



February 14, 2011

Division of Dockets
Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2010-D-0616: *Draft Guidance for Industry on Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination; Availability*; 75 Federal Register 78259; December 15, 2010

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to provide comments to the above noted docket. PhRMA represents the country's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. PhRMA companies are leading the way in the search for new cures. PhRMA members alone invested an estimated \$45.8 billion in 2009 in discovering and developing new medicines. Industry-wide research and investment reached a record \$65.3 billion in 2009.

PhRMA appreciates FDA's efforts in developing guidance for industry concerning the codevelopment of two or more novel not previously marketed drugs to be used in combination to treat a disease or condition. A PhRMA subject matter expert team with expertise in drug regulatory affairs was assembled and has reviewed the draft Guidance. PhRMA's response starts with general comments on the overall Guidance and is then followed by more specific line-by-line comments. These comments are intended to provide constructive feedback and recommendations on the criteria for when codevelopment is an appropriate option, nonclinical and clinical development programs, and regulatory processes.

We appreciate the opportunity to provide comments on the *Draft Guidance for Industry on Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination*, and we trust our comments will be useful to the FDA in finalizing this guidance.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'S. Haverfield-Gross'.

Sascha Haverfield-Gross, Ph.D.
Deputy Vice President
Scientific and Regulatory Affairs

A. Overall Comments

PhRMA commends the Agency for developing guidance on the subject of co-development of two or more un-marketed investigational drugs for use in combination. Co-development in the setting of more than one investigational product raises unique scientific and regulatory questions that, heretofore, have remained unaddressed in formal guidance. The draft guidance provides unambiguous clarification that the co-development of investigational agents, with the aim of supporting significant advances in therapeutic options, is a fully acceptable regulatory principle. In general, the draft provides much-needed, high-level advice that we believe will establish basic principles to guide co-development and, when finalized, will be beneficial, not only to sponsors, but to Agency reviewers as well. Further, we appreciate the fact that, while establishing certain standards for co-development of investigational products, the draft guidance recognizes the need for flexibility, case-by-case assessment, and the need to consult with Agency review staff.

We appreciate the fact that neither the industry nor FDA have significant regulatory experience in co-development of two or more investigational drugs for use in combination. Therefore, we recognize the necessity of maintaining the narrow focus of the current document to facilitate timely publication of advice in this situation. However, we recommend the Agency give consideration to the need for future development of guidance on co-development in other situations excluded from the scope of the current draft. Such situations may include co-development of two or more investigational agents for use in combination for other than serious conditions; co-development when the components can (and perhaps will) also be developed as monotherapy, or co-development of an investigational agent with an approved drug. The latter may include, among other things, development that involve a different dose or dose regimen of the approved drug, development for an indication for the combination that differs from the one approved for the marketed drug, development for use in a different population, or a combination of these purposes.

B. Determination of Whether Codevelopment is an Appropriate Option

The draft guidance provides 4 criteria on which to make a determination that co-development is an appropriate option. These include (1) the seriousness of the disease or condition; (2) a compelling rationale, which, for example, may include the potential for increased safety (reduced doses to minimize toxicity) or decreased resistance; (3) preclinical or short term clinical evidence of substantial activity AND “greater than additive activity” than the individual agents alone; and (4) a compelling reason that the agents cannot be developed individually.

We respectfully request the Agency to reconsider imposing a requirement for “greater than additive” activity. First, it is unclear what this phrase means in the context of a combination that may significantly improve the safety or tolerability of treatment, perhaps with no increase or only a small incremental increase in efficacy. Second, it implies a direct, quantitative relationship between “activity,” as measured in preclinical or early short term clinical studies, and the ultimate benefit to patients. Third, the 2nd criterion requires a compelling biological rationale for which the sponsor would necessarily take into consideration for the target disease and population. If this rationale is compelling there should be no reason for activity to be “greater than additive.” Fourth, potentially

useful combinations with substantial activity should not be categorically rejected for further exploration based on early data simply because those data did not show the combined activity to be greater than additive. We believe imposing a requirement for “greater than additive” activity will inappropriately limit development of potentially valuable products for use in combination.

C. Nonclinical Considerations

The existing FDA guidance on nonclinical safety evaluation to support co-development of investigational drugs, such as ICH S9¹ and ICH M3(R2)², contains valuable general principles that should be emphasized in the draft co-development guidance. PhRMA recommendations are outlined below as follows:

1.) Add reference to ICH S9 guidance and clarify the general principles applicable from both ICH M3(R2) and S9. Although ICH S9 guidance is for oncology candidate drugs, FDA should highlight the general applicability of this guidance for serious diseases, when pharmacology studies may support the conduct of the clinical combination trials based on support from individual-drug nonclinical studies; combination nonclinical programs may not be required, if a complete individual-drug nonclinical set of studies could support the combination human program. The general principle that combination toxicology studies could support a combination only clinical program outlined in ICH M3(R2), in section XVII, is the type of flexibility that is also desirable and could be emphasized in the current draft co-development guidance because this principle represents the situational nature of drug development and is appropriate when the main focus of development is combination therapy. However, reference to ICH M3(R2) and S9 requires some clarification in one instance because of the general nature of the nonclinical guidance cited in ICH M3(R2) compared to ICH S9 (combination program guidance for a serious disease setting). ICH M3(R2) guidance differs from S9 in section XVII. Combination Drug Toxicity Testing (17), where ICH M3(R2) recommends, “For combinations of two early stage entities, nonclinical combination toxicity studies are recommended to support clinical trials.” Consequently, as mentioned previously above, FDA should emphasize the general principle from ICH S9 that combination nonclinical programs may not be required when a complete individual-drug nonclinical set of studies support the combination human program.

2.) Allow for bracket dosing range in nonclinical studies: Since the clinical development of such a combination product can be complicated (see Section V), and especially where optimization of doses of the individual components will be determined based upon clinical experimentation, a comment should be added to Section IV.B stating that dosing ranges of individual components, whether conducted individually or in combination ratios, should be sufficient to bracket the anticipated exposures and combination ratios intended to be studied in clinical trials.

¹ International Conference on Harmonization. Guidance for Industry S9 Nonclinical Evaluation for Anticancer Pharmaceuticals. March 2010

² International Conference on Harmonization. Guidance for Industry M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. January 2010.

In conclusion, PhRMA recommends FDA refer to both existing ICH M3(R2) and S9 guidance with the clarifications identified above and also please emphasize within the co-development guidance that FDA allow for a bracket dosing range in nonclinical studies.

PhRMA Comment on Draft Guidance for Industry on Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination

Docket number: FDA-2010-D-0616

SPECIFIC COMMENTS ON TEXT**GUIDELINE SECTION TITLE: I. INTRODUCTION**

Line Number	Comment and Rationale	Proposed change (if applicable)
42	The guidance is lacking on pharmacovigilance and adverse event reporting. Unclear, if FDA is expecting that the PV plan to be submitted to the review Division prior to first human clinical studies (i.e. part of the IND). It would be good for FDA to clarify/confirm this	Suggest FDA reference existing guidance on pharmacovigilance (Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005), and REMS (Draft Guidance for Industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications).
48	After line 48 please add following statement "For nonclinical development refer appropriate guidance documents (S9, M3(R2))."	For nonclinical development refer appropriate guidance documents (ICH S9, Guidance for Industry S9 Nonclinical Evaluation for Anticancer Pharmaceuticals, March 2010; ICH M3(R2), Guidance for Industry M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals, January 2010).

GUIDELINE SECTION TITLE: II. BACKGROUND

Line Number	Comment and Rationale	Proposed change (if applicable)
64-65	Can reduced side effects be added to this sentence to expand the possible uses?	This increased understanding has provided further impetus for new therapeutic approaches using combinations of drugs directed a multiple therapeutic targets to improve treatment response or minimize development of resistance <i>or reduce toxicity or side effects</i> .

GUIDELINE SECTION TITLE: III. DETERMINING WHETHER CODEVELOPMENT IS AN APPROPRIATE DEVELOPMENT OPTION		
Line Number	Comment and Rationale	Proposed change (if applicable)
83-85	<p>‘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 were developed alone.’</p> <p>It should be clarified that this statement is only true for Clinical data. We would expect to have at least the same amount of nonclinical safety and effectiveness data</p>	Concurrent development of two or more novel drugs for use in combination generally will provide less information about the clinical safety and effectiveness of the individual drugs were developed alone
92	The use of the term “activity” without specifying whether it includes evaluation of safety (in addition to efficacy) leaves the guidance unclear in several areas where the term “activity” is used. By defining the term “activity” this ambiguity can be resolved.	Unless specified otherwise, the use of the term "activity" in this guidance includes an evaluation of both the safety and effectiveness of a drug or combination of drugs. For example, a combination that is judged to have "greater than additive activity" could have equal or even lesser efficacy than the individual agents alone so long as the improved safety of the combination is of particular importance for the intended use.
95	Clarify the term “serious disease or condition”.	Cross reference the following guidances: Jan. 2004 draft “Guidance for Industry: Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions,” and Jan. 2006 “Guidance for Industry: Fast Track Drug Development Programs — Designation, Development, and Application Review” for definition of serious disease or condition, as well as the CFR (21 Part 312.300(b)).
97 – 100	Please provide more guidance on establishing “compelling biological rationale”	Unbiased, high-throughput screening for drug combinations can identify novel and effective treatments without prior knowledge of the underlying scientific rationale. When a drug combination is identified via high-throughput screening, establishing "compelling biological rationale" may prove more challenging. Please clarify the level of biological rationale needed to proceed with clinical testing when the drug combination demonstrates substantial and robust activity in preclinical models.

102 -105	It is unclear how to define additive activity via a biomarker. Some examples would be extremely helpful.	Perhaps an additional step forward is to better understand the guidance for developing these drugs from a biomarker-based strategy. For instance, if we see that there is a biomarker for response in combination compared with single agents -- is that a potential path forward? Also, some clarification about developing within one tumor type versus multiple tumor types if the mechanism (especially if supported by a biomarker) is both conserved and sufficiently compelling.
102-107	The phrase “greater than additive activity” sets a high hurdle for sponsors, particularly in areas where an unmet medical need may exist (e.g. oncology).	The development of combination therapy should be encouraged when the risk:benefit of the combination is reasonably likely to be more clinically meaningful than each component individually (eg. A=5unit effect, B=5units, A+B=8 units; A=5 unit effect, B=5units, A+B=8 units). Lower dose(s) in combination may provide sufficient efficacy but lower toxicity to provide superior risk benefit without greater than additive efficacy.
281	<p>Additivity: Within combinations the term additivity has a specific meaning, usually referring to Loewe additivity, but also sometimes referring to Bliss additivity or other definitions. (These are different to the normal arithmetic additivity of $2+2=4$). There are a number of similar, but technically different, methods for assessing additivity or synergy (a greater response than additivity).</p> <p>A combination can still provide a clinical benefit even while not demonstrating synergy, i.e. just being additive. Consider a situation where 2 drugs both give a response of 5 units at their respective MTDs, and that if they are co-administered at their MTDs this is tolerated by the patients and gives a response of 7 units. There is a clinical benefit of 2 units of the combination over either monotherapy, however this additional response could just be in line with what would be expected from the greater total dosing load from the two compounds in combination, i.e. it is additive rather than synergistic.</p>	<p>Synergy or greater than additivity represents a higher hurdle than clinical benefit over monotherapy. This may be appropriate if the rationale for the combination is purely efficacy driven, but be less appropriate if the rationale for the combination is improved safety and tolerability through dose reduction.</p> <ol style="list-style-type: none"> 1. Does the agency really mean “greater than additive efficacy”, or do they mean “greater than monotherapy efficacy”? 2. Does “greater than additivity” refer to any specific definition of additivity, or method of assessing it?
110	The option of reduced toxicity should be added.	

GUIDELINE SECTION TITLE: IV. NONCLINICAL CODEVELOPMENT		
Line Number	Comment and Rationale	Proposed change (if applicable)
119-126	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.	Consider adding a statement that in some cases, a particular combination may be derived empirically through a combinatorial high-throughput approach, with incomplete understanding of the underlying biology, and such a combination should be a good candidate for co-development.
128-136	The statements made in lines 128-132 of the draft guidance indicate that ordinarily, the combination should be shown to have “greater than additive activity or a more durable response” than either component alone. There are examples, especially with oncology drugs, where compounds do not have to demonstrate greater than additive interactions in preclinical models in order to provide clinical benefit as a combination. The key issue is whether the combination shows greater in vivo activity (e.g., inhibition of tumor growth) than either monotherapy separately. Characterizing the interaction as additive, synergistic, or antagonistic is complex to calculate in vivo and is not as relevant as the net effect.	<p>This sentence could be modified to read: “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 <u>and the predicted clinical safety margin.</u>”</p> <p>If the intent line 133-134 is to indicate that evidence of therapeutic effect or efficacy in a pathophysiological animal model of the intended human disease/condition is not generally necessary, then the following language would be clearer:</p> <p><i>‘An animal model of <u>efficacy</u> generally would not be necessary’</i></p> <p>We suggest that in this guidance the use of ‘activity’ refer to anticipated (e.g. consistent with known or suspected pharmacology) or unanticipated effects observed or measured in non-clinical in vitro and in vivo studies and in clinical trials using volunteers (Phase I), and that ‘efficacy/effectiveness’ be reserved for observations/measurements relevant to the therapeutic indication and made in the relevant human patient population(s), or animal model thereof.</p>

128-129,133-134	In lines 128-129, it is stated that the biological rationale for the combination should be evidenced in an <i>in vivo</i> (preferable) or <i>in vitro</i> model. However, lines 133-134 state that “An animal model of activity generally would not be necessary.” In addition, lines 102-105 also refer to a preclinical model which should be used to show that the combination has substantial activity and provides greater than additive activity. It would be very helpful if these statements are clarified to avoid any potential contradictory interpretations.	
149	How much more and what type of data will be needed?	

GUIDELINE SECTION TITLE: V. CLINICAL CODEVELOPMENT		
Line Number	Comment and Rationale	Proposed change (if applicable)
169	The “safety of the individual components”	We recommend including in the guidance reference to ICH E8 and other relevant guidance documents that address the safety of individual compounds.
171-174	The draft guidance states that whenever possible the maximum tolerated dose (MTD) should be determined for the individual drugs being considered for a combination study. There are instances where MTD may not be reached or required in a study, in lieu of reaching an appropriate therapeutic index. We suggest the reference to determination of MTD be provided as an example rather than a possible requirement.	We recommend replacing “whenever possible” with “in general”.
183-186	Line 186 indicates non clinical data for the combination to include PK, TK and biomarker.	Anti-cancer treatments are an exception, except as outlined in ICH S9 (pages 6-7).
193-202	If the Phase I safety data for the components are unavailable, non clinical data for the combination will be needed to determine the initial combination dose.	Provide more guidance on how to determine the safe starting dose of the combination.

200-202	“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.”	Clarify – is FDA referring to individual patient cross-over of each agent then the combo? If so, in oncology, this is rarely done since treatment in early phase is in late-stage patients, and therapy is administered until response/progression/toxicity. Large molecules (and even some small molecules) often need multiple dosing to get to a steady state. This type of design should not be advocated for all disease states, ie. Oncology.
200-202	We request the Agency to use caution in requesting sequential testing of the combination in order to support dosing in subsequent studies, particularly for indications/drugs where these studies must be conducted in patients. Important patient safety issues such as the development of resistance or tolerance, as well as considerations of suboptimal dosing, in a sequential study must be considered (for example in HIV and oncology). Therefore, it may be most prudent that a case-by-case approach should be recommended for the early combination studies.	
204-236	It is likely that this guidance document will be utilized to develop novel treatments for oncology and antiviral treatments for HIV or HCV. We therefore urge the Agency to consider these types of drugs, and the general concept that treatment most often occurs at MTD, when prescribing recommendations for dose-response and drug-interactions. We would appreciate if the language in the guidance was broadened, or if it was acknowledged that classic dose-response evaluations may not be appropriate for all indications, or all combinations of drugs. For example, in development of oncology or anti-HIV combinations it would be most appropriate to initiate the combination studies as close to MTD for both as is feasible.	
204	It would be preferable to require the same information, rather than prescribing how studies should be done.	The sponsor should obtain the same clinical pharmacology information for each of the individual drugs in the combination...In general, such information...

206-208	The draft guidance recommends extensive clinical pharmacology studies for each individual drug used in the combination. If there are no plans to develop the drugs individually, then undue burden will be placed on the sponsor to evaluate the clinical pharmacology parameters for each drug and the combination. If the drugs will only be developed as a combination, we suggest clarifying these lines to indicate that the clinical pharmacology studies (including special populations, drug interactions) are recommended for the combination and not the individual drugs, as this will be more meaningful for the development process.	
206-212	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 developed separately.	Is it acceptable to do the 14C mass balance/metabolism studies on each individual compound and not on the combination? Please clarify this and include both nonclinical (140-147) and clinical guidelines (206-212).
211-212	The intrinsic (such as renal impairment and hepatic impairment) and extrinsic (such as food effect and drug interactions) factors should be addressed in a combination study.	For the sentence suggesting that intrinsic and extrinsic factors could be addressed in a combo study as opposed to being assessed with individual drugs (as outlined in the accompanying paragraph) it would be helpful to provide examples where the assessment in combination would be preferred over assessment of drugs individually, otherwise delete this sentence.
214-218	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 and pharmacodynamic variability.	This section could be expanded to address the potential impact of drug interactions (e.g. CYP induction/inhibition) by one or both component(s) on the design of clinical trials. Should one of both drugs have a meaningful impact on drug metabolism, the design of clinical trials could become very complex. Additional guidance on these possible scenarios would be helpful.
220-235	<p>Dose-response in man is not possible for all drugs. For anti-bacterial agents for serious infections, doses will generally be selected to be in the predicted therapeutic range based on preclinical PK-PD estimates and all tested dose regimens must be in a plausible predicted therapeutic range — deliberate underexposure in man will not be possible.</p> <p>Concentration-response assessments may also require a substantial number of dose permutations. Given that these agents may be inactive or have low activity as monotherapies, an example as to the potential methodology for assessing concentration-response for each individual agent would be helpful.</p>	<p>Amend text to include the concept that dose-ranging in preclinical models might be used instead where appropriate and convincing.</p> <p>Could in vivo and phase 1 biomarker data alone suffice in defining a dose-response relationship? This would facilitate a reasonable approach in the phase 2 setting.</p>
227	Define what is meant by “inactive drug”. This applies throughout the document.	

232-235	The draft guidance recommends testing of multiple doses in a phase 3 setting to further explore dose response. We suggest that all such parameters should be evaluated in earlier phases of clinical research to enable the most optimal phase 3 study design for the combination. Phase 2 studies are the place to evaluate multiple doses and regimens and investigate the exposure response. Phase 3 studies should have a dose and regimen defined to confirm the phase 2 projections.	
238	It is worthwhile noting that Proof of Concept can also be assessed during Phase 1b trials, depending on the indication.	Would recommend changing the header to Therapeutic Exploratory (Phase 2) as titled in ICH E8.
243-244	When referring to demonstrating the contribution of each component of the combination, further clarity is needed regarding the phrase “to the extent possible and needed”.	Examples outlining different scenarios/thresholds of evidence would provide needed guidance. Please provide examples of evidence that would be needed if two agents are inactive as monotherapies.
245	In this draft guidance, the terms and concepts of ‘activity’ and ‘efficacy’ or ‘effectiveness’ of individual and/or combinations of NCEs are used somewhat interchangeably, leading to potential confusion.	‘Provide evidence of the <u>activity</u> of the combination. We suggest that in this guidance the use of ‘activity’ refer to anticipated (e.g. consistent with known or suspected pharmacology) or unanticipated effects observed or measured in non-clinical in vitro and in vivo studies and in clinical trials using volunteers (Phase I), and that ‘efficacy/effectiveness’ be reserved for observations/measurements relevant to the therapeutic indication and made in the relevant human patient population(s), or animal model thereof.
290	An adaptive trial design with the same four treatment arms might be used where appropriate.	After “design” add a reference to FDA Draft guidance document on <i>Adaptive Design to Clinical Trials for Drugs and Biologics</i> .
252-256	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.	This comment is difficult to understand, given the rest of the section recommends various versions of this very factorial design. Consider clarifying this sentence.
259	In situations where an SOC may not exist, it would be useful to provide guidance regarding alternative phase 2 study designs for each of the 3 scenarios noted.	Examples outlining different study designs to consider may be useful.

264	When a strong biological rationale combined with clinical data indicate that the combination has substantial activity as compared to minimal activity for the monotherapies, then the Phase II should compare the combination alone versus the SOC as it is not ethically acceptable to provide minimally active monotherapy to enrolled patients.	Revise line 264: “known to be ineffective or have minimal activity as monotherapy when compared to the substantial activity noted for the combination in phase I or earlier clinical studies”
266-269	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.	"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." This seems to go against the idea that combination therapy is the path forward. Some novel agents may work primarily by enhancing the efficacy of SOC, and in such cases SOC +/- AB should be the preferred Phase II design, even if SOC is palliative rather than curative.
268	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.	"if SOC is known to be an effective therapy (not solely palliative)" What is meant by the distinction of effective vs. palliative? Palliative therapy is usually effective. There is no such thing as an ineffective SOC. Perhaps some examples would be useful here.
297-298	A credible biomarker...Please clarify the terminology here (validated?, qualified biomarker?). Is there a standard or guidance that can be referred to for this critical issue?	If there is no specific set of guidance to reference here, it may be appropriate to recommend the sponsor have discussions with FDA regarding biomarkers or make reference to a section in the draft guidance that outlines appropriate meetings to have with FDA (i.e. section VI, A “Early interaction with FDA”).
302	Regarding scenario 3, this section is also well written and appropriate. Additionally adaptive trial designs may also be appropriate for this scenario.	An adaptive study design may also be appropriate in this scenario if the activity of one component has some potential activity, but is expected to be less active than SOC or combo.
322	Insert	Select dose or doses

332-334	We fully appreciate the Agency's flexibility in allowing a 2 arm pivotal study if the contribution of each component is demonstrated in vivo, in vitro, and/or Phase 2. We would also encourage the Agency to accept demonstration of the contribution of each component from the FIH combination study, provided it is appropriately designed. For rare indications (orphan diseases), it may not be technically feasible to conduct a rather extensive Phase 2 study in order to demonstrate superiority of the combination over each individual component.	
335	This section outlines an ideal situation in which the contribution of each component is adequately established in Phase 2 trials which would allow a more streamlined Phase 3 trial comparing the combination to SOC or placebo as generally sufficient. The concept outlined by this statement in the guidance is true. However, the FDA guidance should make it clear in the earlier sections, perhaps within section C Proof of Concept Studies, of this draft guidance where it is meant to describe earlier drug development, especially at phase 2, that the downside of not having what FDA will deem as "adequate" data to support the contribution of each component is that a sponsor may be require to conduct a more extensive phase 3 program than what would have been necessary if the earlier stage development work was designed to avoid this pitfall in phase 3.	Please emphasize in the earlier sections, perhaps at section C Proof of Concept Studies, of this draft guidance that cover what would be considered to have "adequate data" to "have defined the contribution of each component" by the time the sponsor reaches end of phase 2 very clearly so that the appropriate work has been conducted at an earlier drug development stage. The concern this comment raises is that if the supporting data are deemed inadequate at end of phase 2 stage of development just before embarking upon the phase 3 program then the sponsor would be required to take on greater risk concerning the certainty of success in the later stage of development (phase 3 program stage) and most likely also represent the need to conduct a large and extensive Phase 3 trial.
338	"If phase 2 data do not provide sufficient evidence...but provide strong strong evidence that..."	This sentence is confusing. Perhaps the text should be organized to read "...but provides strongly suggestive evidence that..."
347	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	Suppose monotherapy studies were deemed unethical for theoretical lack of efficacy, but the combination is toxic yet effective. Are monotherapy studies now justified to determine which agent is responsible for the toxicity? Or would additional doses involve lower doses of the combination?

GUIDELINE SECTION TITLE: VI. REGULATORY PROCESS ISSUES IN CODEVELOPMENT		
Line Number	Comment and Rationale	Proposed change (if applicable)
370-374	To reduce the administrative burden on the FDA and sponsor and propagation of short lived INDs, it is proposed that all studies be submitted under an existing IND when available.	
384-397	<p>Request FDA clarification on this point. Does the FDA expect to see one pharmacovigilance plan for combination therapy or one plan for each product, each containing a special section on risk assessment and mitigation for combination therapy?</p> <p>Regarding “activity”: We would like this term to signify not only activity in terms of increased efficacy of the combination against a disease, but also to include cases of increased safety of the combination. A scenario describing an increased safety may include two compounds, one that is effective on its own, but with significant safety issues, and the other that is not significantly effective on its own in the context of a pathophysiological process of a disease, but is active in counteracting or mitigating the side effects of the first drug, which has the clinical efficacy against the disease. We believe that broadening of the definition of “activity” as described herein will encourage the development of treatment options for patients who are unable to tolerate toxic effects of otherwise effective therapies and for whom such therapies would be therefore unavailable.</p>	

390	<p>Pharmacovigilance plan</p> <p>In addition to factors included in the pharmacovigilance plan, the risk assessment should also consider the target population, disease severity, comorbidities frequently associated in that population and indication of new combination.</p> <p>There should be special consideration given to the individual components, characterized individually and as well as in combination. It is important to be aware that activity is important from both a safety and efficacy perspective and compounds with a low efficacy activity may be highly active from a safety perspective. It may not always be necessary to attribute toxicity to the individual components when they will always be given in combination at this regimen. It could be viewed as a unit.</p> <p>The issue of ascribing toxicity is important if these compounds will also be used separately (or in other combinations) for other indications.</p> <p>Suggest FDA reference existing guidance on pharmacovigilance (Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment, March 2005), and REMS (Draft Guidance for Industry Format and Content of Proposed Risk Evaluation and Mitigation Strategies (REMS), REMS Assessments, and Proposed REMS Modifications).</p>	
-----	--	--