CURRENT VERSION

Guidance for Industry

Nonclinical Safety Evaluation of Drug or Biologic Combinations

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

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Pharmacology and Toxicology

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Nonclinical Safety Evaluation of Drug or Biologic Combinations

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TABLE OF CONTENTS

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Guidance for Industry[1] Nonclinical Safety Evaluation of Drug or Biologic Combinations

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I. INTRODUCTION

This guidance provides recommendations on nonclinical approaches to support the clinical study and approval of fixed-dose combination products (FDCs), co-packaged products, and some adjunctive therapies.[2] The intent of this guidance is to delineate general guiding principles. To receive more detailed advice regarding a particular drug or biologic combination development program, sponsors should contact the appropriate review division before submitting an investigational new drug application (IND). In addition, the Food and Drug Administration (FDA) is in the process of publishing more specific guidance for 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 Food and Drug Administration.

[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 or biologics are not necessarily given at the same time. Adjunctive therapy products may be co-packaged, and may or may not be labeled for concomitant use. However, adjunctive therapies are only covered in this guidance when the adjunctive therapy products are already labeled for concomitant use, a sponsor intends to seek labeling to address concomitant use, or when, in light of the factors described in section II.A, there is an identified cause for concern about a potential serious interaction. For the purposes 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 the draft guidance for industry *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). Sponsors should consult these additional guidances when preparing an application for one of these types of products.

Drug and biologic combinations may involve: (1) two or more previously marketed drugs or biologics[4] (MD/Bs); (2) one or more new molecular entities (NMEs) and one or more previously marketed drugs or biologics; or (3) more than one NME. The nonclinical studies considered important for each type of combination may differ, depending upon the information available on each drug substance. The nonclinical studies that the FDA recommends sponsors use to characterize the combination will depend on the toxicologic and pharmacokinetic profiles of the individual drugs or biologics, the treatment indication or indications, and the intended population. The number and type of studies will depend on the stage of clinical development.

In this guidance, each of the three general types of combinations (i.e., MD/B-MD/B, MD/B-NME, and NME-NME) will be discussed separately. This guidance covers combinations of drugs and biologics regulated by the Center for Drug Evaluation and Research (CDER). The ICH guidance for industry *S6 Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* should also be consulted for nonclinical development of biologic products.[5]

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

II. NONCLINICAL STUDIES FOR A COMBINATION OF TWO OR MORE PREVIOUSLY MARKETED DRUGS OR BIOLOGICS (FIGURE A)

This section addresses the situation in which a sponsor submits an application to develop a combination of two or more previously marketed drugs or biologics or a combination of drugs and biologics. Generally the FDA believes that, in such a situation, sufficient clinical and nonclinical data will exist for each drug product separately. However, the indications for which each drug is marketed should be compared to those for which the combination is being proposed. For example, drug products marketed for acute use may not have nonclinical data to support chronic use. To the extent that there are gaps in the data, the FDA may recommend that additional nonclinical studies be conducted.[6]

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[4] For purposes of this guidance, the phrase *previously marketed drugs or biologics* includes both drug/biologic products and active pharmaceutical ingredients.

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

[6] In certain cases, adequate clinical data may exist not only for the individual components of a drug or biologic 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 the 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 or biologics, a sponsor seeking approval for the drug and biologic combination should contact the appropriate review division to discuss whether any additional nonclinical data are warranted.

A. Safety Considerations

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

1. Information available on prior human experience with the combination. The FDA recommends that the sponsor provide a summary of the available data in humans (if any) on the use of the combination. The FDA also encourages the sponsor to provide copies of any relevant published studies in humans (or animals). Such reports may not provide definitive safety data, but they may provide some measure either of assurance or reasons for concern.

2. Information known about the individual drugs or biologics in animals and humans and concordance of pharmacokinetics (PK), pharmacodynamics (PD), and toxicologic effects in animals with the analogous data for humans.

3. Possibility of a PD interaction. Drugs/biologics may exhibit affinity for the same receptors or biologic targets or may produce similar effects on physiologic function, related or not to their mechanism of action.

4. Possibility of a PK interaction. A PK interaction can manifest in several ways, some of which can be monitored in vivo and some of which cannot. One drug/biologic product may alter the absorption or excretion of another product, change its distribution into one or more tissues, or change its pattern or rate of metabolism. Drugs may compete for serum protein binding, resulting in an increase in circulating free levels and tissue uptake of one drug.

5. Possibility of a toxicologic interaction (i.e., that the target organs for toxicity are similar for each drug/biologic). This situation may result in a lowering of the previously determined no-effect doses for one or both drug/biologic products and more severe toxicities in the affected organs. The FDA will consider all known toxicology on the product (e.g., general toxicity, reproductive toxicity, carcinogenicity, and safety pharmacology studies (cardiovascular, central nervous system (CNS), respiratory)).

6. Margin of safety for each drug/biologic product. If one or more of the drugs/biologics has a narrow margin of safety (i.e., causes serious toxicity at exposures close to the predicted clinical exposure), then the possibility of drug interaction is of particular concern, especially if the toxicity is not reversible or cannot be monitored clinically.

7. Possibility that the drugs/biologics compete for or alter the activity or endogenous levels of the same enzymes or other intracellular molecules (e.g., co-administration of two pro-oxidants could deplete endogenous levels of glutathione).

8. Possibility of a chemical interaction. One drug may chemically modify another drug or biologic (e.g., one drug may oxidize, methylate, or ethylate the other drug or biologic). This could result in NMEs with new toxicities.

9. Possibility that one drug/biologic may compromise the effectiveness of another drug/biologic for a lifesaving therapy.

B. Nonclinical Study Recommendations/General Procedure

If existing clinical and nonclinical safety data for each separate drug or biologic are sufficient to support the safety of the proposed new indication, including the dose, dosing schedule, duration, and new patient population, then additional nonclinical studies may not be needed.

The general approach to addressing the safety concerns posed by the testing or marketing of combinations of previously marketed drugs or biologics is illustrated in Figure A. The safety of the combination should be assessed according to the factors listed in section II.A (see Figure A, Boxes 1 to 2). If neither individual drug or biologic product has serious toxicity at exposures well above the proposed clinical exposure or if there is substantial clinical experience with the combination, the FDA may recommend that additional nonclinical studies do not need to be conducted before testing in humans, during initial studies in humans, or at all (Boxes 2 to 3). The Agency's recommendation to conduct nonclinical studies for further development of the combination will depend on what is learned from initial studies in humans or what is known from prior human use of the combination.[7]

If after evaluating the available data on the individual drug/biologic products and the potential for drug/biologic interaction there is no evidence to suggest a possible interaction, direct assessment of the combination by testing in animals may not be needed before the first small clinical studies with the combination. Even if an interaction is expected, nonclinical studies may not be necessary if the expected interaction is likely to result in predictable, nonserious, monitorable effects in humans. For example, if a metabolic interaction is predicted, the starting dose could be significantly lowered in humans. Metabolic interactions have been seen for combinations of two biologics. There is a possibility of drugs/biologics affecting the same tissue or biologic target or having a PD interaction.

Generally, the FDA recommends that sponsors conduct nonclinical toxicity studies before clinical studies are initiated if: (1) the drug products have similar target organ toxicity or PD activity; and (2) either drug product causes serious or nonmonitorable toxicity in animals or humans at exposures near the clinical exposure; or (3) any other reason exists for serious clinical concern (see section II.A). The particular nonclinical studies recommended by the FDA will depend on a number of factors, including the nature of the toxicity and on the concerns identified in section II.A. For assessment of general toxicity, a bridging study may be appropriate, provided the duration is sufficient to elicit the toxicity of concern. For example, a general

[7] For example, as previously mentioned, the draft HIV guidance discusses the 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.

toxicity bridging study of 3 months' duration could be considered for a chronic indication. The FDA suggests that combination studies include an assessment of several dose levels of the combination and a high dose of each drug alone. Other possible designs can be discussed with the review division. Sponsors are urged to select the doses of each drug used in combination to allow for additive or synergistic effects without unacceptable toxicity in the high-dose groups. Usually, assessment of the drug combination may be conducted in only one species if one of the following conditions exists: (1) toxicity in a particular species has high concordance with human toxicity or the toxicities are similar among species; or (2) one species is a more relevant model for human risk based on other factors such as PK/ADME (absorption, distribution, metabolism, and excretion) or expression of the pharmacologic activity. If a sponsor will be conducting only one general toxicity study, the FDA recommends that the sponsor provide justification for the species selected for testing the combination. There may be cases, however, in which the Agency may recommend conducting studies in two species despite one or both of these conditions being met. For example, depending on the results in the first species, a new cause for concern might warrant follow-up studies in a second species, if there is an appropriate second species.

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 nonsteroidal anti-inflammatory drugs (NSAIDs) and antibiotics). In those cases, general toxicity studies of the combination could be conducted at a dose giving less exposure than that achieved with the recommended clinical dose of the more toxic drug product, provided that a serious dose-limiting toxicity is achieved in the animals. The timing of the studies should be as described in the ICH guidance for industry *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals*.

Combination genotoxicity studies generally will not be necessary if the individual agents have been tested consistent with current standards. Embryo-fetal development studies of the combination *should* be conducted per the timing described in ICH M3, unless the marketed products are already known to have significant risk for developmental toxicity (e.g., one of the marketed drugs has been assigned a pregnancy category "D" or "X"). If combination studies are needed, a single study could be conducted in the most appropriate species, based on what is known about the individual drugs or biologics. If a significant risk is only identified for a particular trimester of pregnancy, such as ACE inhibitors during the third trimester, studies to evaluate the effects of exposure to the NME or the combination during other trimesters may be needed.

For chronic indications, a carcinogenicity study on the drug combination generally will only be recommended if statistically significant incidences of preneoplastic lesions were observed at a new organ or tissue site in nonclinical studies of the combination. Results of the nonclinical studies may be used to recommend modification of the clinical protocol (e.g., starting clinical doses, parameters to monitor) (Box 8).

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

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

A. General Toxicology Studies

The Agency generally suggests that nonclinical studies be conducted on the NME for a product that is a combination of an NME and a previously marketed drug or biologic. The FDA believes that the standard battery of nonclinical studies (i.e., genetic toxicology, pharmacology, safety pharmacology, PK/ADME, general toxicity, reproductive and developmental toxicity, carcinogenicity) generally will be appropriate for the NME, as described in ICH M3. ICH S6 should be consulted for nonclinical development of biologic products. If genotoxicity studies on the previously marketed product are consistent with current standards, it may be appropriate to conduct genotoxicity studies on only the drug NME portion of the combination.

Depending on the duration of the proposed therapy, the FDA recommends that a sponsor conduct a bridging study of up to 90 days with the combination in the most appropriate species. Studies of shorter duration could be appropriate for shorter clinical studies or for nonchronic indications, per ICH M3. There may be cases, however, where studies in a second species may be appropriate. 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. For combinations, the FDA recommends that the exposure to the drugs/biologics be at ratios that are relevant to the intended clinical use.

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 could be conducted at a dose giving less exposure than that achieved with the recommended clinical dose of the more toxic drug product, provided that a serious dose-limiting toxicity is achieved in the animals.

B. Reproductive and Developmental Toxicology

Embryo-fetal development studies on the NME are recommended, as are fertility and other reproduction studies, by the ICH. Studies to evaluate the reproductive toxicity of the combination are not generally needed. Embryo-fetal development studies of the combination *should* be conducted unless the marketed drug substance or the NME is already known to have significant risk for developmental toxicity (e.g., the marketed drug has been assigned a pregnancy category “D” or “X”). If combination studies are needed, a single study could be conducted in the most appropriate species, based on what is known about the individual drugs or biologics. If a significant risk is only identified for a particular trimester of pregnancy, such as

ACE inhibitors during the third trimester, studies to evaluate the effects of exposure to the NME or the combination during other trimesters may be needed.

C. Animal Models of Efficacy

Animal models of efficacy are not generally needed. However, valuable data may be obtained from studying the combination in appropriate animal models of efficacy, if they are available and considered relevant. For example, there are situations in which one drug has been shown to alter the efficacy of the second drug. This information may be important if one or more of the drugs in the combination is for a serious or life-threatening indication. Identifying such an interaction permits an informed choice of dose of each product in the combination and an optimal schedule for the proposed clinical trial.

D. Further Studies

The FDA recommends that a sponsor address any important data gaps for the marketed product or products that may be relevant for the proposed indication. After evaluating the available data on the individual drug products and the data on the bridging study of up to 90 days on the combination, a determination will be made on whether it is appropriate to conduct additional studies to address potential drug/biologic interactions. If a drug interaction is identified in the bridging study (synergistic effects) and the mechanism (e.g., PK, PD, or overlapping toxicity) is not apparent, then the FDA urges sponsors to consider studies to understand the nature of the interaction. The possible mechanisms of drug interaction listed in section II.A would also apply to combinations of one or more previously marketed drugs/biologics and an NME. Other than the general toxicology bridging study of up to 90 days and studies on embryo-fetal development, additional studies on the combination generally will not be needed.

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

A. General Toxicology Studies

The 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, according to the timing as described in ICH M3, and according to ICH S6 for nonclinical development of biologic products. Depending on the duration of the proposed therapy, a bridging study of up to 90 days (for chronic indications) 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 or biologics 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.

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. The FDA recommends that the drugs or biologics be tested at doses that produce exposure ratios that are relevant (i.e., somewhat similar) to the intended clinical use, when feasible.

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 serious dose-limiting toxicity is achieved in the animals at the highest dose.

B. Animal Models of Efficacy

Animal models of efficacy are not generally needed. However, valuable data may be obtained from studying the combination in appropriate animal models of efficacy, if they are available and considered relevant. 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 or biologics in the combination is for a serious or life-threatening indication. Identifying such an interaction permits an informed choice of dose of each product in the combination and an optimal schedule for the proposed clinical trial.

C. Safety Pharmacology

The FDA strongly recommends that sponsors assess the effects of drugs/biologics on a variety of organ systems before dosing in humans. Combination safety pharmacology studies of a particular organ system (e.g., cardiac, respiratory, CNS) may be valuable in many situations, such as when both drugs target the same organ system, a toxicity is associated with a class of compounds (e.g., QT prolongation), or the intended patient population is compromised (e.g., renal impairment). Sometimes when the molecular target is known, effects of the combination can be predicted.

D. PK/ADME and Toxicokinetics

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

E. Genetic Toxicology

Genetic toxicology studies are not needed for biologic or drug/biologic combinations. Assessing the genotoxic potential of a drug/drug combination is generally not necessary, provided that adequate studies of the individual drug substances have been conducted. For the in vitro assays, genotoxic potential is routinely tested in the absence and presence of metabolic activation. Therefore, testing drugs in combination in these assays would not likely provide additional information to assays testing each drug alone, particularly if any potential interaction is expected to be from effects on hepatic metabolism.

F. Special Toxicology

The FDA may recommend that a sponsor conduct special toxicology studies, such as local tolerance studies, with the NME as well as with the combination in a particular therapeutic area relevant to the proposed use. The Agency may also recommend that targeted toxicity studies be conducted, depending upon the nature of toxicities seen in animals and humans with the drug products or drug class.

G. Reproductive and Developmental Toxicology

Embryo-fetal development studies on each NME are generally recommended by the ICH, as are fertility and other reproduction studies. Studies to evaluate the reproductive toxicity of the combination are not generally needed, if this has been evaluated for the individual NME. If developmental toxicity has been assessed only on each NME separately, then the FDA recommends that developmental toxicity studies be conducted on the combination as well, in the most appropriate species, before treatment of women of childbearing potential. Embryo-fetal developmental studies of the combination may not be needed if one of the NMEs is known from the nonclinical studies to have significant risk for developmental toxicity, such as results indicating potential labeling as a "D" or "X." If a significant risk is only indicated for a particular trimester of pregnancy, studies to evaluate the effects of exposure to the combination during other trimesters may be needed.

H. Further Studies

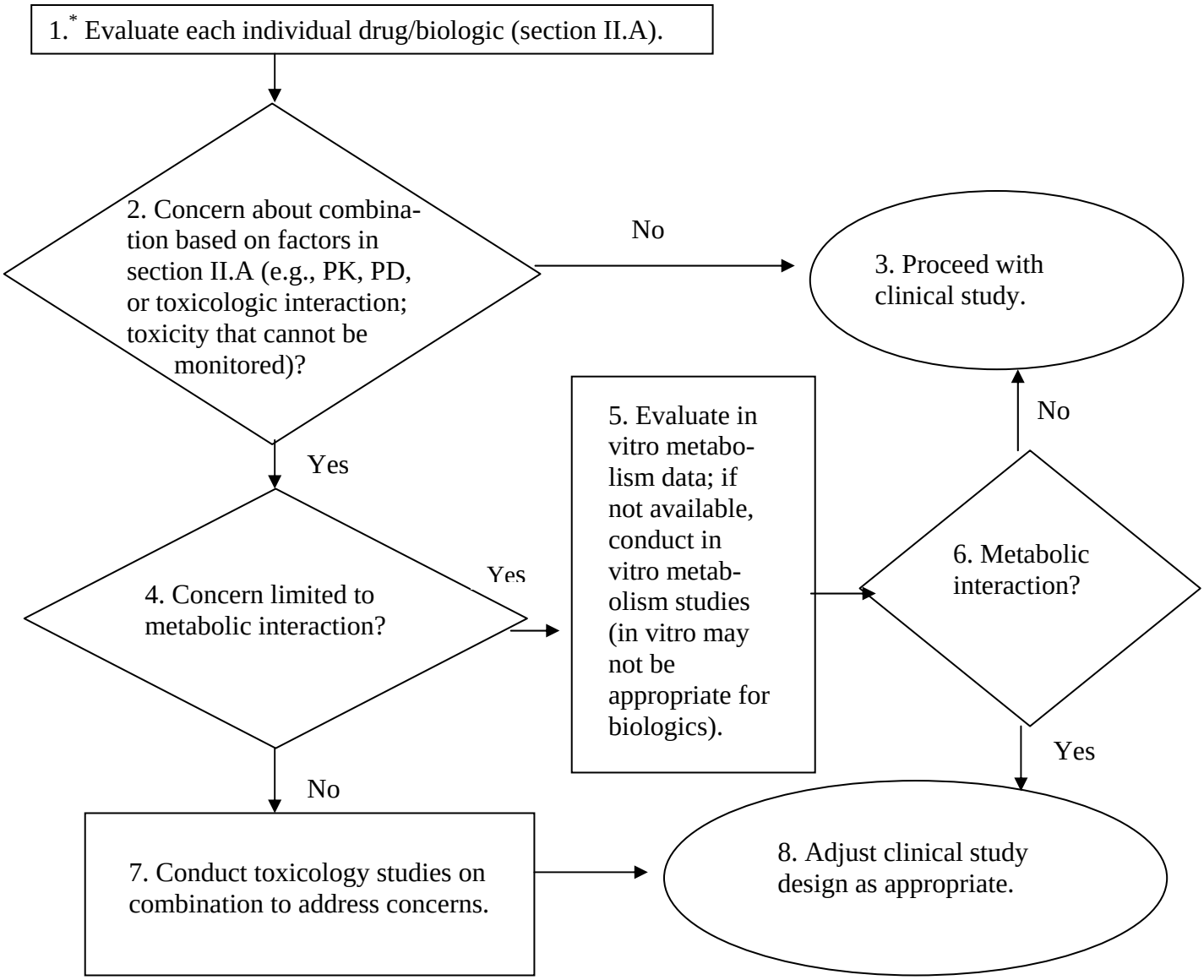
After evaluating the available data on the individual drug/biologic products and the data on the bridging study of up to 90 days on the combination, a determination will be made as to whether it is appropriate to conduct additional studies to address potential drug/biologic interactions. If a drug/biologic interaction is identified in a study and the mechanism (e.g., PK, PD, or overlapping toxicity) is not apparent, then the FDA urges the sponsor to consider studies to evaluate the nature of the interaction. The possible mechanisms of drug/biologic interaction listed in section II.A would also apply to combinations of more than one NME. Generally, studies of the combination other than the general toxicology bridging study of up to 90 days (depending on the chronicity of the indication) and studies on embryo-fetal development will not be needed.

I. Carcinogenicity

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

APPENDIX: RECOMMENDED GENERAL PROCEDURES

Figure A: Combinations of Previously Marketed Drugs or Biologics



*Box numbers correspond to references in the text document and do not depict the order in which one proceeds.

Figure B: Combinations of Previously Marketed Drugs or Biologics with NMEs

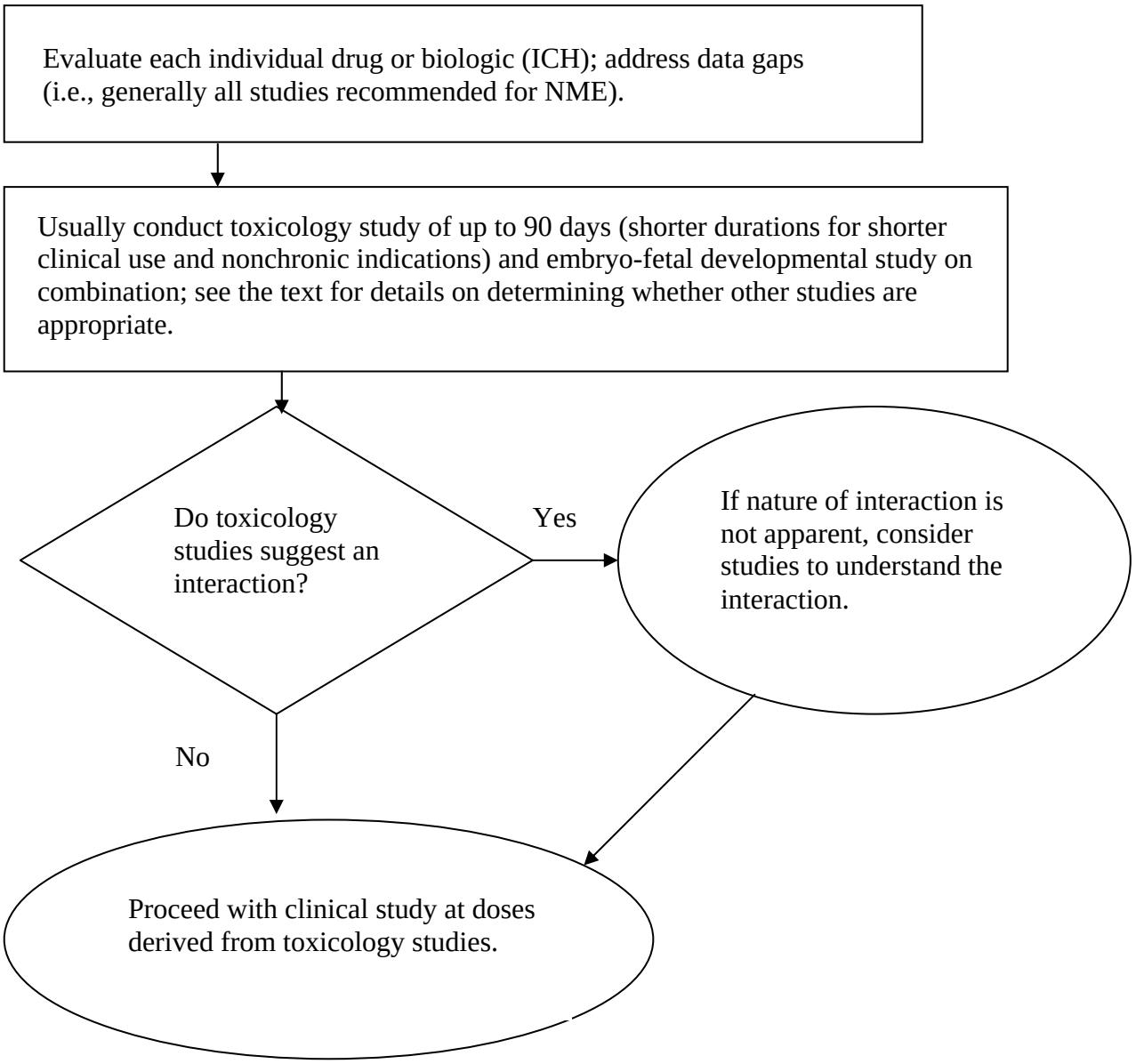


Figure C: Combinations of NMEs with NMEs