
Guidance for Industry

Nonclinical Safety Evaluation of Drug Combinations

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Abby Jacobs at 301-827-2020.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**January 2005
Pharmacology and Toxicology**

Guidance for Industry

Nonclinical Safety Evaluation of Drug Combinations

Additional copies are available from:

*Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
<http://www.fda.gov/cder/guidance/index.htm>*

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**January 2005
Pharmacology and Toxicology**

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	NONCLINICAL STUDIES FOR A COMBINATION OF TWO (OR MORE) PREVIOUSLY MARKETED DRUGS (FIGURE A).....	2
A.	Safety Considerations	2
B.	Nonclinical Study Recommendations.....	3
C.	Combinations of Previously Marketed Drug Products: General Procedure.....	4
III.	NONCLINICAL STUDIES FOR A COMBINATION OF DRUGS WHEN ONE OR MORE IS PREVIOUSLY MARKETED AND ONE IS A NEW MOLECULAR ENTITY (FIGURE B).....	5
A.	General Toxicology Studies	5
B.	Reproductive and Developmental Toxicology	6
C.	Animal Models of Efficacy	6
D.	Further Studies.....	6
IV.	NONCLINICAL STUDIES FOR A COMBINATION OF TWO OR MORE DRUGS WHEN BOTH ARE NEW MOLECULAR ENTITIES (FIGURE C).....	7
A.	General Toxicology Studies	7
B.	Animal Models of Efficacy	7
C.	Safety Pharmacology	7
D.	PK/ADME and Toxicokinetics	8
E.	Genetic Toxicology	8
F.	Special Toxicology	8
G.	Reproductive and Developmental Toxicology	8
H.	Further Studies.....	8
I.	Carcinogenicity.....	9

Contains Nonbinding Recommendations

Draft — Not for Implementation

1 **Guidance for Industry¹**
2 **Nonclinical Safety Evaluation of Drug Combinations**
3
4
5

6
7 This draft guidance, once finalized, will represent the Food and Drug Administration's (FDA's) current
8 thinking on this topic. It does not create or confer any rights for or on any person and does not operate to
9 bind FDA or the public. You may use an alternative approach if such approach satisfies the requirements
10 of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA
11 staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call
12 the appropriate number listed on the title page of this guidance.
13

14
15
16
17 **I. INTRODUCTION**
18

19 This guidance provides recommendations on nonclinical approaches to support the clinical study
20 and approval of fixed-dose combination products (FDCs), co-packaged products, and adjunctive
21 therapies.² This document is only intended to delineate general guiding principles. To receive
22 more detailed advice regarding a particular drug combination development program, a sponsor
23 should contact the appropriate review division before submitting an Investigational New Drug
24 (IND) application. In addition, FDA is in the process of publishing more specific guidance for
25 certain categories of drug combinations.³

¹ This guidance has been prepared by the Pharmacology Toxicology Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the FDA.

² For the purposes of this guidance, a *fixed-dose combination* product (FDC) is one in which two or more separate drug components (active pharmaceutical ingredients) are combined in a single dosage form. A *co-packaged* product consists of two or more separate drug products in their final dosage forms, packaged together with appropriate labeling to support the combination use. An *adjunctive therapy* refers to the situation in which a patient is maintained on a second drug product that is used together with (i.e., in adjunct to) the primary treatment, although the relative doses are not fixed and the drugs need not be given at the same time. Adjunctive therapy products may or may not be labeled for concomitant use. For example, if a hair growth drug is expected to be used by chemotherapy patients, consideration of safety issues arising from the adjunctive use of the drug with chemotherapy drugs may be appropriate, even if the drug is not specifically labeled as an adjunctive therapy. For the purpose of this guidance, the terms *co-packaged product*, *FDC*, and *adjunctive therapy* are collectively referred to as *combinations*.

³ For example, the Agency is developing a draft guidance specifically addressing oncologic drug combinations. In addition, in May 2004 (69 FR 28931) the Agency made available a draft guidance on *Fixed Dose Combination and Co-Packaged Drug Products for Treatment of HIV* (Draft HIV Guidance). When finalized, this guidance will provide recommendations on FDCs and co-packaged versions of previously approved antiretroviral therapies for the treatment of human immunodeficiency virus (HIV). When a sponsor is preparing an application for one of these types of products, FDA recommends consulting these additional guidances.

Contains Nonbinding Recommendations

Draft — Not for Implementation

26
27 Drug combinations may involve (1) previously marketed drugs (MDs), (2) one or more new
28 molecular entities (NMEs) and one or more previously marketed drugs, or (3) more than one
29 NME. The nonclinical studies considered important for each type of combination may differ,
30 depending upon the information available on each drug substance. The nonclinical studies that
31 FDA recommends sponsors use to characterize the combination will depend on the toxicologic
32 and pharmacokinetic profiles of the individual drugs, the treatment indication or indications, and
33 the intended population.

34
35 In this document, each of the three general types of combinations (i.e., MD-MD, MD-NME, and
36 NME-NME) will be discussed separately.

37
38 FDA's guidance documents, including this guidance, do not establish legally enforceable
39 responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should
40 be viewed only as recommendations, unless specific regulatory or statutory requirements are
41 cited. The use of the word *should* in Agency guidances means that something is suggested or
42 recommended, but not required.

43 44 **II. NONCLINICAL STUDIES FOR A COMBINATION OF TWO (OR MORE)** 45 **PREVIOUSLY MARKETED DRUGS (FIGURE A)**

46
47 This section of the document addresses the situation in which a sponsor submits an application to
48 develop a combination of two or more previously marketed drugs. Generally FDA believes that,
49 in such a situation, sufficient clinical and nonclinical data will exist for each drug product
50 separately. However, the indications for which each drug is marketed should be compared to
51 that for which the combination is being proposed. For example, drug products marketed for
52 acute use may not have nonclinical data to support chronic use. To the extent that there are gaps
53 in the data, FDA may recommend that additional nonclinical studies be conducted.⁴

54 55 **A. Safety Considerations**

56
57 If existing clinical and nonclinical safety data for each separate drug are sufficient to support the
58 safety of the proposed new indication, then FDA recommends that the following factors relevant
59 to the safety of the combination be considered to determine whether further nonclinical studies
60 are warranted:

- 61
62 1. Information available on prior human experience with the combination. FDA recommends
63 that the sponsor provide a summary of the available data in humans (if any) on the use of the

⁴ In certain cases, adequate clinical data may exist not only for the individual components of a drug combination, but also for their concomitant use. In such cases, additional nonclinical studies may not be necessary. For example, the Draft HIV Guidance referenced in Footnote 3 discusses FDA's belief that certain antiretroviral therapies previously approved for the treatment of HIV may be approved for use in combination without additional in vitro studies, because the clinical safety and efficacy of concomitant use have been evaluated and described in product labels or peer-reviewed literature. Where adequate clinical data exists for the concomitant use of two previously approved drugs, a sponsor seeking approval for the drug combination should contact the appropriate review division to discuss whether any additional nonclinical data are warranted.

Contains Nonbinding Recommendations

Draft — Not for Implementation

64 combination. FDA also encourages the sponsor to provide copies of any relevant published
65 studies in humans (or animals). Such reports may not provide definitive safety data, but they
66 may provide some measure either of assurance or reasons for concern.

- 67
- 68 2. Information known about the individual drugs in animals and humans and concordance of
69 pharmacokinetics (PK), pharmacodynamics (PD), and toxicologic effects in animals with the
70 analogous data for humans.
71
 - 72 3. Possibility of a pharmacodynamic interaction. Drugs may exhibit affinity for the same
73 receptors or may produce similar effects on physiologic function, related or not to their
74 mechanism of action.
75
 - 76 4. Possibility of a pharmacokinetic interaction. A pharmacokinetic interaction can manifest in
77 several ways, some of which can be monitored in vivo and some of which cannot. One drug
78 product may alter the absorption or excretion of another product, change its distribution into
79 one or more tissues, or change its pattern or rate of metabolism. Drugs may compete for
80 serum protein binding, resulting in an increase in circulating free levels and tissue uptake of
81 one drug.
82
 - 83 5. Possibility of a toxicologic interaction (i.e., that the target organs for toxicity are similar for
84 each drug). This situation may result in a lowering of the previously determined no-effect
85 doses for one or both drug products and/or more severe toxicities in the affected organs.
86 FDA will consider all known toxicology on the product (e.g., general toxicity, reproductive
87 toxicity, carcinogenicity, and safety pharmacology studies (cardiovascular, central nervous
88 system or CNS, respiratory)).
89
 - 90 6. Margin of safety for each drug product. If one or more of the drugs has a narrow margin of
91 safety (i.e., causes serious toxicity at exposures close to the predicted clinical exposure), then
92 the possibility of drug interaction is of particular concern, especially if the toxicity is not
93 reversible or cannot be monitored clinically.
94
 - 95 7. Possibility that the drugs compete for or alter the activity or endogenous levels of the same
96 enzymes or other intracellular molecules (e.g., co-administration of two prooxidants could
97 deplete endogenous levels of glutathione).
98
 - 99 8. Possibility of a chemical interaction. One drug may chemically modify another drug (e.g.,
100 one drug may oxidize, methylate, or ethylate the other drug). This could result in new
101 molecular entities with new toxicities.
102
 - 103 9. Possibility that one drug is compromising the effectiveness of another drug for a lifesaving
104 therapy.
105

B. Nonclinical Study Recommendations

106
107
108 After evaluating the available data on the individual drug products and the potential for drug
109 interaction, if there is no evidence to suggest a possible interaction, direct assessment of the

Contains Nonbinding Recommendations

Draft — Not for Implementation

110 combination by testing in animals may not be needed before the initiation of phase 1 clinical
111 studies. Also, if an interaction is expected, nonclinical studies may not be necessary if the
112 expected interaction is likely to result in predictable, nonserious, monitorable effects in humans.
113 For example, if a metabolic interaction is predicted, the starting dose could be significantly
114 lowered in humans. However, if the proposed dose in humans of any drug product in the
115 combination is close to doses resulting in serious toxic effects (narrow safety margin) or if there
116 is a possibility of severe toxicity (particularly if it is not monitorable in humans), FDA strongly
117 recommends that sponsors conduct nonclinical studies of the combination to better evaluate the
118 interaction potential (see Figure A).

119
120 The particular nonclinical studies recommended by FDA will depend on a number of factors,
121 including the nature of the toxicity. It may be important to repeat some studies, such as
122 equivocal reproductive toxicity studies. For assessment of general toxicity, a bridging study may
123 be appropriate, provided the duration is sufficient to elicit the toxicity of concern. For example,
124 a general toxicity bridging study of 3 months' duration could be considered for a chronic
125 indication. FDA recommends that combination studies include an assessment of several dose
126 levels of the combination and a high dose of each drug alone. Sponsors are urged to select the
127 doses of each drug used in combination to allow for additive or synergistic effects without
128 unacceptable toxicity in the high-dose groups. Usually, assessment of the drug combination may
129 be conducted in only one species if one of the following conditions exists: (1) toxicity in a
130 particular species has high concordance with human toxicity or the toxicities are similar among
131 species or (2) one species is a more relevant model for human risk based on other factors such as
132 PK/ADME (absorption, distribution, metabolism, and excretion). There may be cases, however,
133 in which the Agency may recommend conducting studies in two species despite one or both of
134 these conditions being met. For example, depending on the results in the first species, a new
135 cause for concern might warrant studies in a second species.

C. Combinations of Previously Marketed Drug Products: General Procedure

136
137
138
139 The general approach to addressing the safety concerns posed by the testing or marketing of
140 combinations of previously marketed drugs is illustrated in Figure A. The safety of the
141 combination should be assessed according to the factors listed in section II.A above (see Figure
142 A, Boxes 1 to 2). If neither individual drug product has serious toxicity at exposures well above
143 the proposed clinical exposure or if there is substantial clinical experience with the combination,
144 FDA may recommend that additional nonclinical studies do not need to be conducted before
145 testing in humans or during Phase 1 (Boxes 2 to 3). The Agency's recommendation to conduct
146 nonclinical studies for further development of the combination will depend on what is learned
147 from initial studies in humans or what is known from prior human use of the combination.⁵

148
149 If the available data indicate that an interaction is possible, then FDA advises sponsors to
150 consider the nature of that interaction. If it is likely to be only a metabolic interaction, then

⁵ For example, as mentioned above, the Draft HIV Guidance discusses FDA's belief that certain antiretroviral therapies previously approved for the treatment of HIV may be approved for concomitant use without additional nonclinical (or clinical) studies, because the clinical safety and efficacy of concomitant use have been evaluated and described in product labels or peer reviewed literature.

Contains Nonbinding Recommendations

Draft — Not for Implementation

151 sponsors are urged to conduct studies to characterize that interaction (Boxes 4 to 5). Even when
152 a metabolic interaction is documented, nonclinical toxicity studies may not be needed before a
153 clinical pharmacokinetic study, if the doses proposed for the study in humans are lower than the
154 marketed doses of the individual agents (Box 8). If no metabolic interaction is identified and
155 there are no other concerns, then the clinical studies may be allowed to proceed (Box 3).

156

157 Generally, FDA recommends that sponsors conduct nonclinical toxicity studies before clinical
158 studies are initiated if (1) the drug products have similar target organ toxicity or
159 pharmacodynamic activity, (2) either drug product causes serious or nonmonitorable toxicity in
160 animals or humans at exposures near the clinical exposure, or (3) any other reason exists for
161 serious clinical concern (see section II.A).

162

163 The nonclinical studies (Box 7) recommended will depend on the concerns identified in section
164 II.A. If a sponsor will be conducting only one general toxicity study, FDA recommends that the
165 sponsor provide justification for the species selected for testing the combination. Sometimes one
166 of the drugs proposed for the combination will be much more toxic in animals than in humans,
167 such that animals cannot tolerate the combination at doses that produce exposure relevant to the
168 anticipated clinical exposure (e.g., some nonsteroidal anti-inflammatory drugs (NSAIDs) and
169 antibiotics). In those cases, general toxicity studies of the combination could be conducted at a
170 dose giving less exposure than that achieved with the recommended clinical dose of the more
171 toxic drug product, provided that a maximum tolerated dose is achieved in the animals.

172

173 Combination genotoxicity studies generally will not be necessary if the individual agents have
174 been tested consistent with current standards. Combination developmental toxicity studies need
175 not be conducted if one of the drug products is already known to have significant risk for
176 developmental toxicity, because that risk will already be included in the product labeling for the
177 combination. For chronic indications, a carcinogenicity study on the drug combination generally
178 will only be indicated if preneoplastic lesions were observed at a new organ or tissue site in
179 nonclinical studies. Results of the nonclinical studies may be used to recommend modification
180 of the clinical protocol (e.g., starting clinical doses, parameters to monitor) (Box 8).

181

III. NONCLINICAL STUDIES FOR A COMBINATION OF DRUGS WHEN ONE OR 182 MORE IS PREVIOUSLY MARKETED AND ONE IS A NEW MOLECULAR 183 ENTITY (FIGURE B) 184

185

186 This section of the guidance addresses the situation in which a sponsor submits an application to
187 develop a combination of two or more drugs—one or more previously marketed and one an
188 NME.

189

A. General Toxicology Studies

190

191
192 The Agency generally suggests that nonclinical studies be conducted on the NME for a
193 combination of an NME and a previously marketed drug substance. FDA believes that the
194 standard battery of nonclinical studies (i.e., genetic toxicology, pharmacology, safety
195 pharmacology, PK/ADME, general toxicity, reproductive and developmental toxicity,
196 carcinogenicity) generally will be appropriate for the NME, as described in the ICH guidance *M3*

Contains Nonbinding Recommendations

Draft — Not for Implementation

197 *Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals.*⁶ If
198 genotoxicity studies on the previously marketed product are consistent with current standards, it
199 may be appropriate to conduct genotoxicity studies on only the NME portion of the combination.
200

201 Depending on the duration of the proposed therapy, FDA recommends that a sponsor conduct a
202 bridging study of up to 90 days with the combination in the most appropriate species. There may
203 be cases, however, where studies in a second species may be appropriate. Because the drug ratio
204 may change during drug development, it is important to design the toxicity studies to provide
205 adequate margins of safety for future clinical studies. For combinations, FDA recommends that
206 the drugs be at ratios that are relevant to the intended clinical use.
207

208 Sometimes one of the drugs proposed for the combination will be much more toxic in animals
209 than in humans, such that animals cannot tolerate the combination at doses that produce exposure
210 relevant to the anticipated clinical exposure (e.g., some nonsteroidal anti-inflammatory drugs
211 (NSAIDs) and antibiotics). In those cases, nonclinical studies of the combination could be
212 conducted at a dose giving less exposure than that achieved with the recommended clinical dose
213 of the more toxic drug product, provided that a maximum tolerated dose is achieved in the
214 animals.
215

B. Reproductive and Developmental Toxicology

216
217
218 Embryofetal developmental studies of the combination should be conducted unless the marketed
219 drug substance is already known to have significant risk for developmental toxicity. If there is
220 known significant risk, embryofetal developmental studies on the NME would not be needed,
221 because the labeling would not be changed in this regard for the combination.
222

C. Animal Models of Efficacy

223
224
225 Valuable data may be obtained from studying the combination in appropriate animal models of
226 efficacy. For example, there are situations in which one drug has been shown to alter the
227 efficacy of the second drug. This information is especially important if one or more of the drugs
228 in the combination is for a serious or life threatening indication.
229

D. Further Studies

230
231
232 FDA recommends that a sponsor address any important data gaps for the marketed product or
233 products that may be relevant for the proposed indication. After evaluating the available data on
234 the individual drug products and the data on the bridging study of up to 90 days on the
235 combination, a determination will be made on whether it is appropriate to conduct additional
236 studies to address potential drug interactions. If a drug interaction is identified in the bridging
237 study (synergistic effects) and the mechanism (e.g., PK, PD, or overlapping toxicity) is not
238 apparent, then FDA urges sponsors to consider studies to understand the nature of the interaction.

⁶ We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at <http://www.fda.gov/cder/guidance/index.htm>.

Contains Nonbinding Recommendations

Draft — Not for Implementation

239 The possible mechanisms of drug interaction listed in section II.A would also apply to
240 combinations of one or more previously marketed drugs and an NME. Other than the general
241 toxicology bridging study of up to 90 days and studies on embryofetal development, additional
242 studies on the combination generally will not be needed.

243

IV. NONCLINICAL STUDIES FOR A COMBINATION OF TWO OR MORE DRUGS WHEN BOTH ARE NEW MOLECULAR ENTITIES (FIGURE C)

245

246

247

A. General Toxicology Studies

248

249

250

251

252

253

254

255

256

257

258

259

260

261

262

FDA generally recommends that the sponsor conduct nonclinical studies on each NME to evaluate the safety of a combination of NMEs. Sponsors are encouraged to conduct the standard battery of nonclinical studies (i.e., genetic toxicology, pharmacology, safety pharmacology, PK/ADME, general toxicity, reproductive and developmental toxicity, carcinogenicity) on each NME, as described in the ICH guidance *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals*. Depending on the duration of the proposed therapy, a bridging study of up to 90 days should be conducted with the combination in the most appropriate species if the NMEs were evaluated as separate entities (which is preferred) and not as a combination. There may be cases, however, where studies in a second species may be appropriate. If the two drugs are proposed to be marketed together only, then it is possible that it may be sufficient to conduct toxicology studies only on the combination. However, nonclinical studies conducted on each NME alone can be invaluable should it become important to alter the clinical regimen from what is initially proposed or studied.

263

264

265

266

267

Because the drug ratio may change during drug development, it is important to design the toxicity studies to provide adequate margins of safety for future clinical studies. FDA recommends that the drugs be tested at doses that produce exposure ratios that are relevant to the intended clinical use, when feasible.

268

269

270

271

272

273

274

Sometimes one of the drugs proposed for the combination will be much more toxic in animals than in humans, such that animals cannot tolerate the combination at doses that produce exposure relevant to the anticipated clinical exposure (e.g., some NSAIDs and antibiotics). In those cases, nonclinical studies of the combination might be conducted at a dose giving less exposure than that achieved with the recommended clinical dose of the more toxic drug, provided that a maximum tolerated dose is achieved in the animals.

275

B. Animal Models of Efficacy

276

277

278

279

280

281

Valuable data may be obtained from studying the combination in appropriate animal models of efficacy. For example, there are situations in which one drug has been shown to alter the efficacy of the second drug. This information is especially important if one or more of the drugs in the combination is for a serious or life threatening indication.

282

C. Safety Pharmacology

283

Contains Nonbinding Recommendations

Draft — Not for Implementation

284 FDA strongly recommends that sponsors assess the effects of drugs on a variety of organ
285 systems before dosing in humans. Combination safety pharmacology studies (cardiac,
286 respiratory, CNS) may be valuable in many situations, such as when both drugs target the same
287 organ system, a toxicity is associated with a class of compounds (e.g., QT prolongation), or the
288 intended patient population is compromised (e.g., renal impairment).

289

D. PK/ADME and Toxicokinetics

290

291
292 FDA recommends that sponsors conduct combination PK/ADME studies to assess the potential
293 for a pharmacokinetic interaction between the drugs. These data are valuable for supporting the
294 safety profile and guiding the drug development process. FDA further recommends that
295 PK/ADME combination studies (e.g., in vitro drug metabolism studies) be conducted early in
296 drug development. FDA encourages sponsors to evaluate serum protein binding and to monitor
297 plasma concentrations of each drug in the toxicology studies. It may be possible to collect
298 pharmacokinetic data as part of the toxicology studies instead of in a separate study.

299

E. Genetic Toxicology

300

301
302 Assessing the genotoxic potential of the combination is generally not necessary, provided that
303 adequate studies of the individual drug substances have been conducted. For the in vitro assays,
304 genotoxic potential is routinely tested in the absence and presence of metabolic activation.
305 Therefore, testing drugs in combination in these assays would not likely provide additional
306 information to assays testing each drug alone, particularly if any potential interaction is expected
307 to be from effects on hepatic metabolism.

308

F. Special Toxicology

309

310
311 It is possible that FDA will recommend that a sponsor conduct special toxicology studies with
312 the NME as well as with the combination in a particular therapeutic area relevant to the proposed
313 use. The Agency may also recommend that targeted special toxicity studies be conducted,
314 depending upon the nature of toxicities seen in animals and humans with the drug products or
315 drug class.

316

G. Reproductive and Developmental Toxicology

317

318
319 If developmental toxicity has been assessed only on each NME separately, then FDA
320 recommends that developmental toxicity studies be conducted on the combination as well.
321 Embryofetal developmental studies of the combination may not be needed if one of the NMEs is
322 known from the nonclinical studies to have significant risk for developmental toxicity.

323

H. Further Studies

324

325
326 After evaluating the available data on the individual drug products and the data on the bridging
327 study of up to 90 days on the combination, a determination will be made as to whether it is
328 appropriate to conduct additional studies to address potential drug interactions. If a drug
329 interaction is identified in a study and the mechanism (e.g., PK or PD or overlapping toxicity) is

Contains Nonbinding Recommendations

Draft — Not for Implementation

330 not apparent, then FDA urges the sponsor to consider studies to understand the nature of the
331 interaction. The possible mechanisms of drug interaction listed in section II.A would also apply
332 to combinations of more than one NME. Generally, studies of the combination other than the
333 general toxicology bridging study of up to 90 days and studies on embryofetal development will
334 not be needed.

335

I. Carcinogenicity

337

338 Depending on the duration and intended use of the combination, the Agency may suggest that the
339 sponsor conduct carcinogenicity studies on the combination, if an individual NME has not been
340 tested for carcinogenicity.

341

342

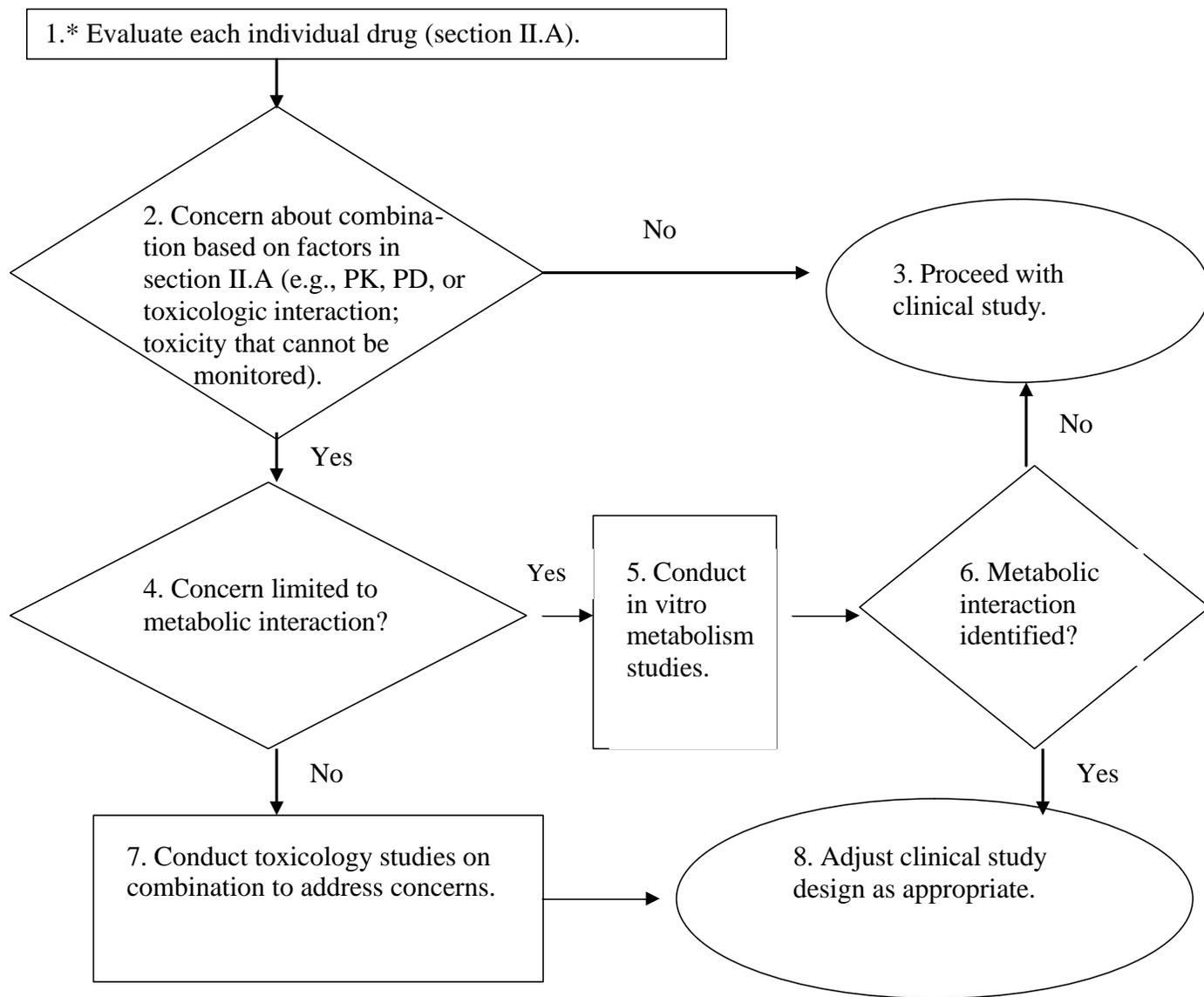
343

344

Contains Nonbinding Recommendations

Draft — Not for Implementation

Figure A. Combinations of Previously Marketed Drugs: Recommended General Procedure

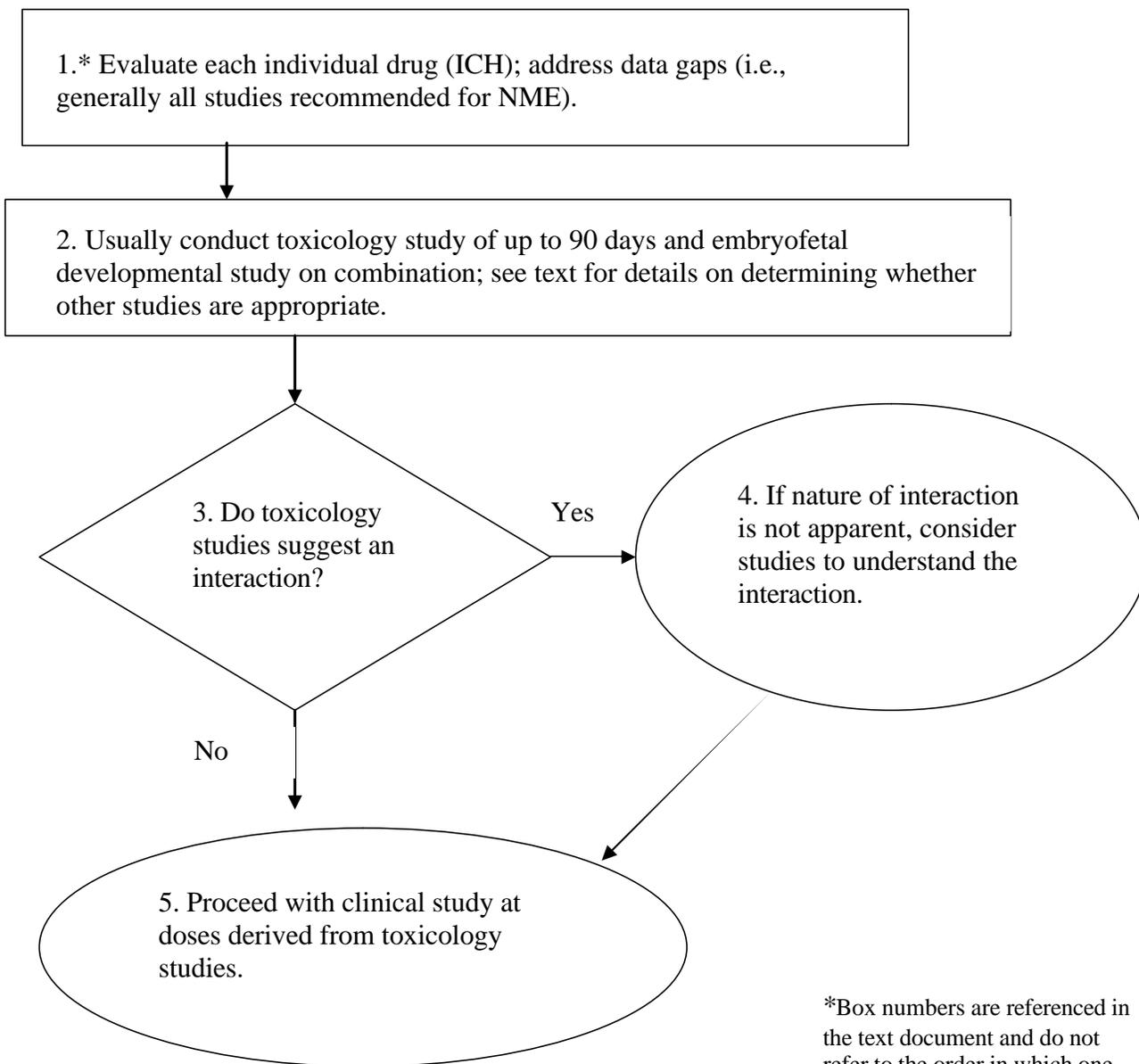


*Box numbers are referenced in the text document and do not refer to the order in which one proceeds.

Contains Nonbinding Recommendations

Draft — Not for Implementation

Figure B. Combinations of Previously Marketed Drugs with NMEs: Recommended General Procedure



*Box numbers are referenced in the text document and do not refer to the order in which one proceeds.

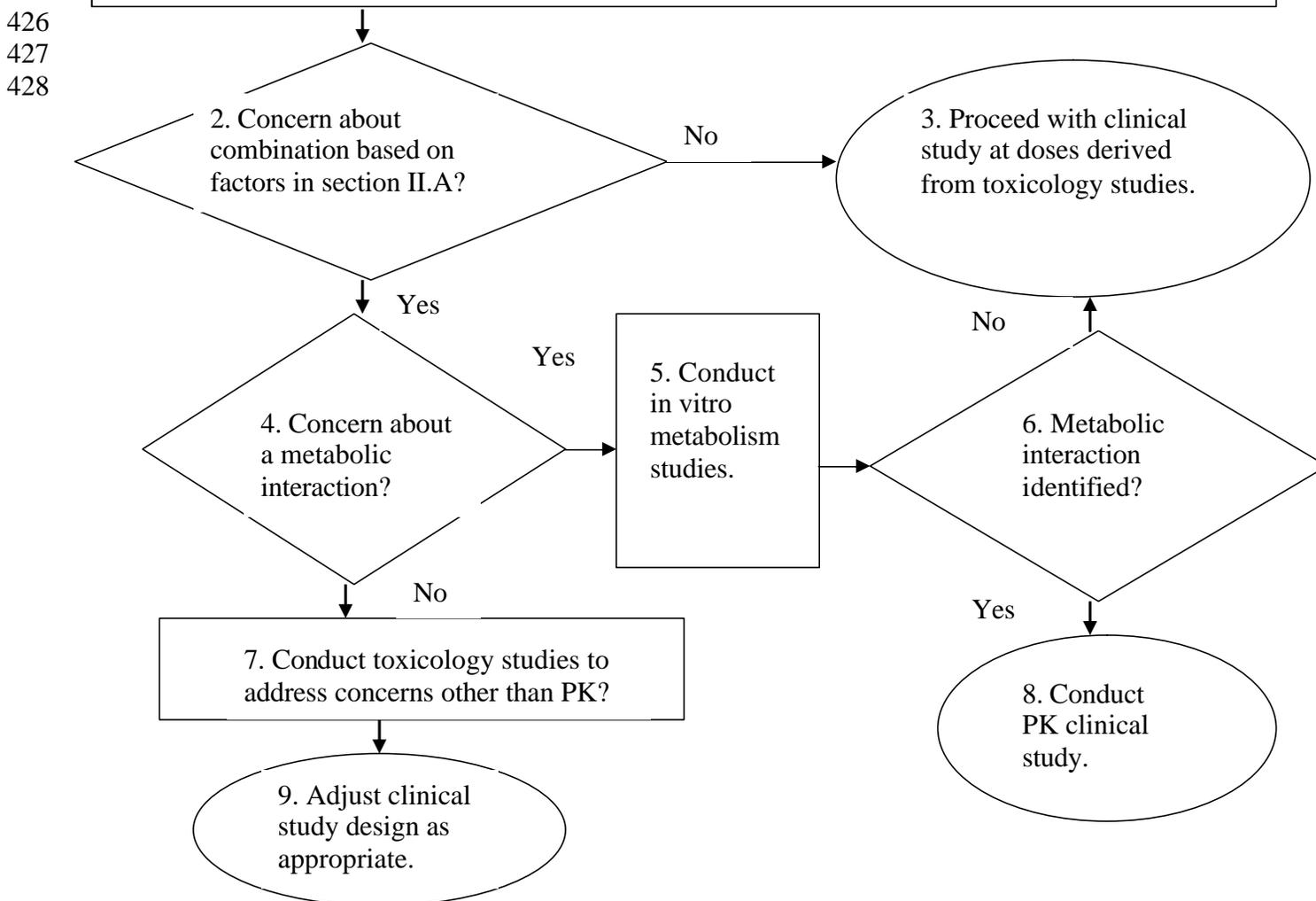
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417

Contains Nonbinding Recommendations

Draft — Not for Implementation

418 Figure C. Combinations of NMEs with NMEs: Recommended General Procedure
419
420
421

422 1.* Preferably, evaluate each NME (ICH) before evaluating the combination. Usually conduct
423 toxicology study of up to 90 days and embryofetal developmental study on combination (see text for
424 details). If only individual NMEs are studied, use the following approach to address safety concerns.
425



*Box numbers are referenced in the text document and do not refer to the order in which one proceeds.