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November 25, 2008

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

**Re: Docket No. FDA-2008-D-0514: End-of-Phase 2A Meetings**

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on FDA's draft guidance for industry on End-of-Phase 2A (EOP2A) meetings. BIO welcomes this guidance and believes that the EOP2A meeting is a valuable opportunity for sponsors to meet with the Agency to discuss quantitative modeling and simulation to determine the optimal dose-response relationship and pharmacokinetic / pharmacodynamic (PK/PD) relationship for new drugs entering Phase 2B and Phase 3 testing. BIO respectfully requests additional clarification to the guidance to further demonstrate the value of an EOP2A meeting as part of a drug development program.

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.

## DRUG SPONSORS VALUE THE OPPORTUNITY FOR EOP2A MEETINGS:

As evidenced by the level of industry participation in the EOP2A meeting pilot program, many BIO members find that EOP2A meetings provide a great deal of value for

sponsors. We are particularly pleased to see that the EOP2A draft guidance encourages the use of quantitative clinical pharmacology in decision making during drug development. Clinical trial simulation and quantitative modeling of prior knowledge enables the design of trials for better dose response estimation and dose selection. BIO believes that FDA-sponsor interaction to facilitate these approaches is an important aspect of improving the efficiency of clinical development plans and minimizing the risk to patients of selecting the wrong doses for further study. We also appreciate the direct line of communication between scientists at the FDA and the sponsor to expeditiously resolve issues related to the exposure-response analyses.

Although there exists a potential for delay in a product development program while the EOP2A meeting is being planned and the models and simulations are analyzed, it is our expectations that this delay via FDA-sponsor interaction would be kept to a minimal amount of time. However, for those companies that choose to have an EOP2A meeting with FDA, this potential for delay may be offset by the increased confidence in the dosing and potential for success in Phase 2B/3 studies. We suggest that the EOP2A meeting process would benefit from additional discussion of the value of the EOP2A meeting for sponsors, or presentation of case-studies of successful EOP2A meetings. For example, it would be helpful for the Agency to note explicitly how an additional four months might contribute to a successful development program that may have failed without such a meeting. This type of feedback could also be delivered via future public meetings, presentations, or other types of publications.

**MEDICAL REVIEWERS SHOULD BE INVOLVED IN EOP2A MEETINGS**:

While BIO member companies particularly welcome the chance to discuss quantitative clinical pharmacology approaches with quantitative groups within the agency, it is important that there is adequate representation, collaboration, and coordination with the review division. The guidance currently states that "FDA pharmacometricians and biostatisticians will generally perform most of the review work for these meetings. Reviewers from other review disciplines will participate in the preparation and conduct of these meetings." (lines 111-113). BIO is pleased that the guidance explicitly mentions that the reviewing division must be closely involved in the meeting and believes that any FDA advice that comes as a result of the meeting should be developed in collaboration with the review division. To increase the ultimate value of an EOP2A meeting to a drug development program, it is important that there be close alignment between the medical reviewers and the pharmacometricians / biostatisticians in order to facilitate and inform later discussions with the review division. The EOP2A meeting would lose much of its value if there is a perception that the review division does not contribute to the final outcome.

**THE GUIDANCE SHOULD ESTABLISH A FORMAL PROCESS FOR VALIDATING SIMULATIONS PRIOR TO THE EOP2A MEETING:**

The draft guidance states, "Ideally, industry and FDA scientific staff will have agreed upon the modeling and simulation approaches before the EOP2A meeting so the meeting time can be used to interpret the results and discuss dose and/or trial design issues."

(lines 134-136) However, the draft guidance provides no mechanism and timing for how and when an agreement can be reached beforehand. We request that the guidance describe the timing and the mechanism by which industry and FDA scientific staff should interact in order to reach agreement prior to the meeting on the modeling and simulation approaches.

The formal EOP2A meeting could be the culmination of 1 or 2 pre-meeting discussions, including provision of preliminary data and modeling, aimed at an EOP2A meeting where data and conclusions can be discussed and a point of view decided. BIO recommends stating in the guidance that sponsors should contact the Office of Clinical Pharmacology and the respective FDA review division to discuss planned modeling and simulation approaches early in the development program (Phase 1, Phase 2A). Additionally, a teleconference between FDA and the sponsor should generally occur within fourteen days of the initial request for agreement and the agency should communicate any recommendations and comments to the sponsor in writing. Also, during the initial teleconference, the agency and sponsor will discuss follow-up procedures and expectations for an EOP2A meeting. If such a formal approach to reaching agreement on the modeling and simulation approaches is established, the actual EOP2A meeting may focus on more productive discussions around the outcomes of the modeling/simulations.

**MEETING PROCEDURES SHOULD BE HARMONIZED WITH THE PDUFA FORMAL MEETINGS GUIDANCE:**

BIO encourages FDA to take steps to harmonize the meeting request timing and submission of the background information with the formal PDUFA Meetings Guidance to improve the consistency and predictability of the meetings process.

For example, although the EOP2A meeting is described as a Type C meeting, the timing suggested in the draft guidance is not in synchronization with either the PDUFA IV goals[1] or the current Formal Meetings Guidance.[2] While the PDUFA IV goals and the meetings guidance provide for a type C meeting to occur within 75 days of Agency *receipt of the meeting request*, the draft EOP2A guidance (line 249) states that the meeting date is usually 6 – 10 weeks after FDA's *receipt of the meeting package.* PDUFA IV goals, on the other hand, indicate that the meeting *package* should be submitted at least 4 weeks before the date scheduled for the meeting. The apparent discrepancy in process and timing for requesting and scheduling the EOP2A meeting compared to the PDUFA IV goals and the formal meeting guidance should be resolved. If these meetings are to be handled differently, the final guidance should specifically state that the normal procedures and timing for type C meetings do not apply.

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[1] FDA, *PDUFA Reauthorization Performance Goals and Procedures: Fiscal Years 2008 Through 2012*, http://www.fda.gov/oc/pdufa4/pdufa4goals.html

[2] FDA, *Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products*, February 2000, http://www.fda.gov/CBER/gdlns/mtpdufa.pdf

With respect to background materials, the draft guidance states that, "Sponsors are strongly encouraged to submit all relevant information with the meeting request, including data, any models or simulations of trial design, or disease or outcome models that have been explored that provide insight into the issues for discussion." (lines 179-181.) However, the guidance later states, "General instructions regarding timing and contents of the information package are found in the Formal Meetings guidance." (lines 209-210.) These two sentences appear to conflict with one another. The former implies that the information package should be submitted approximately 10 weeks before the formal meeting, while the latter implies that the information package should be submitted 2-4 weeks prior to the formal meeting. If the meeting request and the information package are to be submitted approximately 10 weeks before the formal meeting, the initial information package should include the preliminary data analyses, and the final data analyses may be submitted 4 weeks prior to the formal meeting. A four week time frame is consistent with Type B and C meetings as recommended in the FDA Formal Meetings Guidance. This "phased" approach would allow sponsors to submit a meeting request shortly after the completion of phase 2A trials, while providing the agency with sufficient time for review prior to the formal meeting.

**THE EXACT POINT IN DRUG DEVELOPMENT FOR THE EOP2A MEETING SHOULD REMAIN FLEXIBLE:**

The guidance tends to treat drug and biological development as a process where the phases are separate and distinct, but drug development is often a continuum. In many development programs, particularly in the biotechnology industry, there is not a clear separation or transition of phase 2A vs. phase 2B in the development timeline. This fusion of the discrete of the steps of the drug development process is becoming more common, particularly as adaptive "Phase 2/Phase 3 "learn and confirm" trial designs and non-standard development plans become more accepted. Therefore, there should be flexibility regarding the point in development when the EOP2A meeting occurs. We suggest that the overall time frame for such a meeting be widened and that a modeling/simulation meeting should be considered as soon as appropriate data are available that would allow modeling to inform and optimize the clinical development plan.

FDA may also consider amending the title of the EOP2A meeting to acknowledge that not all drug development programs have a discrete separation between phase 2A and phase 2B. Rather the meeting name could focus on the modeling/simulation aspects of the FDA-sponsor interaction.

**CLARIFICATION IS NEEDED ON THE GROUNDS FOR REJECTING EOP2A MEETINGS BASED ON RESOURCE CONSTRAINTS:**

BIO recognizes that the FDA and the drug review divisions currently face challenging circumstances due to increasing responsibilities and corresponding lack of funding. However, we are hopeful that recent increases in FDA appropriations, industry user fees, and staffing will begin to address this significant problem and provide medical reviewers, statisticians, and pharmacometricians with the time to commit to important drug

development activities, such as EOP2A meetings. The guidance notes that one of the considerations used to evaluate EOP2A meeting requests will be "appropriate FDA resources available for the project." We recognize that EOP2A meetings can be resource intensive for all parties involved, but we note that unlike the EOP2A pilot program, industry will be performing the modeling and analysis rather than FDA staff. Additionally, earlier interaction between sponsors and FDA can facilitate drug development and help minimize the potential for other resource-intensive problems arising late in drug development or during FDA review. If FDA anticipates that staff may have to reject EOP2A meetings due to limited resources rather than valid scientific rationale, we request that the guidance provide additional clarity on the criteria used for rejecting a meeting based on resource constraints.

**LESSONS LEARNED AND FUTURE ACTIVITIES:**

Over time the agency will have seen and reviewed modeling and simulation results across a significant number of compounds and across a wide variety of indications based on submissions from a range of sponsors across the industry. As FDA and sponsors gain this experience, there may be an opportunity to disseminate some of the lessons learned through future guidances, presentations at public meetings, or other types of publications. For example, FDA may wish to further articulate certain "best practices" for modeling and simulation. This would be particularly helpful for small and mid-size biopharmaceutical companies that may have less experience in this area. Additionally, based on the experience gained through EOP2A meetings, FDA could detail which diseases or indications would most benefit from quantitative modeling and simulation. These future activities would continue to enhance the value of the EOP2A meeting.

**SPECIFIC COMMENTS**

BIO is pleased to offer the following specific comments in support of the guidance.

| SECTION | ISSUE | PROPOSED CHANGE |
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| **I. INTRODUCTION** | | |
| **Line 20-21:** | Two additional topics, disease progression information and definition of clinical outcomes, are important considerations for EOP2A meetings and should be explicitly mentioned. | Include "disease progression information, definition of clinical outcomes, and other appropriate issues." |
| **Lines 25-33:** | As noted above, there should be adequate flexibility regarding the point in development when the EOP2A meeting occurs. | BIO recommends including the following underlined test to the introduction:<br><br>"An EOP2A meeting would occur after the completion of clinical studies that provide data on the relationship of dosing and response for the particular intended use (including studies on the impact of dose ranging on safety, biomarkers, and proof of concept). For the purposes of this guidance, *end of phase 2A* occurs after the completion of phase 1 studies and early exposure-response studies in patients, and before initiating studies using the final dose selection. The EOP2A meeting should be considered as soon as appropriate data are available that would allow modeling to inform and optimize the clinical development plan, consistent with the Critical Path Initiative. In the context of drug development programs, discussions at an EOP2A meeting could include exploration of dose estimation and dose selection to use in late stage efficacy trials. Where novel trial designs or clinical development strategies are a possibility (e.g., for a new route of administration or new indication), their utility and applicability could be discussed at an EOP2A meeting." |
| **II B. BACKGROUND - EOP2A PILOT PROGRAM** | | |
| **Lines 109-111:** | States that the FDA may perform in-house modeling to address particular problems or to | FDA should provide some guidance on expected time period (range) for performing such analyses. This will help sponsors plan timelines |

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| | independently assess the sponsor's model. | for the meeting. |
| **Lines 111-113:** | As noted above, the review division should also be involved in the EOP2A meeting to promote alignment on any advice or recommendations and facilitate later discussions with the review division. | BIO recommends including the following underlined test to the introduction:<br><br>"It is expected that FDA pharmacometricians and biostatisticians will generally perform most of the review work for these meetings. Reviewers from other review disciplines will participate in the preparation and conduct of these meetings and consolidated FDA advice will be provided to the sponsor." |
| **III A. OBJECTIVES OF AN EOP2A MEETING** | | |
| **Line 120:** | The outcome of the discussion should not only inform dose selection for Phase 2b studies. At a later time, the Sponsor and FDA may even agree to proceed directly to Phase 3 studies evaluating dose response in a series of fixed-dose studies (possibly after a formal EOP2 meeting). | Consider amending the relevant phrase in line 120 to "quantification of the exposure-response information during ~~early~~ drug development". |
| **Line 124:** | Section III introduction states that an additional objective of EOP2A meeting should be to discuss "critical data on drug interactions" (line 124). Further clarification is needed around the objective of any discussion on drug interactions. Consistent with the overall thrust of the draft guidance (section I intro) to utilize modeling and simulation in clinical trial design, the intent should be to utilize drug-drug interaction (DDI) modeling as much as possible to predict DDI in Phase 2b/3 and to outline the risk mitigation plan. Highly predictive modeling tools are now available to quantitatively predict DDI and can be used to obviate the need for extensive clinical | Add an additional meeting topic into section IIIA with following wording:<br><br>"Use of knowledge gained before EOP2A on candidate with regard to human clearance and drug interactions. Discuss further drug-drug interaction data needed and utilization of modeling and simulation to inform the risk mitigation plan in phase 2B/3." |

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| | interaction studies. Indeed such DDI modeling data is being accepted in regulatory review in lieu of further clinical studies. | |
| **Lines 134-135:** | There is a statement that sponsors and the FDA should ideally agree on the modeling approaches prior to the EOP2A meeting. It is not clear how this should be achieved. How is agreement reached on the modeling approaches before the meeting? Is the CDER Project Manager responsible for aligning this, or is it achieved via a pre-meeting discussion between the sponsor and FDA scientific staff? | It is important to clarify how prior engagement with FDA should be achieved, and BIO recommends adding the following sentence:<br><br>"Ideally, industry and FDA scientific staff will have agreed upon the modeling and simulation approaches before the EOP2A meeting so the meeting time can be used to interpret the results and discuss dose and/or trial design issues. <u>This can be achieved through pre-meeting discussions during Phase 1 or Phase 2A and a teleconference 14 days after receipt of the EOP2A meeting request. During the initial teleconference, the Agency and sponsor will discuss follow-up procedures and expectations for an EOP2A meeting. Recommendations and comments to the sponsor will be communicated in writing.</u> |
| **Lines 141-168:** | In terms of content of EOP2A meetings, will the FDA be open to discussions regarding the need to observe a "no effect" dose level, determination of the appropriate comparator arm, and patient population requirement for phase 2 study? | Please clarify. |
| **Lines 146-150:** | Explicit reference should be made to the use of PK/PD relationships for mechanistic biomarkers as a useful dataset to utilize in Phase 2B dose-ranging trial design. Add to examples quoted in section III A, lines 146-150. | BIO recommends adding the following additional bullet:<br><br>"Use of quantitative knowledge of drug effects in animals and human subjects to aid in both dose-ranging trial design and safety assessment. Examples include:<br>- Placebo effect<br>- <u>Target/mechanism biomarker endpoints</u><br>- Disease severity (baseline) effect<br>- Disease endpoint variability and time course" |
| **Line 155:** | Guidance states "Contrasting alternative trial design..." | Please clarify word "contrasting" |

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| **Lines 158-161:** | The implications of genetic factors on PK and PD variability are included as a topic for discussion. Consistent with the overall thrust of the draft guidance (section I intro) to utilize modeling and simulation in clinical trial design, the use of modeling to predict impact of genetic factors on PK/PD should be included as a discussion topic. | BIO recommends modify line 160 to read:<br><br>"might include a quantitative evaluation of genetic effects on dose selection, including experimental and modeling data from preclinical and clinical sources, and the use of genetics to inform assessments of drug safety….." |
| **III B. EOP2A MEETING REQUESTS** | | |
| **Line 180-181:** | Is there an expectation for the briefing package to be submitted with the meeting request? How does the information recommended on lines 180-181 for the meeting request differ from the briefing package? | Please clarify. |
| **Line 181-182:** | FDA recommends to "leave ample time" if data modeling is requested. | Please provide an estimate of ample time. |
| **Line 197:** | The list should be re-ordered by the importance of the items for considerations. | Whether the product fills an unmet therapeutic need should be the utmost important consideration. |
| **Line 200:** | Line 200 requires clarification. Would the FDA be sharing the knowledge of other compounds in development within the same class or therapeutic area? At the proposed EOP2A meeting, sponsors will be sharing with the FDA their early proprietary information on modeling and simulations. How would the confidentiality be maintained with respect to the modeling strategy and technical details? | Please clarify. |
| **Line 196-202:** | The draft guidance is silent on products that are being developed under the provisions of | The guidance should describe whether it would be possible to have an "EOP2A-type" interaction on products undergoing accelerated |

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| | 21 CFR Subpart E (Drugs Intended to Treat Life-threatening and Severely-debilitating Illnesses). Under Subpart E, such programs are on an accelerated schedule with the intent of developing sufficient data by the end of phase 2 to submit a marketing application. | development. |
| **Line 196-202:** | Other considerations that may inform the decision to grant a meeting request include relevance of dose and intrinsic characteristics of the compound. | Include the following bullets:<br>• Relevance of dose - response or exposure - response data for the condition of interest (e.g. anaphylactic reaction that is dose-independent) and therapeutic intent (treatment vs. prevention).<br>• Intrinsic characteristics of the compound (e.g. highly variable PK, irreversible enzyme inhibition or very high receptor affinity) |
| **231-234:** | It is unclear how the analyses and interpretation of available exposure response data requested here differs from what is requested in lines 223-224. | Please clarify. Suggest combining these 2 bullets into one bullet. |
| **III C. USEFUL INFORMATION FOR AN EOP2A MEETING PACKAGE** | | |
| **Line 235:** | Explicit reference should be made to the type of information required with respect to PK and drug-drug interactions including any modeling that has been performed. | BIO recommends adding an additional bullet on background information into section IIIC with following wording:<br>• Appropriate non-clinical and phase 1 data and any modeling performed pertaining to pharmacokinetic variability (e.g. genetic factors) and drug-drug interactions. |
| **III D. EOP2A MEETING ARRANGEMENTS** | | |
| **Line 249:** | Consistent with our previous comment (see page 3), the process for determining the meeting date and provision of the meeting package should be made consistent with that described in the Formal Meetings Guidance. | Please clarify or specifically state that the normal procedures and timing for type C meetings do not apply. |

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| **Line 256:** | In the last paragraph, the draft guidance states that the analyses are of an "exploratory" nature. Does this mean that 21 CFR Part 11 regulations are not applicable? Could a sponsor choose to use open source software? | Please clarify that a sponsor could choose to use open source software? We also propose Part 11 should not apply due to the exploratory nature of the analyses. |

**CONCLUSION:**

BIO appreciates this opportunity to comment on the draft guidance for industry on *End-of-Phase 2A Meetings*. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew J. Emmett
Director for Science and Regulatory Affairs
Biotechnology Industry Organization