Guidance for Industry Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
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Guidance for Industry[1]
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I. INTRODUCTION

This guidance is intended to assist sponsors in the codevelopment[2] of two or more novel (not previously marketed) drugs to be used in combination to treat a disease or condition. The guidance provides recommendations and advice on how to address certain scientific and regulatory issues that will arise during codevelopment. It is not intended to apply to development of fixed-dose combinations of already marketed drugs or to development of a single new investigational drug to be used in combination with an approved drug or drugs. The guidance is also not intended to apply to vaccines, gene or cellular therapies, blood products, or medical devices.[3]

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.

[1] This guidance has been prepared by the Office of Medical Policy in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

[2] *Codevelopment* herein refers to the concurrent development of two or more drug products with the intent that the products be used in combination to treat a disease or condition.

[3] For purposes of this guidance, the term *drug* includes therapeutic biological products that are regulated by CDER. Consult the Therapeutic Biologics web page for further information on the types of biological products to which this guidance applies:
www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/default.htm

II. BACKGROUND

Combination therapy is an important treatment modality in many disease settings, including cancer, cardio-vascular disease, and infectious diseases. Recent scientific advances have increased our understanding of the pathophysiological processes that underlie these and other complex diseases. This increased understanding has provided further impetus for new therapeutic approaches using combinations of drugs directed at multiple therapeutic targets to improve treatment response or minimize development of resistance. In settings in which combination therapy provides significant therapeutic advantages, there is growing interest in the development of combinations of investigational drugs not previously developed for any purpose.

Because the existing developmental and regulatory paradigm focuses primarily on assessment of the effectiveness and safety of a single new investigational drug acting alone, or in combination with an approved drug, FDA believes guidance is needed to assist sponsors in the codevelopment of two or more unmarketed drugs. Although interest in codevelopment has been most prominent in oncology and infectious disease settings, codevelopment also has potential application in other therapeutic settings. Therefore, this guidance is intended to describe a high-level, generally applicable approach to codevelopment of two or more unmarketed drugs. It describes the criteria for determining when codevelopment is an appropriate option, makes recommendations about nonclinical and clinical development strategies, and addresses certain regulatory process issues.

III. DETERMINING WHETHER CODEVELOPMENT IS AN APPROPRIATE DEVELOPMENT OPTION

Concurrent development of two or more novel drugs for use in combination generally will provide less information about the safety and effectiveness of the individual drugs than would be obtained if the individual drugs were developed alone. How much less will vary depending on a variety of factors, including the stage of development at which the individual drug components cease to be studied independently. For example, in codevelopment scenarios in which rapid development of resistance to monotherapy is a major concern, it may not be possible or appropriate to obtain clinical data for the individual components of the combination beyond phase 1 testing. Because codevelopment will generally provide less information about the safety and effectiveness of the individual drugs, it will present greater risk compared to development of an individual drug. Therefore, FDA believes that codevelopment should ordinarily be reserved for situations that meet the following criteria:

- The combination is intended to treat a serious disease or condition.

- There is a compelling biological rationale for use of the combination (e.g., the agents inhibit distinct targets in the same molecular pathway, provide inhibition of both a primary and compensatory pathway, or inhibit the same target at different binding sites to decrease resistance or allow use of lower doses to minimize toxicity).

- A preclinical model (*in vivo* or *in vitro*) or short-term clinical study on an established biomarker suggests that the combination has substantial activity and provides greater than

additive activity or a more durable response (e.g., delayed resistance) compared to the individual agents alone.

- There is a compelling reason for why the agents cannot be developed individually (e.g., monotherapy for the disease of interest leads to resistance and/or one or both of the agents would be expected to have very limited activity when used as monotherapy).

FDA recommends that sponsors consult with FDA on the appropriateness of codevelopment before initiation of clinical development of the combination.

IV. NONCLINICAL CODEVELOPMENT

A. Demonstrating the Biological Rationale for the Combination

The biology of the disease, pathogen, or tumor type should be sufficiently understood to provide a plausible biological rationale for the use of combination therapy to treat the disease or condition. For example, in an oncology setting the biological rationale may be to intervene at different steps in the cell proliferation pathway. The biological rationale for a combination anti-infective therapy may be to target different metabolic pathways or different steps in the replication cycle of the pathogen to reduce the chance of developing resistance to the therapy or increase efficacy in treating disease caused by resistant organisms (e.g., multidrug-resistant atypical tuberculosis).

Sponsors should develop evidence to support the biological rationale for the combination in an *in vivo* (preferable) or *in vitro* model. The model should compare the activity of the combination to the activity of the individual components. Ordinarily, the model should demonstrate that, compared to the individual components, the combination has substantial activity and provides greater than additive activity or a more durable response in a pathophysiological process considered pertinent to the drug's intended use in humans. An animal model of activity generally would not be necessary. However, if there is an animal model relevant to the human disease, valuable activity data, as well as information about the relative doses of the drugs, might be obtained from evaluating the combination in that model.

B. Nonclinical Safety Characterization

For detailed recommendations regarding nonclinical safety characterization for two or more investigational drugs to be used in combination, sponsors should consult the recently revised International Conference on Harmonisation (ICH) Guidance on Nonclinical Safety Studies.[4] Section XVII of that guidance (Combination Drug Toxicity Testing) includes a discussion of nonclinical safety studies appropriate in a combination drug development setting involving two early stage entities. The ICH guidance defines early stage entities as compounds with limited clinical experience (i.e., phase 2 studies or less), so the discussion is specifically applicable to the

[4] Guidance for Industry: M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization, January 2010 (this guidance is a revision of 1997 ICH guidance M3: Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals).

type of development described in this guidance. In situations in which it is possible to obtain only limited clinical data for the individual drugs, additional nonclinical data for the individual drugs or combination may be needed before beginning human studies with the combination. (e.g., see section V.A.1).

V. CLINICAL CODEVELOPMENT

This section provides a general roadmap and guiding principles for concurrent clinical development of two or more investigational drugs to be used in combination. It includes recommendations for characterizing the clinical safety and effectiveness of the combination and, to the extent needed or possible, the individual components of the combination.

Note: The appropriate review division should always be consulted on the specifics of a given clinical development program.

A. Early Human Studies (Phase 1)

The main objectives of early studies in humans are to characterize the safety and pharmacokinetics of the individual components and then the combination and to provide data to support appropriate dosing for the combination in phase 2 testing.

1. Safety of the Individual Components

Whenever possible, the safety profile of each individual drug should be characterized in phase 1 studies in healthy volunteers in the same manner as would be done for development of a single drug, including determination of the maximum tolerated dose (MTD), the nature of the dose limiting toxicity (DLT), and pharmacokinetic parameters. If there is a useful measure (e.g., biomarker) of pharmacologic activity, it will also be important to determine dose-response for that measure. If testing in healthy volunteers is not possible (e.g., if nonclinical data suggest a drug may be genotoxic or otherwise unacceptable for studies in healthy volunteers), the safety profile of the individual drugs should be evaluated in patients with the disease of interest. These safety data will guide decisions in later studies about starting doses, dose escalation increments, and final dose selection.

If it is not possible to characterize the safety of the individual drugs in humans (e.g., where drug toxicity prevents use of healthy volunteers and monotherapy would be unethical in patients with the disease of interest), the sponsor should conduct nonclinical studies of the combination to support initial dosing of the combination in humans. The nonclinical data for the combination should include pharmacokinetic (absorption, distribution, metabolism, and excretion) and toxicokinetic data and appropriate biomarker/target inhibition, if relevant.

2. Safety and Dosing of the Combination

For initial human effectiveness studies of the combination, the combination starting dose, dosing escalation intervals, and doses to be used in dose-response studies should be determined based on phase 1 safety data for the individual components, if available. If phase 1 safety data for the components are unavailable, nonclinical data for the combination will be needed to determine the initial combination dose in humans (see previous paragraph). Phase 1 safety studies of the combination could also be conducted — for example, sequential testing in which subjects get drug A, then drug B, then AB — to support dosing in subsequent studies.

B. Clinical Pharmacology

The sponsor should conduct the same clinical pharmacology studies for each of the individual drugs in the combination as would be done if the drugs were being developed separately. In general, such studies include the assessment of bioavailability, characterization of pharmacokinetics, mass balance, the evaluation of effects of intrinsic (such as renal impairment and hepatic impairment) and extrinsic (such as food effect and drug interactions) factors on pharmacokinetics or pharmacodynamics, and exposure-response. Studies to address intrinsic and extrinsic factors could be conducted with the combination instead of the individual drugs.

The evaluation of drug interaction potential follows the same sequence as in other development programs; results of in vitro drug metabolism and drug transporter studies inform the need for in vivo drug interaction studies. The role of pharmacogenomics should be investigated and incorporated into the combination drug development plan to identify potential sources of pharmacokinetic or pharmacodynamic variability.

Dose-response should be evaluated for each drug of the combination. The results of such studies should be used to determine doses to further explore for the combination. If the drug products cannot be administered alone, various doses of each drug administered as the combination should be assessed.

If one drug has no activity or minimal activity by itself, dose-response should be assessed when the drug products are administered in combination using a number of doses of the active drug and the inactive drug. The same approach should be used in evaluating dose-response for the combination of drugs where each drug has minimal activity when used alone.

In addition to evaluating dose-response, response should be evaluated with respect to systemic drug concentration to provide insight into efficacy and safety as a function of drug exposure. Concentration-response assessments should be done in both phase 2 and phase 3 trials. To increase exposure ranges in phase 3 and to further assess dose-response, the incorporation of more than one dose of each of the drugs used in the combination in the phase 3 trials should be considered.

C. Proof of Concept Studies (Phase 2)

In general, phase 2 testing should accomplish the following to the extent needed for a given combination (e.g., to the extent not sufficiently established by existing data):

- Demonstrate the contribution of each component of the combination to the extent possible and needed (given available nonclinical and pharmacologic data);
- Provide evidence of the effectiveness of the combination; and
- Optimize the dose or doses of the combination for phase 3 trials.

The amount and types of clinical data needed and appropriate study designs will vary depending on the nature of the combination being developed, the disease, and other factors. For the types of combinations contemplated by this guidance, it will often be inappropriate to use monotherapy treatment arms in studies of the disease of interest, or it will be possible to administer the components of the combination as monotherapy only for short durations. In these circumstances, the study design typically employed to determine the contributions of the components to the combination — a four-arm factorial design comparing the combination to individual components and placebo or standard of care (SOC) therapy (AB v. A. v. B v. placebo or SOC) — will have limited utility. The following scenarios illustrate possible phase 2 study designs for combinations of two investigational drugs in different situations.

Scenario 1: The components of the combination cannot be administered individually

If *in vivo* or *in vitro* models, or phase 1 or other early clinical studies make clear that the components of the combination cannot be administered individually in clinical trials in the disease of interest (e.g., because such testing would involve administering treatment known to be ineffective as monotherapy), or can't be administered as monotherapy for the duration needed to evaluate effectiveness (e.g., because of rapid development of resistance), proof-of-concept evidence for the combination ordinarily should come from a study directly comparing the combination (AB) to SOC. Alternatively, if SOC is known to be an effective therapy (not solely palliative), an add-on design could be used comparing the combination plus SOC to SOC alone.

In some resistance scenarios, it may be possible to administer the individual drugs in a combination as monotherapy for a short duration, but long enough to establish proof of concept in humans. For example, direct-acting antivirals (DAAs) to treat chronic hepatitis C virus infection can be administered as monotherapy for three days to establish antiviral activity and for initial dose exploration. For DAA studies of longer duration, the combination should be used or the individual components should be added to an active control.[5]

[5] See draft guidance for industry: Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment (section III. 4. b. – Phase 1b (proof-of-concept) trials) or consult the Division of Antiviral Drug Products in CDER for more specific recommendations.

Scenario 2: Each drug alone has activity and can be administered individually

If *in vivo* or *in vitro* models, or phase 1 or other early clinical studies indicate that each drug has some activity, but the combination appears to have greater than additive activity, and rapid development of resistance is not a concern, a four-arm, phase 2 trial comparing the combination to each drug alone and to placebo or SOC (AB v. A v. B v. SOC or placebo[6]) should be used to demonstrate the contribution of the components to the combination and proof of concept. As noted above, if SOC is a known effective therapy, a study design in which each of the arms is added to SOC could be used (AB + SOC v. A + SOC v. B + SOC v. placebo + SOC).

An adaptive trial design with the same four treatment arms might also be used where appropriate, initially using the treatment arms described above. The single-drug arms could be terminated early if it became clear that they had much less activity than the combination. These designs could demonstrate the activity of each component of (i.e., the contribution of each component to the combination) without exposing the large numbers of patients typically required for phase 3 trials to therapeutic products with inadequate activity. For these trials, it may not be necessary to use a clinical endpoint as a primary efficacy measurement. A credible pharmacodynamic or other biomarker, such as tumor response, may be adequate.

Scenario 3: One drug is active alone and one is inactive

If *in vivo* or *in vitro* models, or phase 1 or other early clinical studies suggest that one of the drugs is inactive or minimally active and one drug is modestly active, but the combination has substantial activity, the more active drug generally will require greater scrutiny and should ordinarily be studied as a single drug in a phase 2 study. The minimally active drug generally would not require study as a single drug beyond initial phase 1 safety studies. In this scenario, proof of concept and the contribution of each component could be demonstrated using a three-arm comparison of the active drug alone, SOC, and the combination (AB v. A v. SOC), or the combination and the individual drug added to SOC where SOC is a known effective therapy (AB + SOC v. A + SOC v. SOC).

If the inactive drug in a combination is a pharmacokinetic or metabolic enhancer that contributes to the activity of the combination only by increasing the therapeutic concentrations of the active drug, human pharmacokinetic data may provide adequate evidence to support the enhanced activity of the combination and demonstrate the contribution of the inactive drug. A confirmatory study of the combination would usually be needed to provide evidence of effectiveness for the combination (see section V.D).

Dose Finding

Dose-finding studies could be very important to refine the combination dose or doses and select doses for phase 3 trials. Depending on the role of each component, it may be

[6] Note that the placebo arm is intended to show the effect size compared to non-treatment, not to show the contribution of each component.

useful to test multiple doses of both components to establish a best dose in terms of risks and benefits. If one component in a two-drug combination is more active than the other, it may be more important to study multiple doses of the more active drug (as part of the combination). For the same reason, it may be more important to study multiple doses of a drug that is significantly more toxic than the other component of the combination. Other study designs and types of studies also may be appropriate.

D. Confirmatory Studies (Phase 3)

If findings from *in vivo* or *in vitro* models and/or phase 2 trials adequately demonstrate the contribution of each component to the combination, phase 3 trials comparing the combination to SOC or placebo generally will be sufficient to establish effectiveness. If the contribution of the individual components is not clear and it is ethically feasible to use a component or components of the combination as monotherapy in a study arm, it may be necessary to demonstrate the contribution of the components in phase 3 studies (e.g., by use of a factorial design). For example, if phase 2 data do not provide sufficient evidence of the contribution of each component of a two drug combination, but provide strong evidence that the combination is superior to one of the components, a phase 3 trial comparing the combination to the more active component alone and SOC may be needed to demonstrate that the less active component contributes to the activity of the combination. In this and other situations, it will often be useful to study more than one dose of the more active drug in phase 3 studies.

Unexpected toxicity (e.g., serious adverse events observed at higher than expected rates) in phase 2 trials is a potential complication for development of a combination and progressing to phase 3 trials. If the toxicity can be attributed to one component of the combination, it may be possible to conduct phase 3 trials with the combination using a lower dose or doses of the more toxic component. If the toxicity cannot be attributed to an individual component of the combination, additional studies may be needed to identify the more toxic component and appropriate dosing for the combination before initiating phase 3 trials. The specifics of any phase 3 design should be discussed with the appropriate FDA review division at an End-of-Phase 2 meeting.

VI. REGULATORY PROCESS ISSUES IN CODEVELOPMENT

Sponsors should consider a number of regulatory issues when planning the codevelopment of two or more novel drugs for use in combination. Key issues are outlined below.

A. Early Interaction with FDA

Sponsors are encouraged to communicate as early as possible (e.g., pre-IND meeting) with the appropriate FDA review division when considering codevelopment of innovative combination therapy. Sponsors also are encouraged to consult FDA frequently throughout the development process. We believe such communication will help facilitate development of the combination therapy.

B. IND Submissions and Marketing Applications

Decisions about the type of IND submission(s) and marketing application(s) needed (e.g., individual component submissions, combination submission) will depend on the sponsor's overall codevelopment and marketing strategy. Until FDA has more experience with codevelopment, FDA recommends that these decisions be made on a case-by-case basis in consultation with the appropriate review division.

C. Labeling Issues

FDA also anticipates that the content of labeling for the combination and/or the components will be case specific, depending on the nature of the combination, the intended uses of the individual components, the marketing strategy, and other factors. Therefore, FDA does not believe it can provide generally applicable labeling guidance at this time. Again, we recommend consultation with the appropriate review division.

D. Pharmacovigilance

Applicants should develop a pharmacovigilance plan that takes into account the additional postmarket risks presented by initial marketing of two or more previously unapproved drugs for use in combination (compared to risks associated with marketing of a single drug). Risk will vary, depending on the nature of the combination and how the combination is marketed. The risk assessment should consider, among other things:

- Potential for use of each drug individually;
- Potential for use of any of the components of the combination in combinations with other drugs; and
- Drugs likely to be co-administered with the combination.

Applicants should discuss their pharmacovigilance plans with the appropriate review division and the Office of Surveillance and Epidemiology.