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September 7th, 2010

Dockets Management Branch (HFA-305)
Food and Drug Administration
5600 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2010–N–0247: Investigational New Drug Applications; Co-development of Investigational Drugs

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on "Investigational New Drug Applications; Co-development of Investigational Drugs." We are pleased that the Agency intends to develop guidance on the co-development of two or more novel drugs and we offer the following recommendations, topic areas, and questions for consideration under the forthcoming guidance.

BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

GENERAL COMMENTS:

General methodologic and regulatory issues which arise in the course of the co-development of two or more investigational drugs may vary depending on the information available on each drug. For example, two or more drugs being co-developed for a particular indication may fall into one of the following categories:

1. Combination of investigational compounds with existing clinical data.

2. Combination of one novel compound with one (or more) compounds for which clinical data exists.

3. Combination of two (or more) novel compounds with no clinical data on any of the compounds.

Therefore, to the extent possible, we request that the Agency provide guidance on general requirements across these development scenarios and requirements that may be specific to each of the development scenarios, including specific aspects to consider if more than two compounds are developed in combination for narrow therapeutic range (NTR) and non-NTR compounds.

In addition, BIO suggests the proposed guidance address the following: dose finding, additive or synergistic efficacy, additive or synergistic safety, drug interactions, special populations, unique toxicities, and study design.

Specifically, follow-up guidance will be needed on labeling for combination drugs under various scenarios, such as drugs used in novel combination only, drugs used in combination with approved drugs for an indication other than its approved indication, and drugs used in novel combination and as a single agent.

CONCLUSION:

We have included specific comments in the chart below. BIO appreciates this opportunity to present our views and we would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Managing Director for Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

Functional Area	Comment
Regulatory	Please clarify if each new molecular entity (NME) needs its own investigation new drug application (IND) or if sponsors can initiate two NME's under one IND application. We suggest broadening the Exploratory IND guidance to be inclusive of co-development of individual agents to allow for more flexibility in exploring combination products. For example, IND reporting responsibilities (adverse events, annual reports, cross-reference letter) should be clarified if there are two different sponsors. If the combination includes two investigational drugs, does the sponsor need a letter of access to the IND of both drugs? If the combination includes a registered product used off-label and an investigational drug, does the sponsor need a letter of access to the IND of the registered drug as it is used off-label? Please clarify the situation if one of the both drugs is already approved, but used in a different indication in the trial/IND ("simplified European Investigational Medicinal Product Dossier (IMPD) situation").
Regulatory	In oncology, the starting dose is derived from nonclinical work at one-tenth the STD10 (Severely Toxic Dose) in rat or one-sixth the no observed adverse effect level (NOAEL) in dog. Therefore, would sponsors continue to use this guideline as a starting dose for adding on a second investigational product? BIO recommends that the Agency provide an algorithm for estimated safe starting dose for the drugs in combination, which would provide guidance for starting dose, dose escalation/de-escalation and dosing schedule as it relates to novel combinations.
Regulatory	Please provide additional guidance for orphan indications such as transplant and acute lung injury/acute respiratory distress syndrome indications where combination therapies can be considered and for which multiple concomitant medications such as antibacterial, immunosuppressive agents, steroids or anti-inflammatory agents are used as standard of care.
Regulatory	Please provide guidance for orphan indications for which challenges for dose combination may require greater use for adaptive studies in Phase 2 to determine correct dose combination.
Regulatory	Please provide guidance on labelling considerations for products co-formulated and/or co-packaged and labelled together.
Preclinical	Please clarify if biomarker data obtained in patients are sufficient to combine two novel agents when the maximum tolerated dose (MTDS) or response data do not exist?

Functional Area	Comment
Preclinical	Please clarify if rationale and preclinical activity data are sufficient for testing two novel (non-registered) drugs in combination in humans in oncology?
Preclinical	If there is single agent non-clinical toxicology support, could a non-clinical pharmacology combination study with additional endpoints (safety) suffice for supporting the combination clinically? Akin to ICH Topic S9 Nonclinical Evaluation for Anticancer Pharmaceuticals. In general, are combination toxicity studies necessary to investigate the potential toxicity of the combination if no overlapping toxic effect is observed from the safety profile of each individual drug? Are combination toxicity studies necessary to investigate the potential toxicity of the combination if expected overlapping toxic effect from the safety profile of each individual drug can be monitored and are clinically manageable?
Preclinical	Is a single agent pharmacokinetics (PK) study needed? If so, could this be demonstrated as a standalone study or as a lead-in during the combination study?
Preclinical/Clinical	Please discuss the co-development of two or more drugs intended to be used in combination where the drugs are directed at providing a therapeutic effect on the same symptom or manifestation of the disease or condition of interest, including relevance and utility of clinical or animal findings for either drug alone. Please also discuss co-development of two or more drugs intended to be used in combination where one or more of the drugs is intended to enhance the effectiveness of the other, but one or more of the drugs does not or may not have an independent therapeutic effect, including relevance and utility of clinical or animal findings for either drug alone. If one of the two or more drugs has no independent therapeutic effect, is it possible to consider registration for this drug? This is especially relevant for co-development in oncology.
Clinical	For the early clinical development Phase I/II, please clarify if each single substance should be tested individually for safety. Is (separate) efficacy/ activity testing of the single compounds also required? What are the requirements for pivotal clinical trials? Is a 4-armed study (2x2 factorial design with Standard of care, Drug A, Drug B and Drug A+B) mandatory or could other designs be acceptable, if justified?

Functional Area	Comment
Clinical	In regards to determining the MTD, does the Agency plan to release a guideline for the novel/novel MTD determinations? We envision three basic scenarios: 1. Neither drug to be developed as a combination has MTD established; 2. One drug has the MTD previously established and the other(s) do not, or 3. Both drugs have single-agent MTD defined. We suggest guidance for the approaches/study designs to determine MTD of the combination drug under various scenarios.
Clinical	Please provide specific recommendation within the forthcoming guidance on co-development of two or more drugs intended to be used in combination for specific therapeutic categories, including oncology, anti-infectives, seizure disorders, cardiovascular diseases, and any other therapeutic category in which such co-development is likely to occur. A separate guidance or annex for oncology combination products could be envisaged, possibly differentiating between combinations of targeted compounds, combination of targeted and cytotoxic compounds or combinations of two cytotoxics. Please provide examples of study designs for registration oncology trials. Should there be a differentiation between late stage and early stage disease? Specific recommendations for oncology (or fatal/life-threatening diseases) aimed at minimizing the dosing of patients at sub-therapeutic levels would be especially welcome.
Clinical	Please provide specific guidance on the clinical design of pivotal study as FDA has typically asked for combination rule for fixed dose combinations (i.e. factorial design with 4 arms Standard of care, Drug A, Drug B and Drug A+B). For cardiovascular indications like acute myocardial infarction or other orphan indications like transplant or acute lung injury and acute respiratory distress syndrome, this could potentially result in an extremely larger study and may render the Phase 3 program impractical and costly if two adequate well controlled trial (AWC) combinatorial studies are required. Some possible considerations are to restrict the design of Phase 3 to 2 arms, i.e. Standard of Care (SOC) and Drug A+B in certain situations: 1. *Combination is potent and individual drugs are not:* Phase 1 studies may include individual drugs, Phase 2 Proof of Concept (POC) may be 4-arm combination and Phase 3 may be restricted to SOC and Drug A+B.

Functional Area	Comment
	2. *Two moderate potency drugs in the combination:* Phase 2 POC may be a 4 arm adaptive design demonstrating effectiveness of combination over SOC first before single drugs arms added. Phase 3 may be restricted to SOC and Drug A+B. 3. *Moderately active + minimally active drug in the combination:* Phase 1 should establish the best dose-exposure of minimally active and Phase 2 could establish contribution of moderate drug to the combination. Phase 3 may be restricted to 2 arms SOC and Drug A+B.
Clinical	Please provide guidance on types of endpoints in a pivotal study such as increased need for potential co-primary endpoint and approval based on statistical significance on both endpoints compared to SOC. In this situation, will a 4 arm factorial Phase 2 POC study be essential to determine the magnitude of effect of each drug on the different symptom?
Clinical	Please provide guidance on the selection of patient population. This may be particularly challenging for patients with both conditions/symptoms are needed to ensure effectiveness on both components of the primary endpoint. Please also comment on the potential for either single or co-primary endpoints to be considered depending on the magnitude of effect of the drug with lesser potency. Other considerations that may potentially affect treatment outcome are sub-populations where underlying disease causes sub-optimal efficacy on either drug or causes drug-resistance to either drug.
Clinical	For special therapeutic diseases and orphan diseases, how will naïve patients be recruited and what are the ethical implications?
Clinical	For certain therapeutic categories, can Response Guided Therapy be considered? For combinations with differential potency where one drug is enhancing the other, patients may receive the drug with lower potency in screening period to determine eligibility before combination treatment starts.
Clinical Pharmacology	How will drug-drug and drug-disease interaction be assessed, and will this require a more pre-defined Population Pharmacokinetic (PK) and exposure-response analysis in the Phase 2 and Phase 3 studies? The guideline for industry on "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term

Functional Area	Comment
	Treatment of Non-Life-Threatening Conditions (ICH-E1A**)"** may need to be updated.
Clinical Pharmacology	In general, are combination pharmacology studies necessary to investigate the potential activity of the combination to support the study rationale or could a mechanistic rationale be considered sufficient?
Drug Safety Evaluation	Please comment on any additional toxicology requirements not already covered in ICH Topic M3 (R2) "Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (ICH M3)" that includes three situations: 1. Two Late stage studies (Phase 3); 2. Late stage study (Phase 3) + Early stage study (Phase 2); 3. Two Early Stage studies (Phase 2 or less). For late stage combinations where adequate clinical experience is available, we do not recommend combination toxicology studies for clinical stage or marketing unless there is a shared organ of toxicity. For late stage combinations without adequate clinical experience, combination toxicology studies are required for marketing or long-term use. For early/late stage combinations, combination toxicology studies are not recommended for POC up to 1 month as long as the duration does not exceed the duration in single toxicology studies, but combination toxicology is required for Phase 3 and marketing. For early stage combinations, combination studies are required to cover the duration of clinical studies up to 3 months and would support marketing. Combination toxicology is recommended in single relevant species. Other combination studies (genotoxicology, safety pharmacology or carcinogenicity) are not recommended if already available for the individual drugs. Some unique considerations include the potential for increased toxicity when both drugs share the same mechanistic pathway or effect the same symptom; and if one drug enhances the other drug.
Drug Metabolism & Pharmacokinetics	Are non-clinical characterizations of individual compounds' absorption, distribution, metabolism, and excretion (ADME) and drug-drug interaction assessments sufficient for registration of the combinations?
Drug Metabolism & Pharmacokinetics/ Drug Safety Evaluation	Simulation may also be used to predict potential drug-drug interaction (DDI), pharmacodynamic (PD) or toxicology with combination therapy, and assist designing rationale dose regime.

Functional Area	Comment
Drug Safety Evaluation	Good Laboratory Practices (GLP)-compliant toxicology studies of individual investigational drugs are sufficient to enable assessment of potential overlapping toxicity and support clinical testing of combination. Therefore, combination toxicology studies are not warranted.
Drug Safety Evaluation	We suggest the Agency follow "ICH Topic *S9*. Nonclinical Evaluation for Anticancer Pharmaceuticals" for oncology agents.
Drug Safety Evaluation	For chronic conditions, please discuss how relapse of one or both conditions will complicate the additional treatment regime? Will safety assessment be influenced by the individual drug for each condition?
Drug Safety Evaluation	Please comment on the potential for smaller safety database for the combination compared to safety database for the individual drugs. For example, a safety database of 1,500 subjects can detect at least 1-5% rate of adverse drug events (ADEs) for the combination and 0.5% rate of ADEs attributed to the individual components. However, special consideration may be needed to differentially attribute new safety findings to a specific drug A or B or A+B. Thus, there may be potential for a larger than expected safety database to account for background rates of ADEs and rare events including the potential for a sufficiently large Phase 2 study to determine the background safety profile of the individual drugs over the combination. Therefore, the nonclinical safety pharmacology of the individual and combination may need to be thoroughly determined in animal models.
Molecular Medicine	Despite the increase in genomic knowledge driving a compilation of genetic changes associated with cancer and drug response, the complexity of interactive biological networks precludes simple solutions to altering disease pathophysiology. Effective targeted cancer therapy requires that the basic mechanisms and interactions of multiple pathways in cancer be understood and that critical arms are inhibited using combination therapies. We believe that combination therapy strategies should be based on biology, monitored in the clinic using PK/PD and pathway/target-specific biomarkers and are very amenable to patient selection strategies. 1. A detailed biological rationale should provide the mechanistic basis for a combination therapy. A molecular description of mechanism of action (MOA) of each drug and how they impact each other's pathways to predict combined effects should be provided. From a pathway biology standpoint, drugs can inhibit different points of the same pathway or affect different pathways such as disrupting a known compensatory pathway

Functional Area	Comment
	or feedback loop for another drug. Combination therapy could also target known mechanisms of resistance elucidated by pre-clinical or clinical data. 2. There is a significant role for biomarkers in combination therapy. Pharmacodynamic (PD) biomarkers can be used to confirm that the targets or pathways of each drug are being hit or that downstream pathways associated with anti-tumor activity are affected by the drug combination as predicted by the mechanistic rationale and compared to the effects observed in single agent studies. The exposures and the extent of PD changes can be correlated with therapeutic outcome to link additive or synergistic effects at the molecular level. This would provide proof-of-concept of the activity of each drug in the combination, support dose/schedule selection and provide guidance for treatment management related to safety. Given a well-defined rationale for the combination therapy patient selection strategies could be devised to enhance the effectiveness of therapy in a patient subpopulation. This is particularly applicable if pathways activated by mutations contribute to drug resistance and this pathway can be targeted by a second drug after prospective selection of patients carrying the activating mutation. Safety biomarkers will need to be chosen which allow for early signals from the combined therapy. 3. Preclinical studies aimed at establishing the need for and feasibility of patient selection are desirable. Patient selection strategies may be tested prospectively or retrospectively depending upon the clinical rationale for a particular drug combination or the prevalence of the patient subpopulation most likely to be sensitive. If the subpopulation with a specific pathway activation constitute a large fraction of the tumor type, then retrospective analysis of the combination's safety/efficacy may be appropriate. If there is a strong rationale or if the target subpopulation is small, it may be necessary and appropriate to evaluate safety/efficacy of a novel combination in a group that is prospectively enriched for that subpopulation.
Legal-Intellectual Property	When approval is sought for two or more drugs intended to be used in combination, and neither drug has previously received market authorization, will applicant(s) separately file NDAs for the individual agents, or file a single NDA for the combination?
Legal-Intellectual Property	If market authorizations are concurrently granted for two or more drugs intended to be used in combination, and neither drug has previously received market authorization, is patent term extension under 35 USC § 156 separately

Functional Area	Comment
	available for both drugs, i.e., can the regulatory review period for the combination therapy be separately relied upon to extend one patent covering the first drug or its approved indication and to extend another patent covering the second drug or its approved indication? Will the answer to this question change if the applicant(s) separately file NDAs for the individual agents, or file a single NDA for the combination?
Pharmacovigilance	If combination of a novel therapy is associated with an already marketed product, to what extend could the known safety profile of the marketed drug be used to trigger thresholds of an acceptable safety profile for the combination, perhaps with greater flexibility regarding a tighter benefit-to-risk ratio?
Pharmacovigilance	The guidance should recognize that different symptoms or manifestations of the disease will add additional confounders for the assessment of the safety profile of the combination therapy.
Pharmacovigilance	It is expected that efficacy would be enhanced by the combination of drugs, but the safety profile may potentially be worsened with cumulative toxicity, exacerbation of toxicity, or new toxicity. A differentiation of the safety profile will be warranted to further evaluate the risks associated with the single agent(s) and how they would apply to the combination. Specific approaches may be needed to assess the safety profile of the combination of two novel therapies versus a novel therapy with an already marketed product. Therefore, please provide guidance on any special pharmacovigilance considerations when developing novel drug combinations.
Pharmacovigilance	Benefits would have to significantly outweigh the safety risks which could be higher. This will impact the threshold of acceptance of the benefit/risk profile especially for a specified disease population with reference oncology treatments.