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February 14, 2011

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

Re: Docket No. FDA–2010–D–0616 Draft Guidance for Industry Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination." BIO applauds the FDA for issuing the Draft Guidance and for acknowledging the potential for drug development programs to harness the synergies discovered in combinations of experimental compounds to treat serious diseases, particularly in oncology and infective disease. We are pleased to offer the following recommendations in support of the Draft Guidance.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:

I. Please Clarify the Need for "Greater than Additive Activity" or Delete This as a Criterion for Co-Development in this Setting

The phrase "greater than additive activity" or similar phrases are used in several sections of the guidance (lines 104, 132, 282). Given the other criteria (serious disease, compelling biological rationale, including potential for improved safety, evidence of substantial activity from either a preclinical model or short term clinical study which may include a more durable response), BIO believes that a requirement that the combined activity must be greater than additive to warrant co-development, without further justification, seems unnecessary and likely cause confusion and discourage development of potential advances in therapy.

In addition, synergy and additivity are complex mathematical constructs, and there are multiple methods for determining them. Without agreement on a particular method of analysis, and given the lack of correlation between in vitro or in vivo synergy or additivity and clinical responses, it seems prudent to avoid language that is overly narrow in scope. For example, "greater than additive activity" is difficult to interpret in a situation in which there is a compelling reason to expect the combination to significantly improve safety with a small increment in efficacy or to improve safety with equivalent efficacy. Therefore, "greater than additive activity" is likely to be interpreted as referring only to efficacy and not safety. We believe that combinations of novel drugs should be eligible for co-development based on the potential for improved safety as long as the combined efficacy is sufficient and the improved safety is potentially clinically significant. Although, in some sections, the guidance already suggests the importance of improved safety in combinations (for example, it acknowledges one possible benefit of a combination may be to "allow use of lower doses to minimize toxicity"), it appears that all four criteria for co-development listed in the guidance must be met. Therefore, a combination likely to improve safety but for which the combined activity is not expected to be greater than additive would not be a candidate for co-development under this guidance. Accordingly, we recommend deleting the requirement for greater than additive activity or adding a discussion and possible example to explain how to interpret it in the context of co-development to improve safety.

In addition, we recommend defining the term "activity" to clearly include both safety and efficacy throughout the guidance.

Therefore, we suggest adding in line 92, or as a footnote:

> "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 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."

II. Please Delete or Revise the Criteria for a "Compelling reason for why the agents cannot be developed individually"

The Draft Guidance states that the co-development process should ordinarily be reserved for four limited situations, including when "There is a compelling reason for why the agents cannot be developed individually." (Bullet 4, lines 107-109). First, this criterion seems to contradict the co-development scenario described on lines 279-288 which discusses development of two drugs when "each drug alone has activity and can be administered individually." Second, the three preceding bullets in the guidance adequately define conditions under which it is reasonable to accept less information about the safety of the individual drugs. These include the intent to treat a serious disease; a compelling biological rationale which, for example, may decrease resistance or allow use of lower doses to minimize toxicity; and evidence of substantial activity or a more durable response compared to the individual agents. We note that the examples in bullet 4 reiterate some those given in the preceding 3 bullets (development of resistance or limited individual activity). This suggests that this criterion adds little benefit in defining appropriate candidates for co-development while placing an unnecessary additional requirement that may impair the development of some combination drugs.

Therefore, we suggest striking bullet 4 in its entirety. Alternatively, bullet 4 could be modified to read,

> "There is a compelling reason for why the agents ~~cannot be developed individually~~ should be developed as a combination."

III. The Draft Guidance Should Discuss Co-Development of Existing Compounds for Use in Combination in Unapproved Indications

The guidance states that "It is not intended to apply to development of fixed-dose combinations of already marketed drugs or to development of a single new investigational drug to be used in combination with an approved drug or drugs." (Lines 44-46). However, we note that drugs are often used for non-approved indications. Therefore, we request clarification of the Agency views co-development of a new/approved drug with a drug with non-approved uses. For example, would the guidance still apply if the approved drug is used in a non-approved indication, such as breast cancer, but tested in combination in renal cancer or if a drug is approved for anti-inflammatory disease, but shows anticancer activity? BIO suggests that FDA expand the scope of the guidance to be more inclusive of these situations.

IV. The Draft Guidance Should Include Oncology Drugs

The reading of section IV B Nonclincial Safety Characterization and of ICH M3 "Guidance on Non-Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals", gives the impression that it is more restrictive for toxicology studies of *non*-oncology combinations intended for life-threatening diseases (cardiovascular indications, for example), than for oncology drugs

which are often inherently very toxic when given alone. This fundamental and unique aspect, of oncology drugs should also be addressed in the guidance in order to allow for a broader interpretation of nonclinical data requirements prior to first-in-human (FIH) combination studies.

Further, it is likely that this guidance document will be utilized to develop novel treatments for oncology and antiviral treatments for human immunodeficiency virus (HIV) or hepatitis C virus (HCV). We therefore urge the Agency to consider these types of drugs, and the general concept that treatment most often occurs at maximum tolerated dose (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.

V. We Recommend a Case-by-Case Approach for the Early Combination Studies

The Guidance suggests that "Phase 1 safety studies of the combination could also be conducted…to support dosing in subsequent studies" (lines 200-202). We request the Agency 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.

VI. Proof of Concept Studies

We appreciate and agree with the Agency's comment that the amount and type of data, as well as appropriate study design is dependent on the specific combination that is being investigated as well as the indication. We also want to underscore and expand on the Agency's comment that for many life-threatening indications it will not be appropriate to administer monotherapy as there will already be preclinical evidence and Phase 1 combination data that monotherapy my represent suboptimal treatment.

VII. Confirmatory Studies

We fully appreciate the Agency's flexibility in allowing a two arm pivotal study if the combination of each component is demonstrated in vivo, in vitro, and/or Phase 2 (lines 332-332). 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.

We appreciate that the Division recommends an "early and often" approach during development of two new molecular entities (NMEs) and recognizes the regulatory complexities involved in such approaches to development. We also encourage the Agency to maintain the "case-by-case" approach to decisions regarding investigational new drug application (IND) and new drug application (NDA) and/or a biologic license application (BLA**)** submissions (individual vs combination).

VIII. Opportunities for Ongoing Collaboration with FDA

Sponsors are interested in an ongoing dialogue with FDA to share information and ensure transparency on the status of ongoing studies involving co-developed NMEs and the utility of these studies for an effective and efficient path to registration. Considering the importance of these issues, we would like to propose a joint working group composed of representatives from FDA, industry, academic medical centers, and patient groups to discuss and address these issues. Alternatively, this can be pursued through public workshops or advisory committees. For example, we believe that additional stakeholder dialogue will be helpful in further articulating ongoing issues around pharmacovigilance and labeling for co-developed products.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination." Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

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

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
III. NONCLINCIAL DEVELOPMENT A. DEMONSTRATING THE BIOLOGICAL RATIONALE FOR THE COMBINATION		
Lines 133-136:	These lines state that "An animal model of activity generally would not be necessary. However, if there is an animal model relevant to the human disease, valuable activity data, as well as information about the relative doses of the drugs, might be obtained from evaluating the combination in that model."	The Draft Guidance implies that FDA would prefer to see 'in vivo' animal evidence of activity. Is FDA intending to communicate that activity does not need to be demonstrated in an animal model of the specific disease? For example, an animal model would be created for each of these cancers: multiple myeloma or thyroid cancer. Some diseases have useful models and some do not. We request that FDA please clarify this position.
IV. NON CLINICAL DEVELOPMENT B. NONCLINICAL SAFETY CHARACTERIZATION		
Lines 151:	---	For recommendations regarding nonclinical evaluations of combinations anticancer pharmaceuticals, FDA should consider allowing Sponsors to consult the recently developed ICH Guidance on Nonclinical Evaluation of Anticancer Pharmaceuticals (S9), specifically section 3.5 of that guidance.
V. CLINICAL CODEVELOPMENT C. PROOF OF CONCEPT STUDIES (PHASE 2)		
Lines 279-317:	---	For each of the phase 2 scenarios presented in the Draft Guidance, placebo and/or Standard of Care (SOC) is included as a control arm. Currently novel oncology combinations are not always tested this way (i.e. phase 2 controlled studies). If the SOC of that population is well characterized, the control arm may not be necessary.