

**OFFICE OF THE CENTER DIRECTOR**

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**Clinical Pharmacology and Biopharmaceutics Review Template**

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**Attachment A — Outline of Clinical Pharmacology and  
Biopharmaceutics Review Template**

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**PURPOSE**

- This MAPP establishes an outline for reviews of new drug applications (NDAs) and supplements (sNDAs) in the Office of Clinical Pharmacology and Biopharmaceutics in the Center for Drug Evaluation and Research (CDER).
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**POLICY**

- The Clinical Pharmacology and Biopharmaceutics Review Template is to be used by all reviewers within the Office of Clinical Pharmacology and Biopharmaceutics.
  - The Clinical Pharmacology and Biopharmaceutics Review Template will be used to document primary reviews of all original NDAs and sNDAs.
  - Conventions of the CDER Style Guide are to be followed in completing the clinical pharmacology and biopharmaceutics review.
  - The template may be modified by individual review divisions if necessary to accommodate unique application issues or division specific procedures.
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**PROCEDURES**

- Reviewers in the Office of Clinical Pharmacology and Biopharmaceutics will use the attached Clinical Pharmacology and Biopharmaceutics NDA review template to document their reviews. The template is annotated to provide additional explanations of the content for each heading and subheading.
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**EFFECTIVE DATE**

- This MAPP is effective upon date of publication.
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**ATTACHMENT A**

**The Clinical Pharmacology and Biopharmaceutics  
(CPB) Review Template:  
The Question-Based Review (QBR)**

**Office of Clinical Pharmacology and Biopharmaceutics  
Center for Drug Evaluation and Research**

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36		previously conducted fed study comparing to-be-marketed to the
37		clinical trial formulations pre-approval (immediate release products
38		only)

39 **INTRODUCTION**

40  
41 CDER is implementing Good Review Practices (GRPs) for NDA and sNDA reviews in  
42 all disciplines. The goal of this document is to present an outline of GRPs for the Office  
43 of Clinical Pharmacology and Biopharmaceutics (OCPB) that will facilitate  
44 accomplishing our mission as stated below.

45  
46 **OCPB MISSION**

47  
48 To assure that an individual patient receives the right drug, in the right dose, at the  
49 right time and in the right dosage form.  
50

51  
52 The GRPs for OCPB consist of (1) a MAPP defining good review practices, (2) a  
53 standardized Clinical Pharmacology and Biopharmaceutics (CPB) review template, and  
54 (3) procedures for the Clinical Pharmacology and Biopharmaceutics Briefing (CPBB),  
55 which is intended as a quality assurance process, an educational opportunity, and a forum  
56 for advancing interdisciplinary communications.

57  
58 This MAPP contains:

- 59  
60 (1) A general template for the CPB review showing the sections that should be included  
61 in the review and the order of presentation, and  
62  
63 (2) Appendices that provide a link to the electronic table of contents, a link to examples  
64 of reviews, and several decision trees and tables useful for reviewers (note: the  
65 examples are NOT intended to be a “checkbox” for the actual review).  
66

67 All primary CPB reviews of NDAs and sNDAs should be prepared using the CPB  
68 template. The CPB template is intended to standardize the ordering and placement of  
69 subject matter within reviews. The GRPs in OCPB incorporate the principles and format  
70 of the Question Based Review (QBR). Standardization of the review will provide  
71 consistency and promote interdisciplinary communication. The QBR focuses on the most  
72 important scientific, clinical, and regulatory review issues related to the efficacy, safety,  
73 risk/benefit ratio, and label claims for the drug and drug product. The QBR does not  
74 focus on individual studies. Emphasis is placed on integrating scientific information and  
75 using various technical tools (e.g., modeling and simulation) to understand the exposure-  
76 response relationship for a drug and, using these data, to address questions related to  
77 initial and maintenance doses and dosing regimens, and the need for dose and dosing  
78 regimen adjustments based on intrinsic (e.g., age, gender, race, disease states) and  
79 extrinsic (e.g., food, drugs, smoking) factors.  
80

81 The review template provides a format preferred by OCPB and other disciplines on the  
82 review team, including an easy-to-follow executive summary, a set of conclusions, and a  
83 list of recommendations. It is intended to provide answers to key questions identified by  
84 the review team. The detailed review should be organized with a table of contents and

85 informative headings for easy reference. The CPB review and briefing are intended to  
86 place the review in a clinical context (i.e., how to use the drug effectively and safely  
87 according to the label), using a deductive approach (i.e., starting with a conclusion and  
88 followed by supportive details).  
89  
90 The CPB template is not directive about the contents of the review. The review examples  
91 provide ideas on how to complete the various sections. Using the QBR should facilitate  
92 the implementation of the CPB template. On rare occasions, for a particular NDA or  
93 sNDA, the reviewer may feel that a different organization of the main headings would  
94 best suit a specific review. However, this should be discussed with the team leader  
95 and/or deputy or division director.  
96  
97 Medical officers rely upon the CPB reviews, but they are not the only discipline to do so.  
98 The reviews are also important to other members of the NDA review team and  
99 subsequently to the Office of Generic Drugs. In addition, the OCPB Immediate Office  
100 and other division directors, deputies, team leaders, and reviewers are also readers of  
101 CPB reviews, and the finished reviews serve as a resource of information and data  
102 applicable to future CPB reviews. Review documents for approved products are posted  
103 on CDER's Web site for access by the public  
104 (<http://www.fda.gov/cder/approval/index.htm>). For these reasons, reviewers are asked to  
105 write clearly for medical officers, other professionals, and the educated lay public.

## PURPOSE OF GRPs IN OCPB

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The QBR and the CPB review template are based on five important principles.

- (1) To foster good communication and teamwork with medical officers and other disciplines (see quote below), the CPB review should lead the reader logically through the thought process used in resolving scientific, clinical, and regulatory questions and issues.

“The challenge is not the science, but communicating the science and the discovery of facts to the medical community, and meeting their expectations.”

-- Dr. Janet Woodcock, Director of CDER, 7/25/00

- (2) To optimize the quality of the NDA or sNDA review, the CPB review should consider and support the needs of other regulatory scientists in communicating key CPB review findings.
- (3) To maximize economy of time and effort, the CPB review should focus on important issues and good management of the review process.
- (4) To ensure the scientific rigor and quality of the review, the CPB review should demonstrate a commitment to keep current on the sciences of clinical pharmacology and biopharmaceutics and their impact on therapeutics.
- (5) To strive for relevance, the CPB review should integrate the CPB information and knowledge across individual studies, and place the information and knowledge into a clinical framework with the main focus on the dose and dosing regimen for all patients and subgroups of patients.

137 **GENERAL CLINICAL PHARMACOLOGY AND**  
138 **BIOPHARMACEUTICS REVIEW**

139  
140 All CPB reviews should contain the following sections organized as shown below. If  
141 necessary because of a specific NDA or sNDA, reviewers should feel free to organize  
142 subsections under these main headings, as needed, using standard outline conventions.

143  
144 ***Header of Review***

145  
146 ***Table of Contents***

147  
148 ***1 Executive Summary***

149  
150 ***1.1 Recommendations***

151  
152 ***1.2 Phase 4 Commitments***

153  
154 ***1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics***  
155 ***Findings***

156  
157 ***2 Question Based Review***

158  
159 ***2.1 General Attributes of the Drug***

160  
161 ***2.2 General Clinical Pharmacology***

162  
163 ***2.3 Intrinsic Factors***

164  
165 ***2.4 Extrinsic Factors***

166  
167 ***2.5 General Biopharmaceutics***

168  
169 ***2.6 Analytical Section***

170  
171 ***3 Detailed Labeling Recommendations***

172  
173 ***4 Appendices***

174  
175 ***4.1 Proposed Package Insert (Original and Annotated)***

176  
177 ***4.2 Individual Study Review***

178  
179 ***4.3 Consult Review (Including Pharmacometric Reviews)***

180  
181 ***4.4 Cover Sheet and OCPB Filing/Review Form***

182 **OUTLINE OF THE GENERAL CLINICAL PHARMACOLOGY AND**  
183 **BIOPHARMACEUTICS REVIEW**

184  
185 ***Header of Review***  
186

187 List the product’s brand name, generic name, type of dosage form and strengths,  
188 indications; also, the NDA number, type, applicant name, and submission date (letter  
189 date); finally, the OCPB and OND (Office of New Drugs) division names, and the OCPB  
190 reviewers and team leader names.

191  
192 ***Table of Contents (TOC)***  
193

194 The TOC as listed in page 6 should generally be used for all NDAs and efficacy sNDAs.  
195 When applicable, the TOC on page 6 (or its condensed form) should also be used for  
196 other sNDAs, such as pediatric and labeling sNDAs. An electronic copy of the TOC is  
197 available (see Appendix 1).  
198

199 ***1. Executive Summary (2-5 pages)***  
200

201 The Executive Summary should contain the reviewer’s recommendations about the  
202 acceptability of the CPB information, significant omissions from the CPB database, a  
203 summary of risks and risk management procedures, any Phase 4 recommendations, and a  
204 summary of key clinical pharmacology and biopharmaceutics findings.  
205

206 ***1.1. Recommendations***  
207

208 Assess the overall scope and quality of the CPB information in terms of its  
209 credibility, acceptability, and possible omissions. Summarize any significant  
210 risks related to CPB issues (e.g., any changes in exposure related to intrinsic or  
211 extrinsic factors) and state how these risks should be managed (e.g., dosing  
212 adjustments). Other options for risk management can include appropriate label  
213 language, alteration in the dose or dosing regimen, label warnings, or label  
214 contraindications. List any comments that you conveyed to the sponsor or that  
215 you wish to convey to the sponsor.  
216

217 The recommendation can be one of the following categories:  
218

219 A “Acceptable” is used when there are no deficiencies or when the  
220 deficiencies can be addressed through Phase 4 commitments.  
221

222 B “Acceptable provided that...” is used when there are unresolved issues  
223 that can be addressed without additional studies or data. Examples include  
224 “acceptable provided that satisfactory agreement is reached between the  
225 sponsor and the Agency regarding (1) language in the package insert, (2)  
226 specifications for the in vitro release test, and others.”  
227



228 C. “Not Acceptable” is used when there are major CPB deficiencies and the  
229 deficiencies cannot be addressed by either labeling or Phase 4  
230 commitments.  
231  
232

233 **1.2. Identify recommended Phase 4 study commitments if the NDA is judged**  
234 **approvable**  
235

236 The reviewer should describe recommendations and thought processes regarding  
237 any Phase 4 study commitments or risk management steps needed as they pertain  
238 to CPB information.  
239  
240

241 **1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings (1-3**  
242 **pages)**  
243

244 The summary is intended to pull together all of the clinical pharmacology and  
245 biopharmaceutics assessments, conclusions, and recommendations made during  
246 the review. The summary should provide a brief overview of the clinical  
247 pharmacology and biopharmaceutics drug development program and an  
248 orientation to the review (e.g., what studies were reviewed thoroughly, what were  
249 not, if any, and why). The summary also should serve as a stand-alone document  
250 communicating the most important findings of the review without documenting  
251 the assessment process or detailed study reviews.  
252

253 This summary should be written in plain language appropriate for professionals in  
254 other disciplines and educated lay persons. This may include figures or tables as  
255 appropriate to illustrate relevant changes in exposure and/or response  
256 measurements (e.g., PK and/or PK-PD) that depend on various extrinsic and  
257 intrinsic factors. The summary should also be a **bottom-line** document without  
258 equivocation.  
259

260 **2. Question-Based Review (QBR) (12-15 Pages)**  
261

262 The QBR focuses on key questions pertinent to the review, and integrates information  
263 across studies. The examples below are some typical questions posed during the review  
264 of NDAs and sNDAs. These examples are not intended to be either inclusive of all, or  
265 exclusive of any, questions that specific reviews address. The specific questions for a  
266 given review depend on the characteristics of the drug, drug product, patient population,  
267 and indication. Reviewers should answer the questions using a deductive approach (i.e.,  
268 starting with the conclusion and following with supportive details).  
269

270 **2.1. General attributes of the drug**  
271

272 This section contains background information about the drug and drug product to  
273 provide a context for assessing the results of the clinical pharmacology and  
274 biopharmaceutics studies.

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What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug? (May not apply to some drugs. Be as brief as possible.)

2.1.1. What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review? (Do not include full details of formulation here. Details go in Biopharmaceutics section.)

2.1.2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

2.1.3. What are the proposed dosage(s) and route(s) of administration?

## 2.2. General clinical pharmacology

This section provides information pertinent to the PK and PD properties of the drug substance and drug product and their relationship to dose and each other.

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? (If yes, refer to 2.6, Analytical Section; if no, describe the reasons.)

2.2.4 Exposure-response (refer to the following guidance for industry: Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications, <http://www.fda.gov/cder/guidance/5341fnl.pdf> )

2.2.4.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy? If relevant, indicate the time to the onset and offset of the desirable pharmacological response or clinical endpoint.

(If necessary, indicate in your answer the degree of linearity or nonlinearity in the dose-concentration relationship and how PK parameters change with time on chronic dosing, however, do not provide data or details for those topics. Those topics are addressed in question 2.2.5.)

321 2.2.4.2 What are the characteristics of the exposure-response relationships  
322 (dose-response, concentration-response) for *safety*? If relevant, indicate the  
323 time to the onset and offset of the undesirable pharmacological response or  
324 clinical endpoint.  
325  
326 *(If necessary, indicate in your answer the degree of linearity or nonlinearity*  
327 *in the dose-concentration relationship and how PK parameters change with*  
328 *time on chronic dosing. However, do not provide data or details for those*  
329 *topics. Those topics are addressed in question 2.2.5.)*  
330  
331 2.2.4.3 Does this drug prolong the QT or QTc interval? *(You must answer*  
332 *this question, unless this is addressed in the question above.)*  
333  
334 2.2.4.4 Is the dose and dosing regimen selected by the sponsor consistent  
335 with the known relationship between dose-concentration-response, and are  
336 there any unresolved dosing or administration issues? *(In some cases, it may*  
337 *be possible to combine this with 2.2.4.2 and 2.2.4.3.)*  
338  
339 2.2.5 What are the PK characteristics of the drug and its major metabolite?  
340  
341 2.2.5.1 What are the single dose and multiple dose PK parameters?  
342 *(Provide tables to refer to in subsequent questions in this section.)*  
343  
344 2.2.5.2 How does the PK of the drug and its major active metabolites in  
345 healthy volunteers compare to that in patients?  
346  
347 2.2.5.3 What are the characteristics of drug absorption? *( This may include*  
348 *discussion of transporter or pH effect.)*  
349  
350 2.2.5.4 What are the characteristics of drug distribution? *(Include protein*  
351 *binding.)*  
352  
353 2.2.5.5 Does the mass balance study suggest renal or hepatic as the major  
354 route of elimination? *(This may include table with results of mass balance*  
355 *study.)*  
356  
357 2.2.5.6 What are the characteristics of drug metabolism? *(This may*  
358 *include data on extraction ratio; metabolic scheme; enzymes responsible for*  
359 *metabolism; fractional clearance of drug.)*  
360  
361 2.2.5.7 What are the characteristics of drug excretion?  
362  
363 2.2.5.8 Based on PK parameters, what is the degree of linearity or  
364 nonlinearity in the dose-concentration relationship?  
365

366 2.2.5.9 How do the PK parameters change with time following chronic  
367 dosing? (*This may include time to steady-state; single dose prediction of*  
368 *multiple dose PK; accumulation ratio.*)  
369

370 2.2.5.10 What is the inter- and intra-subject variability of PK parameters in  
371 volunteers and patients, and what are the major causes of variability?  
372

### 373 **2.3. Intrinsic Factors**

374  
375 2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic  
376 polymorphism, pregnancy, and organ dysfunction) influence exposure (PK  
377 usually) and/or response, and what is the impact of any differences in exposure on  
378 efficacy or safety responses?  
379

380 2.3.2 Based upon what is known about exposure-response relationships and  
381 their variability and the groups studied, healthy volunteers vs. patients vs. specific  
382 populations (examples shown below), what dosage regimen adjustments, if any,  
383 are recommended for each of these groups? If dosage regimen adjustments are  
384 not based upon exposure-response relationships, describe the alternative basis for  
385 the recommendation.  
386

387 2.3.2.1 Elderly (see Study of Drugs Likely to be used in the Elderly,  
388 <http://www.fda.gov/cder/guidance/old040fn.pdf> )  
389

390 2.3.2.2 Pediatric patients. Also, what is the status of pediatric studies  
391 and/or any pediatric plan for study? (Refer to International Conference on  
392 Harmonization; E11: Clinical Investigation of Medicinal Products in the  
393 Pediatric Population; <http://www.fda.gov/cder/guidance/4099FNL.PDF> and  
394 General Considerations for Pediatric Pharmacokinetic Studies for Drugs and  
395 Biological Products; <http://www.fda.gov/cder/guidance/1970dft.pdf> and  
396 Appendix B in “Exposure-Response Relationships — Study Design, Data  
397 Analysis, and Regulatory Applications”  
398 <http://www.fda.gov/cder/guidance/5341fnl.pdf> )  
399

400 2.3.2.3 Gender (see Study and Evaluation of Gender Differences in the  
401 Clinical Evaluation of Drugs,  
402 <http://www.fda.gov/cder/guidance/old036fn.pdf> )  
403

404 2.3.2.4 Race, in particular differences in exposure and/or response in  
405 Caucasians, African-Americans, and/or Asians (see 21 CFR 314; Final Rule  
406 on Investigational New Drug Applications and New Drug Applications (63  
407 FR 6854, February 11, 1998); <http://www.fda.gov/oashi/patrep/demo.html>  
408 and Collection of Race and Ethnicity Data in Clinical Trials,  
409 <http://www.fda.gov/cder/guidance/5054dft.pdf> ) is an important co-variate and  
410 should be discussed.  
411

412 2.3.2.5 Renal impairment (Refer to Appendix 3 — Figure 2, Renal Study  
413 Decision Tree, and Pharmacokinetics in Patients with Impaired Renal  
414 Function, <http://www.fda.gov/cder/guidance/1449fnl.pdf>)  
415

416 2.3.2.6 Hepatic impairment (Refer to Pharmacokinetics in Patients with  
417 Impaired Hepatic Function: Study Design, Data Analysis, and Impact on  
418 Dosing and Labeling, <http://www.fda.gov/cder/guidance/3625fnl.pdf> .)  
419

420 What pharmacogenetics information is there in the application and is it  
421 important or not (Refer to Pharmacogenomic Data Submissions,  
422 <http://www.fda.gov/cder/guidance/5900dft.pdf> )  
423

424 2.3.2.7 What pregnancy and lactation use information is there in the  
425 application?  
426

427 Other human factors that are important to understanding the drug’s efficacy  
428 and safety  
429

## 430 **2.4. Extrinsic Factors**

431  
432 2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol  
433 use) influence dose-exposure and/or -response and what is the impact of any  
434 differences in exposure on response?  
435

436 Based upon what is known about exposure-response relationships and their  
437 variability, what dosage regimen adjustments, if any, do you recommend for each  
438 of these factors? If dosage regimen adjustments across factors are not based on  
439 the exposure-response relationships, describe the basis for the recommendation.  
440

441 2.4.2 Drug-drug interactions (Refer to Drug Metabolism/Drug Interaction  
442 Studies in the Drug Development Process: Studies In vitro,  
443 <http://www.fda.gov/cder/guidance/clin3.pdf>, and In Vivo Drug Metabolism/Drug  
444 Interaction Studies - Study Design, Data Analysis, and Recommendations for  
445 Dosing and Labeling, <http://www.fda.gov/cder/guidance/2635fnl.pdf>, and  
446 Appendix 3 —Figure 3, Drug-Drug Interaction Studies — Decision Tree). Some  
447 typical questions include:  
448

449 2.4.2.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?  
450

451 2.4.2.2 Is the drug a substrate of CYP enzymes? Is metabolism influenced  
452 by genetics?  
453

454 2.4.2.3 Is the drug an inhibitor and/or an inducer of CYP enzymes?  
455

- 456 2.4.2.4 Is the drug a substrate and/or an inhibitor of P-glycoprotein  
457 transport processes?  
458
- 459 2.4.2.5 Are there other metabolic/transporter pathways that may be  
460 important?  
461
- 462 2.4.2.6 Does the label specify co-administration of another drug (e.g.,  
463 combination therapy in oncology) and, if so, has the interaction potential  
464 between these drugs been evaluated?  
465
- 466 2.4.2.7 What other co-medications are likely to be administered to the  
467 target patient population?  
468
- 469 2.4.2.8 Are there any in vivo drug-drug interaction studies that indicate the  
470 exposure alone and/or exposure-response relationships are different when  
471 drugs are co-administered?  
472
- 473 2.4.2.9 Is there a known mechanistic basis for pharmacodynamic drug-  
474 drug interactions, if any?  
475
- 476 2.4.2.10 Are there any unresolved questions related to metabolism, active  
477 metabolites, metabolic drug interactions, or protein binding?  
478
- 479 2.4.3 What issues related to dose, dosing regimens, or administration are  
480 unresolved and represent significant omissions?  
481

## 482 **2.5. General Biopharmaceutics**

483

484 This section should summarize the salient points about the attributes of the drug  
485 product.  
486

487 2.5.1 Based on the biopharmaceutics classification system (BCS) principles, in  
488 what class is this drug and formulation? What solubility, permeability, and  
489 dissolution data support this classification? (Refer to the guidance for industry on  
490 Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-  
491 Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification  
492 System (BCS), <http://www.fda.gov/cder/guidance/3618f1.pdf> )  
493

494 2.5.2 What is the relative bioavailability of the proposed to-be-marketed  
495 formulation to the pivotal clinical trial? (Refer to 21 CFR 320; also the guidance  
496 for industry on Bioavailability and Bioequivalence Studies for Orally  
497 Administered Drug Products - General Considerations,  
498 <http://www.fda.gov/cder/guidance/5356f1.pdf> ).  
499

500 2.5.2.1.1 What data support or do not support a waiver of in vivo BE data?  
501

502 • BCS classification system  
503 • Formulation ingredient information  
504 • Dissolution profiles  
505 • Others  
506 Refer to guidance for industry on SUPAC-IR: Immediate-Release Solid Oral  
507 Dosage Forms: Scale-Up and Post-Approval Changes: Chemistry,  
508 Manufacturing and Controls, In Vitro Dissolution Testing, and In Vivo  
509 Bioequivalence Documentation:  
510 <http://www.fda.gov/cder/guidance/cmc5.pdf>  
511 SUPAC-IR Questions and Answers about SUPAC-IR Guidance,  
512 <http://www.fda.gov/cder/guidance/qaletter.htm>  
513 SUPAC-IR/MR: Immediate Release and Modified Release Solid Oral  
514 Dosage Forms Manufacturing Equipment Addendum,  
515 <http://www.fda.gov/cder/guidance/1721fnl.pdf>  
516 SUPAC-MR: Modified Release Solid Oral Dosage Forms Scale-Up and  
517 Postapproval Changes: Chemistry, Manufacturing, and Controls; In Vitro  
518 Dissolution Testing and In Vivo Bioequivalence Documentation ,  
519 <http://www.fda.gov/cder/guidance/1214fnl.pdf>  
520 SUPAC-SS: Nonsterile Semisolid Dosage Forms; Scale-Up and Post-  
521 Approval Changes: Chemistry, Manufacturing and Controls; In Vitro  
522 Release Testing and In Vivo Bioequivalence Documentation,  
523 <http://www.fda.gov/cder/guidance/1447fnl.pdf>  
524  
525 2.5.2.2 What are the safety or efficacy issues, if any, for BE studies  
526 that fail to meet the 90% CI using equivalence limits of 80-125%?  
527  
528 2.5.2.3 If the formulations do not meet the standard criteria for  
529 bioequivalence, what clinical pharmacology and/or clinical safety and  
530 efficacy data support the approval of the to-be-marketed product?  
531  
532 2.5.3 What is the effect of food on the bioavailability (BA) of the drug from the  
533 dosage form? What dosing recommendation should be made, if any, regarding  
534 administration of the product in relation to meals or meal types?  
535  
536 (Refer to the guidances for industry on Food-Effect Bioavailability and  
537 Fed Bioequivalence Studies or and Bioavailability and Bioequivalence  
538 Studies for Orally Administered Drug Products — General  
539 Considerations, <http://www.fda.gov/cder/guidance/5356fnl.pdf> )  
540  
541 2.5.4 When would a fed BE study be appropriate and was one  
542 conducted? (Refer to Appendix 3 — Table 1, When to Request a Fasted BE  
543 Study.)  
544

- 545 2.5.5 How do the dissolution conditions and specifications ensure in  
546 vivo performance and quality of the product?  
547  
548 (Refer to guidances for industry on Dissolution Testing of Immediate  
549 Release Solid Oral Dosage Forms:  
550 <http://www.fda.gov/cder/guidance/1713bp1.pdf>, and Extended Release  
551 Oral Dosage Forms: Development, Evaluation and Application of In  
552 Vitro/In Vivo Correlations, <http://www.fda.gov/cder/guidance/1306fnl.pdf>  
553
- 554 2.5.6 If different strength formulations are not bioequivalent based on  
555 standard criteria, what clinical safety and efficacy data support the approval of  
556 the various strengths of the to-be-marketed product?  
557
- 558 2.5.7 If the NDA is for a modified release formulation of an approved  
559 immediate product without supportive safety and efficacy studies, what dosing  
560 regimen changes are necessary, if any, in the presence or absence of PK-PD  
561 relationship?  
562
- 563 2.5.8 If unapproved products or altered approved products were used as  
564 active controls, how is BE to the approved product demonstrated? What is the  
565 basis for using either in vitro or in vivo data to evaluate BE?  
566
- 567 2.5.9 What other significant, unresolved issues related to in vitro  
568 dissolution or in vivo BA and BE need to be addressed?  
569

## 570 **2.6 Analytical section**

571  
572 This section should address issues related to the analytical and bioanalytical  
573 methods used to support the CPB studies.  
574

575 2.6.1 How are the active moieties identified and measured in the plasma in the  
576 clinical pharmacology and biopharmaceutics studies?  
577

578 2.6.2 Which metabolites have been selected for analysis and why?  
579

580 2.6.3 For all moieties measured, is free, bound, or total measured? What is the  
581 basis for that decision, if any, and is it appropriate?  
582

583 2.6.4 What bioanalytical methods are used to assess concentrations? (Refer to  
584 the guidance for industry on Bioanalytical Method Validation,  
585 <http://www.fda.gov/cder/guidance/4252fnl.pdf> )  
586

587 2.6.4.1 What is the range of the standard curve? How does it relate to the  
588 requirements for clinical studies? What curve fitting techniques are used?  
589



- 590 2.6.4.2 What are the lower and upper limits of quantification  
591 (LLOQ/ULOQ)?  
592
- 593 2.6.4.3 What are the accuracy, precision, and selectivity at these limits?  
594
- 595 2.6.4.4 What is the sample stability under the conditions used in the study  
596 (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?  
597
- 598 2.6.4.5 What is the QC sample plan?  
599

### 600 **3 Detailed Labeling Recommendations**

601  
602 This section describes recommendations for the label, based on evidence contained in the  
603 detailed clinical pharmacology and biopharmaceutics database. As appropriate,  
604 reviewers can provide comments for any section of the label. Recommendations can be  
605 in the form of an annotated label indicating which lines in the label, or label claims, are  
606 supported by the clinical pharmacology and biopharmaceutics data. Alternatively,  
607 reviewers can provide a list of recommendations.  
608

### 609 **4 Appendices**

#### 610 4.1 Package insert (proposed and annotated)

611  
612  
613 A copy of the entire proposed labeling should be attached here. Include an  
614 annotated labeling, if available.  
615

#### 616 4.2 Clinical pharmacology and biopharmaceutics individual study review

617  
618 This is a review of the individual clinical pharmacology and biopharmaceutics  
619 studies. The individual study reviews should contain adequate details to allow the  
620 reader to assess the validity of the reviewer's conclusions.  
621

#### 622 4.3 Consult reviews (including pharmacometric reviews)

#### 623 4.4 Cover sheet and OCPB filing/review form (2-3 pages)

624  
625 The standard OCPB filing/review form provides a line listing of all studies.  
626 The form can be found on the CDER Internet page:  
627 [http://www.fda.gov/cder/ops/ocpb\\_home\\_page.htm](http://www.fda.gov/cder/ops/ocpb_home_page.htm).  
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## Appendix 1

### Links to the Electronic Table of Contents

Two versions of electronic table of contents are located at the *Policy* Tab on the CDER Internet site, [http://www.fda.gov/cder/ops/ocpb\\_home\\_page.htm](http://www.fda.gov/cder/ops/ocpb_home_page.htm), and are labeled MAPP\_4000.4\_appendix1\_full\_eTOC and MAPP\_4000.4\_appendix1\_partial\_eTOC, respectively.

## Appendix 2

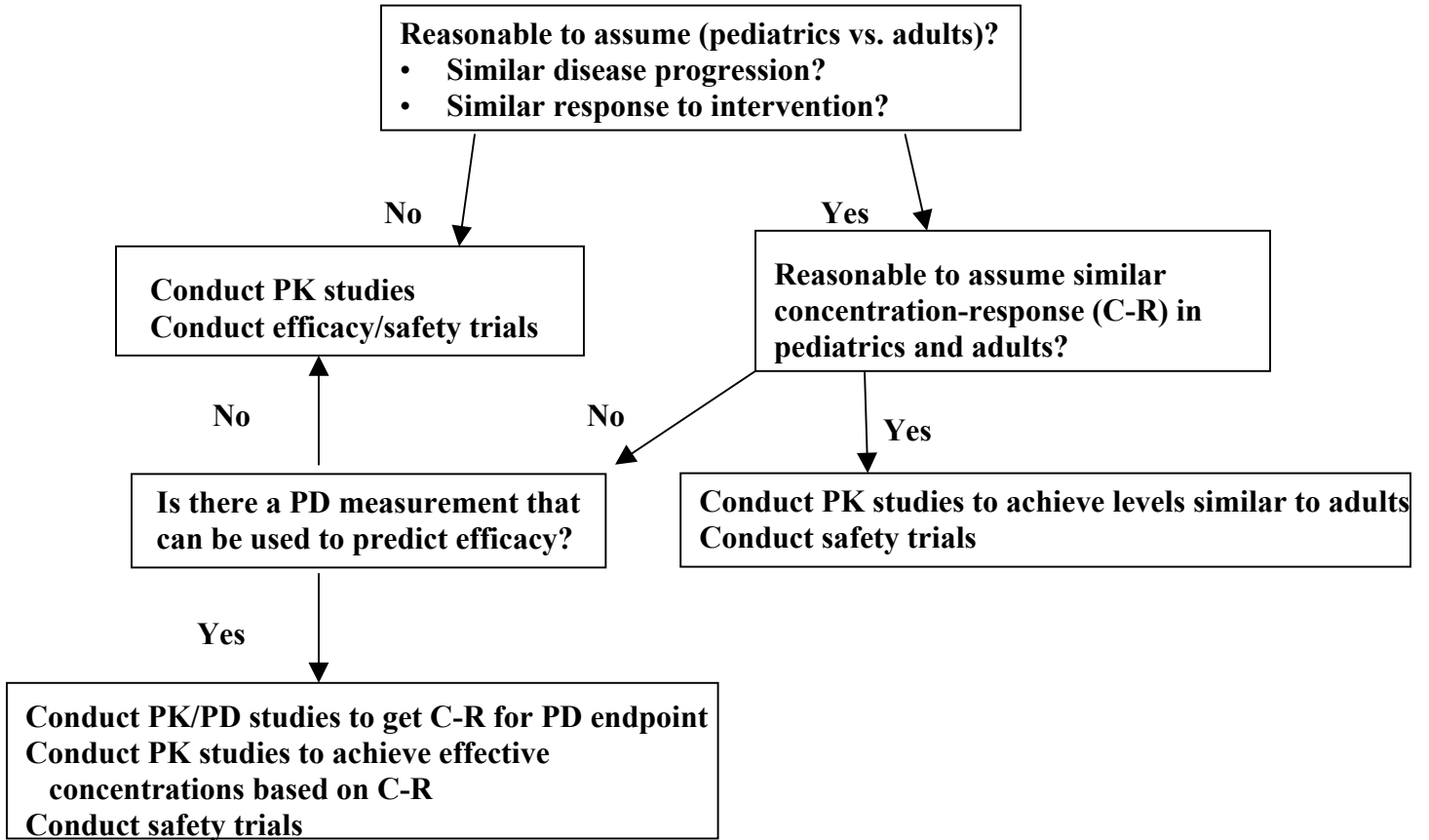
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Review examples are located at the *Policy* Tab on the CDER Internet site, [http://www.fda.gov/cder/ops/ocpb\\_home\\_page.htm](http://www.fda.gov/cder/ops/ocpb_home_page.htm), and are labeled MAPP\_4000.4\_appendix 2.


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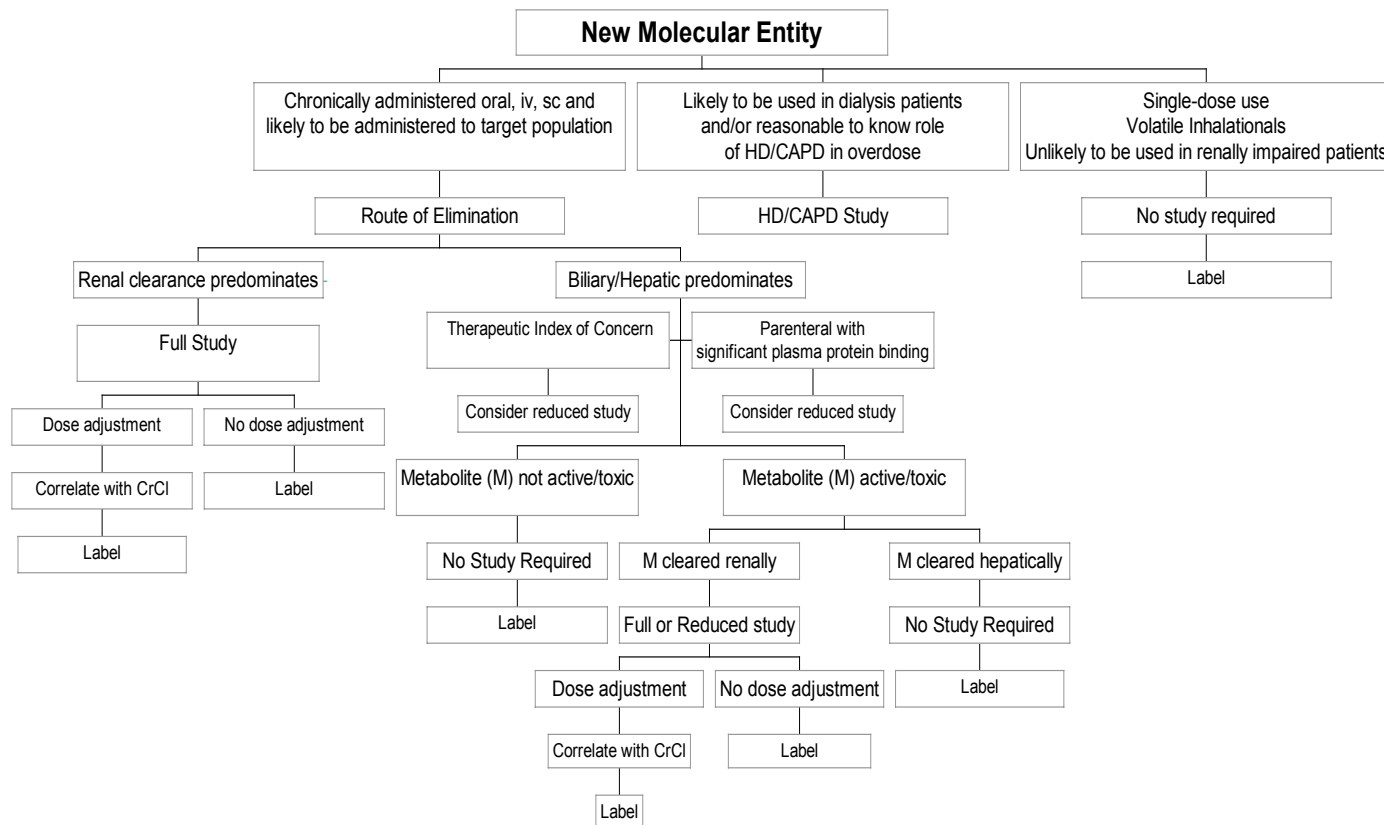
### Appendix 3

**Figure 1. Pediatric Decision Tree, Integration of PK/PD**  
(Refer to “Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications” [\[Word\]](#) or [\[PDF\]](#))



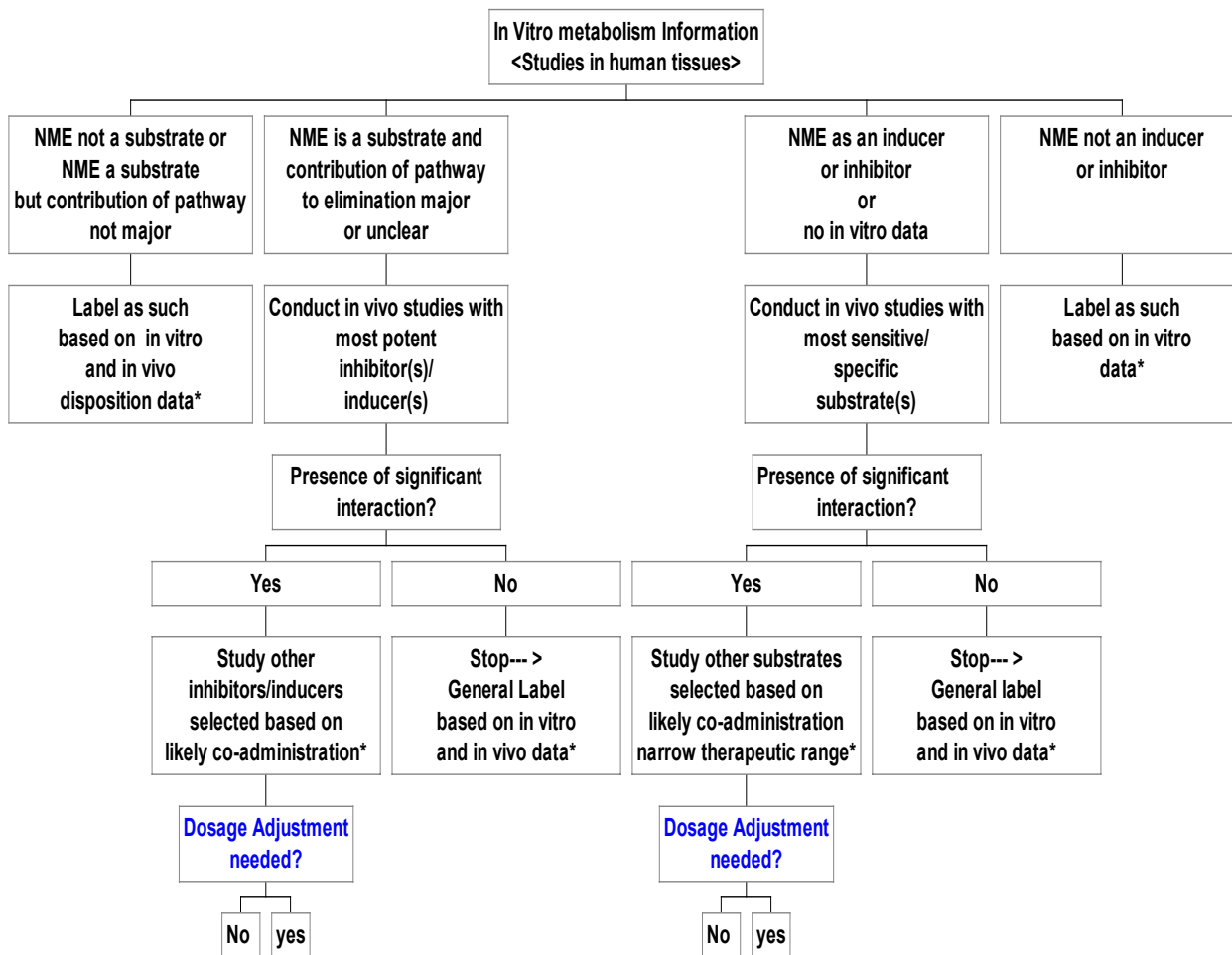
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**Figure 2. When to Conduct a Pharmacokinetic Study in Renal Impairment**  
(Refer to [Pharmacokinetics in Patients with Impaired Renal Function](#) )



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**Figure 3. Drug-Drug Interaction Studies-Decision Tree**  
 (Refer to Journal of Clinical Pharmacology 39:1006-1014, 1999)



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\* Additional population pharmacokinetic analysis may assist the overall evaluation

**Table 1. DECISION CHART FOR WHEN TO REQUEST A FASTING STUDY IN ADDITION TO A PREVIOUSLY CONDUCTED FED STUDY COMPARING TO-BE-MARKETED TO THE CLINICAL TRIAL FORMULATIONS PRE-APPROVAL (IMMEDIATE RELEASE PRODUCTS ONLY)**

<b><i>Attributes</i></b>	<b><i>CASE A</i></b>	<b><i>CASE B</i></b>	<b><i>CASE C</i></b>	<b><i>CASE D</i></b>	<b><i>CASE E</i></b>	<b><i>CASE F</i></b>
Food effect on BA? <sup>1</sup>	≤ 20% <b>INC</b> or <b>DEC</b>	> 20% <b>INC</b>	> 20% <b>DEC</b>	> 20% <b>INC</b>	> 20% <b>DEC</b>	> 20% <b>INC</b>
Safety concern?	N	N	N	Y	N	N
Efficacy concern?	N	N	N	N	Y	Y
Label language (typical)						
Take on empty stomach (fasting)	N	N	N	Y	Y	N
Take without regard to meals	Y	Y	Y	N	N	N
Take with food or meals	Y	Y	Y	N	N	Y
With light meal or low fat/low calorie meal	NA	NA	NA	Y, if "Y" below	Y, if "Y" below	NA
Tolerability concern (local irritation)?	Doesn't matter	Doesn't matter	Doesn't matter	Y	Y	Doesn't matter
Absorption in fasting state?	Good <sup>2</sup>	Good	Better	Good	Good	<b>TOO POOR</b>
Absorption in fed state?	Good	Better	Good	<b>TOO HIGH</b>	<b>TOO LOW</b>	Good
Absorption sensitive to meal fat content?	N	Y (II)	N	Y (II)	N	Y (II)
Probable BCS Class?	I	II or III	III	II or III	III	II, III or IV
Possible rate-limiting steps in absorption						
Gastric emptying	X	X	X	X	X	X
Rate of dissolution		X	X	X	X	X
Permeability		X	X	X	X	X
Possible mechanisms of food effect	NA					
Increase solubility/rate of dissolution		X		X		X
Decrease first pass effect		X		X		X
Decrease solubility/rate of dissolution			X		X	
Adsorb or chelate			X		X	
Reduce access to absorption site			X		X	
Example	theophylline	ciprofloxacin	Atorvastatin	halofantrine	alendronate	atovaquone
In vitro dissolution (optional) <sup>3</sup>	Y	Y	Y	N	N	Y
<b>ASK FOR FASTING STUDY?<sup>6</sup></b>	<b>NO<sup>4</sup></b>	<b>NO</b>	<b>NO</b>	<b>YES<sup>5</sup></b>	<b>YES<sup>5</sup></b>	<b>NO</b>

<sup>1</sup> Food effects are on Cmax and/or AUC; changes in Tmax are assumed to be unimportant (there may be exceptions, e.g., analgesics)

<sup>2</sup> Drugs represented by CASE A are generally well-absorbed (extent of BA > 80%)

<sup>3</sup> Generally use three media covering the pH range of 1 - 6.5, comparing profiles using f2 (supportive evidence)

<sup>4</sup> Fasting and fed BE studies should produce the same result since there are no significant food effects on BA

<sup>5</sup> Sponsor should not have conducted a fed BE study to start out with, because the label states to "take fasting or on an empty stomach"

<sup>6</sup> Differences between the test and reference formulations may exist with excipients; the importance of these differences is unclear