Guidance for Industry

Codevelopment of Two or More New Investigational Drugs for Use in Combination

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

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Clinical Medical

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Office of Communications
Division of Drug Information, WO51, Room 2201
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993
Phone: 301-796-3400; Fax: 301-847-8714
druginfo@fda.hhs.gov
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

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Contains Nonbinding Recommendations

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I. INTRODUCTION

This guidance is intended to assist sponsors in the codevelopment[2] of two or more new drugs that have not been previously developed for any indication to be used in combination to treat a disease or condition. For purposes of this guidance, these not-previously-developed drugs are referred to as *new investigational drugs*. The guidance provides recommendations and advice on how to address certain scientific and regulatory issues that may arise during codevelopment of two or more new investigational drugs. It is not intended to apply to development of fixed combinations of previously approved drugs or to development of a single new investigational drug to be used in combination with a previously approved drug or drugs. FDA believes the recommendations in this guidance relevant to demonstrating the contribution of the individual new investigational drugs to the effect(s) of the combination are consistent with the requirements of 21 CFR § 300.50, "fixed-combination prescription drugs for humans." This guidance applies only to drugs and biological products regulated by the Center for Drug Evaluation and Research.[3] The guidance is not intended to apply to biological products regulated by the Center for Biologics Evaluation and Research or medical devices.

[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] The term *codevelopment* as used in this guidance refers to the concurrent development of two or more new investigational drug products that are intended to be used in combination to treat a disease or condition. A sponsor may elect to codevelop two or more new investigational drug products to be marketed as individual agents intended to be used in combination as a fixed-combination or co-packaged drug.

[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, on the Internet at

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. BACKGROUND

Combination therapy is an important treatment modality in many disease settings, including cancer, cardiovascular 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 to develop new therapeutic approaches using combinations of drugs directed at multiple therapeutic targets to improve treatment response, minimize development of resistance, or minimize adverse events. In settings in which combination therapy provides significant therapeutic advantages, there is growing interest in the development of combinations of new investigational drugs.

Because existing developmental and regulatory pathways focus primarily on assessment of the safety and effectiveness of a single new investigational drug acting alone, or in combination with a previously approved drug, FDA believes guidance is needed to assist sponsors in the codevelopment of two or more new investigational 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 new investigational 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

Codevelopment generally will provide less information about the clinical safety and effectiveness and dose-response of the individual new investigational drugs intended to be used in combination than would be obtained if the individual drugs were developed alone. How much less information will vary depending on a variety of factors, including the stage of development at which the individual new investigational drugs 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 each drug in the combination beyond phase 1 testing. Because co-development generally will provide less information about the individual new investigational drugs, it may present greater risk compared

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http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/default.htm.

to clinical development of an individual drug. Given this concern, FDA believes that codevelopment should ordinarily be reserved for situations that meet all of the following criteria:

- The combination is intended to treat a serious disease or condition.[4]

- There is a strong biological rationale for use of the combination (e.g., the agents inhibit distinct targets in the same molecular pathway or steps in disease pathogenesis, 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 full nonclinical characterization of the activity of both the combination and the individual new investigational drugs, or a short-term clinical study on an established biomarker, suggests that the combination may provide a significant therapeutic advance over available therapy and is superior to the individual agents[5] A nonclinical model should demonstrate that the combination has substantial activity and provides greater activity, a more durable response (e.g., delayed resistance), or a better toxicity profile than the individual agents.

- There is a compelling reason why the new investigational drugs cannot be developed independently (e.g., monotherapy for the disease of interest leads to resistance, 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 a combination.

[4] For purposes of this guidance, the term *serious disease or condition* refers to a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one. This definition is consistent with various statutory and regulatory provisions concerning the use of FDA-regulated medical products to treat serious or life-threatening diseases and conditions. See, e.g. § 561 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 USC § 360bbb) and corresponding regulations (21 CFR part 312 subpart I) regarding expanded access to unapproved therapies and diagnostics; § 505-1 of the FD&C Act (21 USC § 355-1) regarding Risk Evaluation and Mitigation Strategies; FDA regulations at 21 CFR part 314 subpart H and 21 CFR part 601 subpart E regarding accelerated approval; and § 506 of the FD&C Act (21 USC 356 regarding fast track development and designation.

[5] For purposes of this guidance, the term "available therapy" is interpreted as it is described in the guidance for industry on *Available Therapy*. This guidance is available on the CDER guidance page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

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 tuberculosis).

Sponsors should develop evidence to support the biological rationale for the combination in an in vivo (preferable) or in vitro model relevant to the human disease or condition the product is intended to treat. The model should compare the activity of the combination to the activity of the individual drugs. The model should demonstrate that the combination has substantial activity and provides greater activity, a more durable response (e.g., delayed resistance), and/or a better toxicity profile than the individual new investigational drugs. In addition to valuable activity data, a relevant model may provide information about the relative doses of the individual new investigational drugs.

B. Nonclinical Safety Characterization

For detailed recommendations regarding nonclinical safety characterization for two or more new investigational drugs to be used in combination, sponsors should consult the International Conference on Harmonisation (ICH) guidance on nonclinical safety studies (ICH M3(R2)).[6] Section XVII of ICH M3(R2) (Combination Drug Toxicity Testing) includes a discussion of nonclinical safety studies appropriate in a combination drug development setting involving two early stage entities. ICH M3(R2) 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 type of development described in this guidance. In situations in which it is possible to obtain only limited clinical data for the individual new investigational 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 below). For codevelopment of anticancer combinations, sponsors should consult the guidance for industry ICH *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals*.[7]

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[6] See the ICH guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization* at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. ICH M3(R2) is a revision of the 1997 ICH guidance *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals.*

[7] See the ICH guidance for industry ICH *S9 Nonclinical Evaluation for Anticancer Pharmaceuticals* at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm085389.pdf

V. CLINICAL CODEVELOPMENT

This section provides a general roadmap and guiding principles for concurrent clinical development of two or more new 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 drugs in the combination.

Note: The appropriate review division should 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 both the individual new investigational drugs and the combination and to provide data to support appropriate dosing for the combination in phase 2 testing.

1. Safety of the Individual New Investigational Drugs

Whenever possible, the safety profile of each individual new investigational drug should be characterized in phase 1 studies in the same manner as would be done for the 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 new investigational drugs in humans (e.g., where drug toxicity prevents use of healthy volunteers and even short duration 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 interaction data, 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 primarily from the phase 1 safety data for the individual new investigational drugs, if available. If phase 1 safety data for the individual drugs are unavailable, nonclinical data for the combination may be needed to determine the initial combination dose in humans (see previous section). Phase 1 safety studies of the combination may also be important in some cases because

of the potential for additive toxicity. One study design that could be used is sequential testing in which subjects get drug A, then drug B, then A and B together.

B. Clinical Pharmacology

The sponsor should conduct the same clinical pharmacology studies for each of the individual new investigational drugs in the combination as would be done if the drugs were being developed separately — including assessment of bioavailability, characterization of pharmacokinetics, and mass balance. Studies to evaluate the effects of intrinsic (such as renal impairment and hepatic impairment) and extrinsic (such as food effect and drug interactions) factors on pharmacokinetics and pharmacodynamics, and exposure-response could be conducted either with the individual drugs or the combination. The role of pharmacogenomics should be investigated and incorporated into the combination drug development plan to identify potential sources of pharmacokinetic or pharmacodynamic variability.

The evaluation of drug interaction potential should follow the same sequence as is used in other development programs; results of in vitro drug metabolism and drug transporter studies would inform the need for in vivo drug interaction studies.

If feasible, dose-response should be evaluated for each individual new investigational drug in the combination. The results of such studies should be used to determine doses at which to further explore the combination. If the individual new investigational drugs cannot be administered alone, various doses of each drug administered in combination should be assessed. If one drug has no activity or minimal activity when used alone, dose-response should be assessed when the individual drugs are administered in combination using a number of different doses of both the active drug and the inactive drug. A similar approach should be used to evaluate dose-response where each drug in the combination has minimal activity when used alone.

Response should also 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 phase 2 and phase 3 trials. In phase 3 trials, use of more than one dose of each of the drugs in the combination should be considered to increase exposure ranges and further assess dose-response.

C. Proof of Concept Studies (Phase 2)

In general, phase 2 testing should accomplish the following for a given combination:

- Further demonstrate the contribution of each individual new investigational drug in the combination to the extent possible and needed (i.e., to the extent not sufficiently established by existing 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 or condition the combination is intended to treat, and other factors. A factorial study designed to assess the effects attributable to each drug in the combination is generally the preferred design to support combination use. However, there may be circumstances in which it would be inappropriate to use one or more of the drugs in the combination as monotherapy in studies of the disease or condition of interest, or it would only be possible to administer the individual drugs in the combination as monotherapy for short durations. In these circumstances, a factorial design will have limited utility.

The following scenarios illustrate possible phase 2 study designs for combinations of two new investigational drugs in different situations. Scenario 1 includes a discussion of a standard factorial design as well as an adaptive factorial design that could be used if there is uncertainty about using the individual drugs as monotherapy. Scenario 2 describes an alternative design that may be useful when the drugs in the combination cannot be administered as monotherapy. Scenario 3 describes a design that might be used when one drug in the combination has minimal or no activity and is intended primarily to enhance the activity of the other drug.

Scenario 1: Each new investigational drug alone has activity and they can be administered separately

If in vitro studies, in vivo animal models, or phase 1 or other early clinical studies indicate that each new investigational drug has some activity, but the combination appears to have greater activity, and rapid development of resistance is not a concern, a four-arm, phase 2 trial in the disease or condition of interest comparing the combination to each drug alone and to placebo or standard of care (SOC) (AB v. A v. B v. SOC or placebo[8]) should be used to demonstrate the contribution of the individual drugs to the combination and proof of concept. If SOC is a known effective therapy (not solely palliative), 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[9] with the same four treatment arms might also be used where appropriate, initially using the treatment arms described above and terminating the single-drug arms early if it becomes clear that the single agents have much less activity than the combination. Such a design may demonstrate the contribution of each drug to the activity of the combination without exposing the large number of patients typically required for phase 3 trials to therapeutic products with inadequate activity. When determining whether to terminate monotherapy treatment arms early, it may be necessary to use endpoints that provide evidence of treatment effect more readily than endpoints that would be used in confirmatory phase 3 trials to minimize the amount of time subjects may be exposed to a low activity drug. For example, it may be preferable to use viral

[8] Note that in this scenario the placebo arm is intended to show the effect size compared to no treatment, not to show the contribution of each drug.

[9] See the draft guidance for industry *Adaptive Design Clinical Trials for Drugs and Biologics.* This draft guidance is available at http://www.fda.gov/downloads/Drugs/.../Guidances/ucm201790.pdf.

load, response rate, or a persuasive pharmacodynamic or other biomarker rather than survival or cure rate.

Scenario 2: The individual new investigational drugs in the combination cannot be administered separately

If in vitro studies, in vivo animal models, or phase 1 or other early clinical studies indicate that the individual new investigational drugs in the combination cannot be administered separately in clinical trials in the disease of interest (e.g., because such testing would involve administering treatment known to be ineffective as monotherapy), or cannot 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 effective therapy (not solely palliative), an add-on design could be used comparing the combination plus SOC to placebo plus SOC.

In some resistance scenarios, it may be possible to administer the individual drugs in the 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 could be administered as monotherapy for 3 days to establish antiviral activity and for initial dose exploration. For DAA studies of longer duration, the combination should be used or the individual drugs should be added to an active control.[10]

Scenario 3: When administered separately, one new investigational drug in the combination is active and one is inactive

If in vitro studies, in vivo animal models, or phase 1 or other early clinical studies suggest that one of the new investigational drugs in the combination 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 new investigational drug could be demonstrated using a three-arm comparison of the active drug alone, the combination, and SOC (A v. AB 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. placebo + SOC).

If the inactive drug in a combination contributes to the activity of the combination only by increasing the systemic concentrations of the active drug, human pharmacokinetic data

[10] See the draft guidance for industry *Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Agents for Treatment* (section III.A.4.b – Phase 1b (proof-of-concept) trials)) or consult the Division of Antiviral Drug Products in CDER for more specific recommendations. This draft guidance is available on the CDER guidance page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

may provide adequate evidence to support 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 new investigational drug, it may be useful to test multiple doses of both drugs to establish the optimal combination dose in terms of risks and benefits. If one new investigational drug 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 drug in the combination. Other study designs and types of studies also may be appropriate.

D. Confirmatory Studies (Phase 3)

The appropriate phase 3 study design generally will be a case-by-case determination based on what has been previously demonstrated about the effects of the combination and the individual new investigational drugs, the feasibility of monotherapy and SOC alone treatment arms, and other factors. For example:

- If findings from in vivo or in vitro models and/or phase 2 trials adequately demonstrate the contribution of each new investigational drug 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 new investigational drugs is not clear and it is ethically feasible to use one or more of the individual drugs as monotherapy in a study arm, the contribution of the individual drugs could be demonstrated using a factorial design (see Scenario 1 in section V.C). It may be possible to do a factorial study using only active drug treatment arms (AB v. A v. B). This design would be adequate to demonstrate the contribution of each new investigational drug, but would not be able to directly measure the overall treatment effect. However, if the effect of SOC is well-established and known to be small, it may be possible to estimate the treatment effect of the combination without a concurrent SOC or placebo arm.

- If phase 2 data do not provide sufficient evidence of the contribution of each new investigational drug in a two-drug combination, but do provide strong evidence that the combination is superior to one of the drugs alone, a two-arm design comparing the combination to the more active drug alone (AB v. A) may be needed to demonstrate that the less active drug (B) contributes to the activity of the combination. In this situation, it may be useful to study more than one dose of the more active drug.

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 drug in the combination, it may be possible to conduct phase 3 trials with the combination using a lower dose or doses of the more toxic drug.

If the toxicity cannot be attributed to an individual drug in the combination, additional studies may be needed to identify the more toxic drug 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 new investigational 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 CDER review division when considering codevelopment. Sponsors also are encouraged to consult FDA as needed throughout the development process. We expect that such communication will help facilitate development of the combination therapy.

B. Investigational New Drug Applications (INDs)

1. INDs for the Combination and the Individual New Investigational Drugs

Decisions about IND submissions required under 21 CFR part 312 for the combination and individual new investigational drugs in the combination will depend on the development objectives and the timing of the decision to pursue codevelopment. The following general principles apply:

- If a sponsor intends to undertake codevelopment as described in this guidance, there should be one IND for the combination that covers all of the drugs in the combination at the point in time at which the sponsor initiates clinical studies of the combination.

- If a sponsor is undecided about development of a combination, it may be appropriate to conduct preliminary proof-of-concept clinical studies for the combination under an IND for one of the drugs in the combination, provided that there is a single agent IND in effect for each drug in the combination (i.e., provided FDA has the information required under the IND regulations for each of the drugs). If the sponsor then decides to pursue development of the combination, it could do so under the single agent IND (which will become the combination IND) or submit a new IND for the combination.

- If a sponsor intends to develop a combination and develop one or more of the drugs in the combination for use as a single agent, there should be a separate IND for the combination and each of the individual drugs being developed.

- If the individual drugs in a combination would be reviewed by different review divisions within FDA, the combination IND should be submitted to the division that has jurisdiction over the indication for the combination.

Decisions about IND submissions for codevelopment scenarios that are not covered by these general principles will be determined on a case-by-case basis in consultation with the appropriate review division(s).

When submitting an IND for a combination, sponsors may cross-reference existing INDs for the individual drugs in the combination. If the sponsor of the combination IND is not the sponsor of the IND for one of the drugs used in the combination, the sponsor of the combination IND must obtain written authorization to cross-reference any content in the other sponsor's IND that is used to support the combination IND (§ 312.23(b)).

2. IND Safety Reports

In cases in which there is an active IND for the combination and active INDs for one or more of the individual drugs in the combination, IND safety reports required under § 312.32(c) for adverse events that occur in studies of the combination should be submitted to the IND for the combination and all INDs for the individual drugs in the combination. If a reportable adverse event occurs in a study of one of the individual drugs in the combination, the report should be submitted to the IND for that individual drug and to the IND for the combination.

The IND safety report submitted to the IND for the study in which the adverse event occurred is considered the original report. Reports submitted to other INDs should be clearly identified as duplicates to ensure that the same adverse event is not counted more than once. If a report is submitted to multiple INDs, each IND safety report should identify all INDs to which the report is submitted.

3. IND Annual Reports

There must be separate IND annual reports (21 CFR 312.33) for the combination IND and any individual drug INDs. The reports should cross-reference each other. Each annual report should identify all INDs to which the report is cross-referenced.[11]

4. Other IND Submissions

Where there is a combination IND and INDs for one or more individual drugs, sponsors should consider whether the information in a planned IND submission is relevant to only one IND or to multiple INDs. Consider the following examples:

- A protocol submission for a study of the combination should be submitted only to the combination IND.

- Chemistry, manufacturing, and controls for the combination should be submitted only to the combination IND.

[11] Also see the ICH guidance for industry *E2F Development Safety Update Report*, section II.E, available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

- A nonclinical information amendment describing carcinogenicity studies with the combination should be submitted to the combination IND and any INDs for the individual drugs in the combination.

Where information is relevant to more than one IND, the information can be submitted in its entirety to each IND or can be submitted to one IND and cross-referenced in the other INDs.

C. Marketing Applications

In general, decisions about the type or types of marketing application(s) to be submitted for a drug-drug combination (e.g., combination application, individual drug applications) will depend on how the applicant intends to market the combination and the individual drugs, as well as the data submitted in support of the application. We anticipate that applications will be submitted and user fees assessed consistent with FDA's user fee bundling policy (see Guidance for Industry, *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*). The following examples illustrate how we anticipate applications may be submitted for different types of combinations, but FDA should be consulted prior to making any of the submissions discussed in this section:

Example 1: If the individual drugs in the combination will be marketed as distinct products (separate packaging), a separate marketing application for each drug in the combination should be submitted.

Example 2: In Example 1, if the applicant also intends to market one or more of the drugs in the combination for use as monotherapy, the same marketing application can be used for the combination and monotherapy uses.

Example 3: If the drugs in the combination will be marketed as a combination drug product (i.e., either a co-packaged or a fixed-combination drug), a single marketing application for the combination should be submitted.

Example 4: In Example 3, if the applicant also intends to market one or more of the drugs in the combination for use as monotherapy, a separate marketing application should be submitted for the individual drug(s) for monotherapy use.

Example 5: If the individual drugs in a combination drug product are marketed first as a co-packaged drug, an application for a corresponding fixed-combination drug may be submitted as a supplement to the co-packaged drug application.

Other examples not listed here should be discussed with FDA.

If an application cross-references any information in an IND or marketing application not owned by the applicant that is needed to support approval of the marketing application, the application must contain a written authorization to cross-reference such information (21 CFR 314.50(g)(1)).

D. Labeling

Decisions about how to meet the labeling requirements in 21 CFR 201.57 will also depend on how the applicant intends to market the combination.

- If the individual drugs in the combination will be marketed together as a combination drug product (either a fixed-combination or co-packaged drug), the prescribing information for the combination should be a single document describing use of the combination.

- If the individual drugs in the combination will be marketed as distinct products intended for use in combination, there should be separate prescribing information for each distinct product. The prescribing information for each drug should include pertinent information concerning the safe and effective use of the combination, reference the labeling of the other product(s), and state that the drug was developed and studied for use in combination with the other drug(s).

There are a range of other potential scenarios in which one or more of the drugs in a combination may be limited to combination use only, or may be indicated for combination use, monotherapy, and/or in combination with drugs other than those with which the drug was codeveloped. It is advisable for applicants to consult FDA concerning their specific circumstances.

Decisions about how to provide patient-directed information such as a Medication Guide or administration instructions should be made on a case-by-case basis in consultation with FDA.

E. Postmarketing Safety Monitoring Considerations

Postmarketing safety monitoring should consider additional postmarketing risks that may be presented by initial marketing of two or more new investigational drugs for use in combination as compared to the risks associated with marketing a single new investigational drug. Risks will vary depending on the nature of the combination and how the combination is marketed. Applicants should consider potential postmarketing risks from, among other things:

- Potential for use of each drug individually;
- Potential for use of any of the drugs in the combination with marketed drugs other than those with which the drugs were codeveloped; and
- Other drugs likely to be co-administered with the combination.

FDA encourages sponsors to consult with the appropriate FDA divisions to discuss their proposed approach to postmarketing safety monitoring.