849 relationships.

- 850
851 1. *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological*
852 *Products* (May 1998)

853
854 This guidance provides general information about the efficacy standard (section I) and
855 comments further on the quantity (section II) and quality (section III) of efficacy
856 information needed for a regulatory determination of efficacy based on both statutory
857 and scientific considerations. The guidance focuses on (1) when efficacy for a new
858 product can be extrapolated entirely from existing efficacy studies, (2) when one
859 adequate and well-controlled study of a particular condition, regimen, or dose
860 supported by information from other adequate and well-controlled studies may be
861 appropriate, and (3) when information from a single multicenter study may be
862 appropriate.

- 863
864 2. *Guideline for the Format and Content of the Clinical and Statistical Sections of an*
865 *Application* (July 1988)

866
867 This guidance provides a description of the format and content of the clinical and
868 statistical data package required as part of a new drug application under CFR 314.50.
869 It emphasizes the importance of conducting an integrated analysis of all clinical and
870 preclinical exposure-response data that forms the foundation for dose and dosing
871 regimen determinations and dose adjustments for subpopulations.

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

875
876 This guidance describes the purpose of exposure-response information and the uses of
877 dose-response and/or concentration-response data in choosing doses during the drug
878 development process. The guidance emphasizes the importance of developing exposure-
879 response data throughout development. It further comments on the use of population and
880 individual dose-concentration, and concentration- and/or dose-response relationships to
881 provide dosage and administration instructions in product labeling. The guidance notes
882 that these instructions should include information about both starting dosages and
883 subsequent titration steps based on response to the drug, as well as information on how to
884 adjust dose in the presence of factors that are intrinsic (age, gender, race, organ
885 dysfunction, body size, differences in absorption, distribution, metabolism, and excretion)
886 and extrinsic (diet, concomitant medications). The guidance emphasizes the importance
887 of early exposure-response data to allow efficient design of later studies and the value of
888 examining the entire database to assess exposure-response relationships. The guidance
889 further comments on strengths and limitations of various study designs to assess
890 exposure-response. The guidance comments briefly on the use of models to amplify
891 understanding of exposure-response-relationships and, consistent with 21 CFR 314.126,
892 indicates that a well-controlled dose-response study may be one type of study that
893 supports efficacy.

894
895 4. ICH E5, *Ethnic Factors in the Acceptability of Foreign Clinical Data* (June 1998)

896
897 This guidance provides descriptions of PK and PD studies and expresses PD endpoints as
898 safety and/or efficacy measures of activity thought, but not documented, to be related to
899 clinical benefit (biomarkers), surrogate endpoints, and clinical benefit endpoints. The
900 guidance further defines a PD study as one that describes the relationship between a
901 pharmacological effect or clinical benefit effect in relation to dose or drug concentration.
902 The guidance establishes a classification system of intrinsic (genetic polymorphism, age,
903 gender, height, weight, lean body mass, body composition, and organ dysfunction) and
904 extrinsic (medical practice, diet, use of tobacco, use of alcohol, exposure to pollution and
905 sunshine, practices in clinical trial design and conduct, socioeconomic status, compliance
906 with medication) ethnic factors that can affect safety, efficacy, dosage, and dosage
907 regimen determinations. The guidance provides an additional set of factors that indicate
908 whether a drug may be sensitive to ethnic factors (linear PK, flat PD curve, wide
909 therapeutic range). It focuses on the bridging studies that may be critical for an
910 application in a new region based on a clinical data package developed in another region.
911 These bridging studies range from those that establish similarity of exposure-response
912 relationship in the two regions for a well-established PD effect (e.g., ACE inhibition or
913 short-term blood pressure response) to a controlled trial in the new region, preferably a
914 dose-response study, using the pertinent clinical endpoint.

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916 **B. Guidances Providing Specific Statements**

917
918 FDA has issued final or draft³ guidances that focus on how to adjust dosages and dosing
919 regimens in the presence of selected intrinsic and extrinsic factors. A general theme of these
920 guidances is that information relating exposure to response can be used to adjust dosages and
921 dosing regimens in the presence of influences on PK such as age, gender (demographic
922 factors), impaired organ function (intrinsic factors), or concomitant medications and diet
923 (extrinsic factors). In many circumstances, where the assumption can be made that the
924 exposure-response relationships are not disturbed by these factors, PK data alone can be used
925 to guide dosages and dosing regimens. This principle is articulated in the following FDA
926 guidances:

- 927
928 1. *ICH E7, Studies in Support of Special Populations: Geriatrics* (August 1994)
929
- 930 2. *Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*
931 *(July 1993)*
- 932
933 3. *General Considerations for Pediatric Pharmacokinetic Studies for Drugs and*
934 *Biological Products* (draft) (November 1998)
- 935
936 4. *Pharmacokinetics in Patients with Impaired Renal Function: Study Design, Data*
937 *Analysis and Impact on Dosing and Labeling* (May 1998)
- 938
939 5. *Pharmacokinetics in Patients with Hepatic Insufficiency: Study Design, Data*
940 *Analysis and Impact on Dosing and Labeling* (draft) (November 1999)
- 941
942 6. *In Vivo Metabolism/Drug Interactions Studies: Study Design, Data Analysis and*
943 *Recommendations for Dosing and Labeling* (draft) (November 1999)
944

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

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

Pediatric Study Decision Tree

