Biotechnology Industry Organization

March 18th, 2012

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA–2012–D–1145:

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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products." BIO commends FDA on the release of this Draft Guidance, which will help to increase the efficiency of clinical research and, ultimately, to facilitate the development of therapies with better defined benefit-risk relationships for relevant patient populations.

BIO represents more than 1,100 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:

A. Improving the Utility of the Draft Guidance

In general, the Draft Guidance is very helpful and well written, providing useful examples and references to illustrate the important principles underlying each section. BIO believes, however, that the overall utility of the Draft Guidance would be enhanced by more explicit and deliberate discussions of the labeling implications for the specific enrichment strategies presented, as well as a discussion that identifies the common factors that prevent achievement of various enrichment goals and provides recommendations to address them. Additionally, there is confusion and concern with the definition offered for "prognostic enrichment," which is highlighted in several specific questions and comments in the table below.

B. Broadening the Scope of the Draft Guidance

BIO suggests that several sections of the Draft Guidance should broaden their focus beyond pivotal registration trials and point out relevant enrichment approaches for non-

1201 Maryland Avenue SW
Suite 900
Washington DC 20024
202.962.9200 P
202.488.6306 F
bio.org

registration Phase 1 and 2 trials. The distinction between registration and non-registration studies is important, particularly for co-development of a drug with a predictive biomarker. In non-registration programs, all studies will generally be purely inductive in nature until both the dose(s) and population for registration studies are selected. Often the selection will not be achieved until the end of Phase 2b studies. This sets non-registration programs apart in that there is typically not an expectation that Phase 2 studies would be used to support registration of the drug, and this may permit greater flexibility with respect to enrichment programs.

C. Highlighting the Relationship to Other, Relevant Guidance Documents

BIO shares the Agency's commitment to modernizing the conduct and improving the efficiency of clinical research, while ushering in an era of more personalized care to patients.[1][2][3] To advance this commitment, BIO enthusiastically supports efforts by the FDA to address regulatory aspects of Adaptive Design Clinical Trials[4], Drug Development Tools[5], In Vitro Companion Diagnostic Devices[6], and related guidance documents and encourages FDA to cross-reference, where appropriate, these and other important guidance documents to provide a more cohesive view of the Agency's current regulatory policies related to clinical research and development of more personalized therapies for patients.

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products." Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

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[1] FDA Draft Guidance, *In Vitro Companion Diagnostic Devices* http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM262327.pdf

[2] FDA Draft Guidance, Adaptive Design Clinical Trials for Drugs and Biologics http://www.fda.gov/downloads/Drugs/.../Guidances/ucm201790.pdf

[3] FDA Draft Guidance, Qualification Process for Drug Development Tools http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM230597.pdf

[4] BIO Comments on FDA Draft Guidance on Adaptive Design Clinical Trials http://www.bio.org/sites/default/files/20100527a.pdf

[5] BIO Comments on FDA Draft Guidance on Qualification Process for Drug Development Tools http://www.bio.org/sites/default/files/20110124.pdf

[6] BIO Comments on FDA Draft Guidance on In Vitro Companion Diagnostic Devices http://www.bio.org/sites/default/files/BIO_Comments_to_FDA_Companion_Dx_Draft_Guidance_Document_.pdf

Biotechnology Industry Organization

Sincerely,

/S/

Andrew W. Womack, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
II. BACKGROUND		
Line 62:	The enrichment strategy to decrease heterogeneity includes an approach to exclude patients likely to have high placebo effect. This approach affects not only variability, but also the expected treatment effect –such that it may be misleading to have it as part of a strategy to reduce variability.	BIO recommends that FDA create a fourth category on "reducing placebo effect."
Lines 67-69:	The discussion of prognostic strategy seems to imply that there could only be two types of endpoints, events (binary endpoint) and continuous responses, and does not acknowledge other types of responses (*e.g.*, ordinal, counts, etc).	BIO recommends that FDA comment on additional endpoints in the discussion of prognostic strategies.
Lines 69-70:	Increasing the absolute and not altering the relative effect may not always be possible, *e.g.,* "absolute" and "relative" effects are not necessarily always separate and distinct. Additionally, the definition of "relative effect" may vary from user to user, and therefore, use of this phrase may cause confusion.	BIO requests that FDA clarify this statement and explain why prognostic enrichment strategies can only increase the absolute effect difference but not the relative effect.
Lines 73-77:	The Draft Guidance states that choosing patients more likely to respond to the drug can lead to a larger effect size, both absolute and relative.	BIO requests that FDA provide more explanation of why predictive enrichment would lead to both relative and absolute increases in effect size and why this differentiation between the two types of enrichment is relevant.

SECTION	ISSUE	PROPOSED CHANGE
Lines 84-85:	In some designs, there may be more than one randomization. For example, a randomized withdrawal study may be embedded within a more complex design.	BIO suggests the text be revised to: "In almost all cases, the strategies affect patient selection ~~before~~ prior to the relevant randomization step (with a few exceptions for adaptive strategies to be noted later)."
Lines 94-95:	BIO believes the issues in this portion of the guidance extend beyond accuracy and should encompass reproducibility.	BIO suggests the text be revised to: "In addition, the accuracy and reproducibility of the measurements used to identify the enrichment population and the sensitivity and specificity of the enrichment criterion in distinguishing responders and non-responders are also critical issues."
III. DECREASING HETEROGENEITY		
Lines 105-122:	The bulleted list does not address differential pharmacokinetic (PK) effects or enrollment strategies based on "time from diagnosis."	BIO suggests that FDA consider inserting new bullets to address (1) the potential for differential pharmacokinetic (PK) effects (*e.g.*, metabolism of the experimental agent) and (2) inclusion only of patients with newly-diagnosed disease to decrease heterogeneity.
Lines 109-112:	In certain circumstances, Risk Evaluation and Mitigation Strategies (REMS) or educational materials intended to demonstrate an improvement in compliance may create such a subpopulation in the market place.	BIO suggests that FDA consider adding the qualifier that this is true unless the patient population for market is similarly selected.
Line 120:	Cross-referencing this topic, and in general under section III, would improve usability of the Draft Guidance.	BIO suggests that FDA consider cross-referencing section(s) where "Excluding patients unlikely to tolerate the drug" points are listed.
Lines 120-122:	Exclusion criteria should be based on objective criteria to facilitate construction of the label.	BIO recommends noting that any exclusion criteria should be based on objective criteria to facilitate construction of the label.

SECTION	ISSUE	PROPOSED CHANGE
B. Decreasing Placebo Responses and Spontaneous Improvement		
Lines 154-165:	BIO is interested in additional discussion of the use of molecular biomarkers as an exclusion criterion for identification of patients more likely to have placebo response in a clinical trial.	BIO recommends that FDA consider additional discussion of the use of molecular biomarkers as an exclusion criterion for identification of patients more likely to have placebo response in a clinical trial.
Lines 156-159:	The strategy to have a single-blind, placebo lead in period has been shown not to be effective.[7]	BIO suggests that alternative examples be used.
IV. PROGNOSTIC ENRICHMENT STRATEGIES – IDENTIFYING HIGH-RISK PATIENTS		
Lines 171-172:	BIO believes it is important to specifically mention "substantive improvement in an ordinal categorical variable" as a prognostic enrichment strategy.	BIO recommends revising this text to read: "A wide variety of prognostic indicators have been used to identify patients with a greater likelihood of having the event (or a large change in a continuous measure or substantive improvement in an ordinal categorical variable) of interest in a trial."
Lines 171-184:	For prognostic enrichment strategies, it should be made clear that high-risk patients are not always those who are already in a late stage of the disease. It may be that new pathway-specific drugs under development actually act at a relatively early stage, when patients still have a low risk of displaying any serious event in the short-term. This paragraph	BIO requests that FDA provide clarification that risk status is not dependent upon the stage of disease. Please also provide clarification on the burden of proof for "prognostic indicators" to allow a healthy "at risk" patient to be included in a drug trial.

[7] Trivedi MH and Rush J (1994) Does a placebo run-in or a placebo treatment cell affect the efficacy of antidepressant medications? *Neuropsychopharmacology* 11: 33-43.

SECTION	ISSUE	PROPOSED CHANGE
	seems to put emphasis on serious events only (*i.e.*, such as rate of death) which could make such a strategy only valuable for long-term trials.	
Lines 186-187:	This is applicable to studies with an active control group and, as such, the reference to the placebo group should be generalized to the control group (active or placebo).	BIO recommends revising this text to read: "For any given desired power in an event-based study, the appropriate sample size will depend on effect size and the event rate in the ~~placebo~~ control group."
Lines 187-189:	The use of relative and absolute effect is confusing. With more events under standard of care or placebo, it is easier to detect differences between treatment arms since more events can be prevented, as long as event rate is below 50%. With prognostic enrichment, the selected population provides more events in a given time interval than a non-enriched population. With time-to-event and odds-ratio analysis, the number of events is a key quantity for power; therefore enrichment will allow for smaller sample sizes if it is assumed that the treatment effect is the same for the enriched and the non-enriched population.	BIO requests FDA provide additional clarification about the effect of prognostic enrichment on sample size.
A. Experience with Prognostic Enrichment Strategies		
Lines 199-206:	This portion of the guidance should acknowledge that there is the potential for different benefit-risk profiles in different subgroups of the patient population. Also, duration of follow-up may need to be	BIO requests that FDA (1) acknowledge that there is the potential for different benefit-risk profiles in different subgroups of the patient population and (2) offer guidance on the duration of follow-up needed in lower risk patients to

SECTION	ISSUE	PROPOSED CHANGE
	longer in lower risk patients as drug effects on markers of disease may take longer to manifest into clinical benefit.	observe manifestations of clinical benefit.
Lines 208-218:	As defined in the Draft Guidance, prognostic enrichment results in a constant "relative effect" of treatment (*e.g.*, a risk ratio) over subgroups with different risks or prognoses (in the absence of treatment). Yet in the example of the enalapril trials, both the absolute and the relative effect sizes increase in the more ill populations.	BIO suggests FDA provide an alternate example, as the enalapril example does not conform to the definition for prognostic enrichment previously offered in the guidance.
Lines 236-239:	BIO believes it would be helpful to have further guidance on the impact of demonstrating, only in an enriched population, non-inferiority of an investigational anti-diabetic drug to placebo in terms of cardiovascular risk.	BIO requests that FDA provide further guidance on the impact of demonstrating, only in an enriched population, non-inferiority of an investigational anti-diabetic drug to placebo in terms of cardiovascular risk.
B. Potential Strategies for Prognostic Enrichment		
Line 263:	There is minimal discussion of what constitutes a good predictor, and how to identify and validate these markers.	BIO recommends introduction of a cross reference to the Drug Development Tools FDA draft guidance within an enrichment strategy context.
V. PREDICTIVE ENRICHMENT		
Lines 320-321:	The statement "antibacterial drug effects are best analyzed in patients whose organism is sensitive to the antibacterial drug" implies that it is an analytical issue. It would be helpful to separate out design	BIO suggests clarifying those effects that are easier to detect in patients who are sensitive to treatment by amending the text: "antibacterial drug effects are best ~~analyzed~~ detected in patients whose organism is sensitive to the antibacterial

SECTION	ISSUE	PROPOSED CHANGE
	issues from analytical issues.	drug"
Lines 320-328:	In a predictive enrichment design, if responders are identified based on post-randomization/treatment results, restricting the primary analysis to responders would violate the intention to treat (ITT) principle and would not preserve the randomization.	BIO requests that FDA clarify whether the benefit-risk assessment would have to be based on all randomized/treated patients, even though demonstration of efficacy is confined to the responder population subset. Please also comment on the acceptability of the approach proposed in the guideline despite potential methodological concerns.
Lines 324-328 and 338-341:	This discussion points out an effective way to identify a potential responder population, however, employing this strategy may trigger important implications for labeling.	BIO recommends that FDA provide some clarification regarding how this strategy would affect labeling.
Lines 345-349:	Certain therapeutic modalities do not have traditional treatment responders.	BIO requests clarification that these concepts apply to different types and levels of responders.
Line 358:	BIO believes the reference to Table 2 is intended to refer to Table 1.	BIO suggests revising this text to read: "…marker-negative populations. ~~Table 2~~ Table 1…"
Lines 369-376:	In general, sample size is determined by the expected effect in the enriched population, not the difference in response between marker-positive and marker-negative populations. In the example provided in support of this strategy, the expected treatment effect in marker-negative patients is 0%, which is unlikely.	BIO recommends an alternate example to help illustrate this important point.
Lines 393-401:	This passage conveys the value of data for the non-selected population. BIO believes that a reasonable approach would be to	BIO recommends that FDA comment on the possibility of developing the compound solely in a marker positive population, then determining efficacy in the broader,

SECTION	ISSUE	PROPOSED CHANGE
	first develop the compound solely in a marker positive population, then evaluate the broader population as part of label expansion, or potentially as part of a post-marketing commitment.	marker negative population as part of label expansion or, potentially, as part of a post-marketing commitment. Also, to ensure consistency between lines 393-395 and 982-984, it should be clarified that testing the marker negative population is not always needed.
Lines 394-395:	BIO believes that Sponsors will only be able to expect an estimate, and as is stated in the document, the non-enriched patient group may be smaller than the marker-positive patient group, and hence have less precision.	BIO recommends revising to read: "It is therefore generally desirable to have some data in the non-selected (non-enrichment) population to ~~determine~~ estimate whether they respond less well, or indeed do not respond at all."
Line 398:	For the statement "A qualitative estimate of effectiveness might also be based on pharmacologic or even pre-clinical data," examples are needed to clarify the extent to which preclinical data can be used to justify excluding the unselected patient population from further study.	BIO requests that FDA provide examples (outside the infectious disease setting, if possible) to better understand the extent to which preclinical data can be used to justify excluding the unselected patient population from further study.
Lines 399-400:	There is a wide body of literature that supports this notion in oncology. Examples include BRAF $V600^{E}$, KRAS, mEGFR, cKit in Melonoma. In the future, this may be a likely scenario with other targeted therapies.	BIO requests that FDA provide an example whereby a strong mechanistic rationale might obviate the need to study a non-enriched population.
Lines 405-408:	This suggests the effect of a drug on a subset of patients based on characteristics that are only determined after randomization may be acceptable in certain circumstances. It is clear that this would not be an issue if the marker were	BIO requests that FDA clarify whether the effect of a drug on a subset of patients for whom a non-baseline characteristic is only measured post-randomization would be acceptable.

SECTION	ISSUE	PROPOSED CHANGE
	based on a patient's baseline characteristic and the marker test resulted after randomization. It is not clear whether the effect of the drug on a subset of patients for whom a non-baseline characteristic is only measured post-randomization would be acceptable.	
A. Empiric Strategies		
Lines 425-435:	This approach may be problematic in the setting of advanced cancer and other advanced, life-threatening diseases or when the treatment effect is permanent (is curative). The approach by Freidlin and Simon, outlined in Section C, could be an alternate approach for these populations.	BIO recommends adding: This approach may be problematic in the setting of advanced cancer. It would be difficult, and potentially unethical, to randomize a responding patient with advanced disease to a placebo, once the patient has demonstrated a response. It may be more appropriate to discontinue treatment in non-responders. Then, utilize a genomic approach to compare pre- and post-treatment biopsies to identify biologic characteristics of the tumors of patients most likely to respond (or not respond). Identified characteristics could be utilized to develop future predictive marker strategies.
Lines 425-435:	It may be necessary to evaluate both safety and efficacy markers during the open-label lead-in period.	BIO recommends clarifying that in a case when both safety and efficacy markers are evaluated during the open-label lead-in period, only those patients who experience (1) benefit with respect to the efficacy marker(s) and/or (2) demonstrate an acceptable benefit:risk ratio, would be randomized to study therapy.
Lines 494-497:	Examples of cases where this enrichment strategy could be used would be helpful.	BIO recommends that FDA provide examples of cases where this enrichment strategy could be used.

SECTION	ISSUE	PROPOSED CHANGE
Lines 499-504:	It is unclear whether the information about a patient's response to a treatment class would only apply to so-called "me-too" compounds.	BIO requests that FDA clarify the scope to which information about a patient's response to a treatment class would apply.
Lines 504-505:	If the study enrolls patients who have failed treatment from one class of drug, and the study shows a new class to be superior to placebo, then clinical practice should restrict use of the new drug to those who failed on the other class of drugs. Similarly, if the study enrolls only patients who have found a certain level of efficacy from a drug in the same class, and randomizing those patients to the new drug or placebo shows superiority, then the clinical practice and labeling would indicate patients eligible to be treated with the new drug are those who have shown a level of efficacy on other drugs in the same class.	BIO requests that FDA provide a rationale for the statement, "In most cases, however, it will not help identify the population to be treated in clinical practice."
B. Pathophysiological Strategies		
Lines 625-628:	In the statement, "tumor receptor variables that could be described as proteomic variables," it is unclear what is meant by "proteomic variables."	BIO requests that FDA clarify what is meant by "proteomic variables."
C. Genomic Strategies		
Lines 639-650:	BIO agrees that use of genomic markers could be an empiric strategy for identifying responders without providing a	BIO recommends that FDA clarify that pre-planned, retrospective analyses of sufficient size can lead to convincing confirmations of a newly observed effect.

SECTION	ISSUE	PROPOSED CHANGE
	pathophysiologic basis for the difference in response (for example, the employment of complex algorithms for enrichment and to predict response may not be the result of having a primary pathophysiologic basis) and acknowledges that markers discovered this way may have credibility problems related to the *post-facto* nature of the finding. However, BIO disagrees that these *post-hoc* correlations between genetic patterns and outcomes will almost always need confirmation in a prospectively planned, enriched study. There are instances where this is not the case (*e.g.,* when pre-planned, pre-specified analyses of data of sufficient size from retrospective studies in patients with and without the exploratory marker are employed to confirm such a finding).	
Lines 642-643:	This suggests that the mechanism of any enrichment strategy ***must*** be understood and not be simply empiric. Although generally this would be the case, it may exclude an enrichment strategy (*i.e.*, a large gene signature) where the pathophysiological mechanism is not readily apparent, despite having clinical utility and validity. If there is such a complex genetic signature involving many genes that is strongly predictive, a lack of	BIO recommends revising to read: "Any genetic differences that predict response ~~must~~ should in the end have some pathophysiologic basis, but enrichment strategies to identify responsive patients could be used before recognition of a mechanism." Additionally, please clarify that lack of knowledge regarding the mechanism of a strongly predictive, complex genetic signature would not delay product approval.

SECTION	ISSUE	PROPOSED CHANGE
	knowledge regarding its mechanism should not delay approval.	
Lines 642-649:	In many situations, the enriched study is based on a genomic classifier that has been derived retrospectively from earlier studies. In most situations, the estimate and statistical significance of treatment effect based on retrospective analysis suffers from selection bias and inflation of type 1 error.	BIO requests that FDA provide strategies for treatment effect estimated from retrospective analysis to address problems of selection bias and multiplicity, either via cross-validation methods, permutation methods, or a combination of the two.
Lines 655-671:	The strategy described by Freidlin and Simon presumably requires an independent data monitoring committee (DMC) to conduct the interim analysis. In a time-to-event setting, dividing the study in two halves would presumably be based on the accumulated number of events. In this case, the subset of patients included in an interim analysis (for example, when 50% of the target number of events are achieved) may overlap with the subset of patients who contribute to the 2nd stage (when the remaining 50% of events are accumulated) and hence it may be less straightforward to select the "second half" in which the genetically identified subset is tested.	BIO requests that FDA comment on the appropriateness of this approach for clinical outcomes trials with time-to-event endpoint.
Lines 655-688:	It is unclear whether these examples for trial design are theoretical or have been	BIO requests that FDA clarify whether these examples for trial design are theoretical or have been validated in trials

SECTION	ISSUE	PROPOSED CHANGE
	validated in trials adequate to support approval.	adequate to support approval.
Lines 664-665:	If the Sponsor is aware that a subpopulation has been identified and will be tested at a particular nominal alpha level (*e.g.,* 0.01), then sites may enroll a disproportionate number of enriched patients, potentially creating interpretability and even multiplicity issues, due to potential for bias in the second half enrollment. Additionally, BIO believes that the Sponsor also has the ability to switch to a new enriched-only population (so the final analysis would not include the patients in the first half, leading up to the interim analysis).	BIO suggests that the point made on lines 684-688 also be included or cross-referenced in item 3. Additionally, BIO requests that FDA clarify that the Sponsor also has the ability to switch to a new enriched-only population (so the final analysis would not include the patients in the first half, leading up to the interim analysis).
D. Randomized Withdrawal Studies		
Lines 709-745:	The word "withdrawal" is used with different meanings: first as withdrawal from treatment as the consequence of randomization (*i.e.*, by design) and second as withdrawal from study due to angina as the outcome measure of a trial.	BIO recommends that FDA clarify these distinct events (*e.g.,* "withdrawal" for the design aspects and "discontinuation" for the outcome).
E. Studies in Non-responders or Patients Intolerable to Other Therapy		
Line 779:	The enrichment strategies that are being discussed refer to specific methodologies used to identify a sub-population that may have a greater response to treatment than	BIO suggests separating and individually addressing these concepts.

SECTION	ISSUE	PROPOSED CHANGE
	the general population. But the statement "**Studies in Non-responders or Patients Intolerant to Other Therapy**" does not seem to be purely an enrichment strategy. Studies using such patients are intended to address an unmet medical need, and do so by assessing whether a new therapy offers a better therapeutic effect than the currently available therapies. But such studies do not necessarily provide answers to questions related to treatment effect in the general population.	
Lines 808-809:	This note refers to two approaches for using studies in non-responders or patients intolerant of other therapy, and discusses how an effect may be demonstrated. Lines 798-799 discuss demonstration of a treatment effect that is "moderately superior," yet the note says that neither approach would establish overall superiority of the new drug.	BIO suggests clarifying this situation and explaining further what more would be needed to establish overall superiority of a new drug.
Lines 837-848:	The study described appears to be a standard comparative study in a refractory population.	BIO requests that FDA provide examples in addition to Clozapine.
VI. ENRICHMENT STUDY DESIGN AND OTHER CONSIDERATIONS		
A. General Considerations		
Lines 900-901:	Potential multiplicity issues often arise in simultaneous development of a new drug	BIO requests that FDA provide guidance on whether the utility of the companion diagnostic should be included in a

SECTION	ISSUE	PROPOSED CHANGE
	with a companion diagnostic for identification of patients who are likely to benefit from the drug. While the primary objective of such a study is usually to demonstrate efficacy in a specific patient sub-population, guidance on whether the utility of the companion diagnostic should be included in a multiplicity adjustment would be helpful.	multiplicity adjustment.
Lines 912-938:	Subsection 1 describes the performance characteristics of classifiers that may use high dimensional proteomic and genomic level markers. It is not clear what type of performance metrics should be used to evaluate the performance of the classifier.	BIO encourages FDA to consider providing guidance on re-sampling, cross-validation, or permutation-based methods to assess the performance of a classifier that has been derived retrospectively from the data of an existing study.
Lines 923-924:	While patients who might benefit may not always be studied, this approach is an efficient demonstration of drug effect.	BIO encourages FDA to consider including the concept that excluding patients who might benefit, but for whom the rationale is less strong, may be an appropriate approach to quickly demonstrate that a novel compound is active, and halt development if it is not; activity in a broader population can be addressed at a later time, if there is a scientific rationale.
Lines 924-925:	For a sponsor to conduct a non-inferiority enriched design, the product labeling for the active control should include the enriched population to be studied, in order to avoid compromising interpretability.	BIO requests that FDA clarify that for a sponsor to conduct a non-inferiority enriched design, the product labeling for the active control should include the enriched population to be studied in order to avoid compromising interpretability.
Lines 947-954:	It is unclear how a classifier can be both developed/defined and used to assess response in the same study.	BIO recommends that FDA explain how a classifier can be both developed/defined and used to assess response in the same study.

SECTION	ISSUE	PROPOSED CHANGE
Lines 954-957:	BIO believes that minimization enjoys a number of advantages as a randomization scheme, but it is unclear whether it can be used as an alternative.	BIO requests that FDA clarify whether minimization can be used as an alternative randomization scheme.
Line 956:	BIO believes that the practical and statistical shortcomings of stratification need to be considered.	BIO requests that FDA consider discussing practical and statistical shortcomings of stratification, citing: Therneau, T.M. (1993) "How many stratification factors are "too many" to use in a randomization plan?" *Controlled Clinical Trials*, 14(2): 98–108.
B. Which Populations to Study		
Lines 984-985:	This text suggests that marker-negative patients may not need to be studied in the event that there is sufficient evidence to contraindicate usage in these patients. An example of this situation is thiopurine dosing in thiopurine S-methyltransferase (TPMT) poor metabolizers.	BIO requests that FDA clarify that this situation would only occur when there are compelling prior preclinical/clinical results that, on their own, would preclude the use of the test agent in marker-negative patients.
Lines 1007-1010:	BIO believes the marker-positive only study design should be considered in a broader set of circumstances.	BIO recommends adding that a marker-positive only approach is also appropriate in order to make a rapid assessment of activity in a small patient population. Please also discuss the risk of missing a signal of activity by not selecting patients when a marker positive population is a small fraction of the total and the marker-negative population is not likely to respond.
Lines 1010-1013:	BIO believes there is value in broadening the possibility of using data from other sources to determine the appropriateness of potential study populations.	BIO recommends revising to read: "For example, if it appears clear, based on mechanistic, pre-clinical, or early clinical data from the study drug or

SECTION	ISSUE	PROPOSED CHANGE
		other drugs in the same class, that the marker-negative patients will have no or minimal response or would be exposed to unreasonable risk, inclusion of the marker-negative patients would, in most cases, not be justified."
Lines 1029-1032:	The Draft Guidance indicates that an enrichment marker could be measured after drug approval using an established, FDA-approved diagnostic test as a companion diagnostic. It is possible that such an *in vitro* diagnostic (IVD) would not yet be ready at the time of product approval. If the therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists, the benefits from the use of the therapeutic product with an unapproved IVD companion diagnostic device can be so beneficial as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device.	BIO requests that FDA consider providing guidance to Sponsors who receive an approval for a therapeutic product intended to treat a serious or life-threatening condition that would normally require a companion diagnostic but for which the companion diagnostic is not yet approved or cleared. Also, please clarify whether an Investigational Device Exemption (IDE) is required for the use of exploratory laboratory tests for trial enrichment.
Lines 1050-1067:	It is not clear how this theoretical consideration can be implemented in a clinical trial with regard to the overall success of the study.	BIO requests that FDA discuss the scenario where a pivotal trial shows effect only in the group that is marker positive and not in the overall trial population, even if this is described in the protocol. Please also discuss appropriate analysis methods for the full population (Stratified test? Pre-test of difference in treatment effects?).
Lines 1058-1062:	BIO believes that randomization between marker-positive and marker-negative	BIO requests that FDA add, in order to limit the exposure of marker-negative patients to a non-effective or limited-

SECTION	ISSUE	PROPOSED CHANGE
	patients does not necessarily need to be 1:1.	effective drug, that the randomization between marker-positive and marker-negative patients can be uneven, especially if treatment effect is expected to be small in the marker-negative patients.
Lines 1062-1064:	If the proportion of patients in the marker-negative subgroup in the clinical trial is substantially less than the relative prevalence of the marker negative group in the general population, the naïve estimate of the treatment effect in the overall population in the clinical trial may be a biased estimate of the treatment effect in the overall population for clinical practice. A weighted average of the marker-positive and marker-negative treatment effects, weighted by the underlying prevalence of marker-positive and marker-negative patients, may have less bias.	BIO recommends that if the proportion of patients in the marker-negative subgroup in the clinical trial is substantially less than the relative prevalence of the marker negative group in the general population, a weighted average of the treatment effects in the marker subpopulations should be used to estimate the treatment effect in the overall population to prevent potential bias.
Lines 1064-1067:	Some alpha-sharing strategies between the marker-positive and overall population have been criticized because of concerns that the treatment effect in the overall population is driven primarily by the treatment effect in the marker-positive population.	BIO requests that FDA consider adding that studies should demonstrate the treatment effect for the overall population is not unduly influenced by the treatment effect in the marker positive subpopulation.
Lines 1079-1082:	BIO believes that "patient management decisions" refers to decisions made during the conduct of the trial, not decisions to be	BIO recommends revising to read: "…and if no patient management decisions in the trial will be made…"

SECTION	ISSUE	PROPOSED CHANGE
	made in clinical practice.	
Lines 1098-1100:	BIO believes that asking patients who have had a non-response to a standard drug to consent to participate in a trial where they might not respond again may not only pose significant ethical questions, as mentioned, but could also jeopardize recruitment and alter the feasibility of such a trial.	BIO encourages FDA to consider adding that careful consideration to study feasibility should be applied in the planning stage of such a trial, since patients who have not responded to a treatment might not consent to participate in a trial in which they may once again not have a response.
Lines 1114-1117:	BIO believes that asking patients who have had an adverse effect to a standard drug to consent to participate in a trial where they might again experience this adverse effect may not only pose significant ethical questions, as mentioned, but could also jeopardize recruitment and alter the feasibility of such a trial.	BIO encourages FDA to consider adding that careful consideration to study feasibility should be applied in the planning stage of such a trial, since patients who have experienced an adverse effect to a treatment might not consent to participate in a trial in which they may again experience an adverse effect.
C. Type I Error Rate Control for Enriched Study Subpopulations		
Lines 1130-1133:	BIO believes that this approach requires a strong treatment effect in the selected subset and will only be successful if the treatment effect is much stronger in the selected subpopulation.	BIO requests that FDA provide examples estimating the required treatment effect in the entire population and the marker-positive subset if alpha is divided 0.04 and 0.01, respectively.
Line 1133:	BIO believes an additional reference to the paper by Alosh and Huque (regarding simultaneous testing of the overall population and a subset) would be appropriate.	BIO recommends referencing: Alosh M and Huque MF (2009) A flexible strategy for testing subgroups and overall population. *Statist Med*, 28: 3–23.

SECTION	ISSUE	PROPOSED CHANGE
D. Adaptive Enrichment		
Lines 1147-1150:	In such a design there will be data from marker-positive and marker-negative subgroups, since both sub-populations are enrolled in the beginning of the trial. If there are interim analyses being conducted to *potentially* focus the remainder of the trial on only marker-positive patients, it is difficult to identify a case where alpha adjustment would not be required in the event that no such marker was identified, and thus the final analysis is of the full population enrolled into the trial.	BIO requests that FDA include some examples where alpha adjustment would not be necessary.
Line 1152:	The reference document (#52) provided through the link cannot be identified.	BIO suggests a new link may be needed.
Lines 1163-1164 and 1175-1180:	BIO believes that the adaptive enrichment approach is an intriguing prospect that should be further explored and promoted. A number of examples of such trials have been reported in the literature, but there is little experience with their use in drug development. The idea of modifying the cut-off during the course of the study to increase the response rate is something that could be explored further; however, this may become a challenge for smaller oncology trials with limited room for change due to the power.	BIO encourages FDA to explore further and promote the adaptive enrichment approach.

SECTION	ISSUE	PROPOSED CHANGE
Lines 1187-1191:	BIO believes that the approach described in this statement could erroneously conclude that the drug is effective in the full population, when that significant result occurred because the entry criterion was modified to enriched-only at the interim analysis.	BIO requests that FDA clarify how the approach described in this statement would avoid erroneously concluding that the drug is effective in the full population, when that significant result occurred because the entry criterion was modified to enriched-only at the interim analysis.
E. Cautions in Interpretation		
Lines 1210-1213:	Analytical validity should be noted as important prior to the initiation of the pivotal study. With respect to performance, it should be made clear that "sensitivity and specificity" refers "clinical sensitivity and specificity" and these are relative to final validation of the test, including positive predictive value (PPV) and negative predictive value (NPV) intended for a post marketing setting.	BIO requests that FDA clarify that "sensitivity and specificity" refers "clinical sensitivity and specificity" and these are relative to final validation of the test, including positive predictive value (PPV) and negative predictive value (NPV) intended for a post marketing setting.
Lines 1210-1219:	It can be difficult to determine sensitivity, specificity and positive/negative predictive value prior to early clinical studies for markers of efficacy. In cases of a novel assay for a novel marker, it may not be possible at all due to the lack of a "gold standard" assay for comparison.	BIO requests that FDA consider (1) acknowledging that the performance characteristics of an assay may not be known during early clinical development, (2) providing perspective on the increasingly common situation where traditional assay performance characteristics cannot be defined at all because there is no "gold standard" assay for reference, and (3) discussing the use of false positive and false negative rates, as they may be more relevant in early studies, and can be measured with smaller sample sets.
VII. ENRICHMENT – REGULATORY ISSUES		
A. Summary – The Decision to Use an Enrichment Strategy		

SECTION	ISSUE	PROPOSED CHANGE
Lines 1266-1273:	If a subpopulation that is responsive to treatment can only be identified after certain duration of exposure, then that uncertainty about the possible treatment effect may make it less likely that the treatment will be used in clinical practice. Would this situation then affect the label?	BIO suggests clarifying how the label will be handled in such a situation.
B. Data That Should Be Obtained for the Marker-Negative Patients		
Lines 1352-1356:	BIO believes it would be useful to consider including published literature as another basis for providing a rationale for not pursuing biomarker-negative patients in a clinical study (*e.g.*, if there is published literature pertaining to a competitor molecule in the same pharmacological class). Other preclinical information and early clinical data could be used to corroborate literature on a competitive molecule.	BIO requests that FDA clarify that published literature, including competitive evidence, may support an appropriate rationale for not pursuing a biomarker-negative patient population.
Lines 1358-1359:	Presumably, the degree of efficacy (or lack thereof) in a marker negative group may be a factor in setting the specification for the positive predictive value (PPV) of the diagnostic (more stringent if there is lack of benefit or harm in the marker negative group). Therefore, the existence of an approved companion diagnostic should be a requirement for collecting less data in a marker-negative group.	BIO requests that FDA consider adding "existence of an approved companion diagnostic" as a third bullet.
C. Labeling		

SECTION	ISSUE	PROPOSED CHANGE
Lines 1370-1382:	The labeling section does not address situations described earlier, such as reducing placebo responses and encouraging compliance.	BIO recommends that FDA consider updating the labeling section to address situations described earlier, such as reducing placebo responses and encouraging compliance.
Line 1382:	BIO believes incorrect references were cited.	BIO recommends revising to read: "…should be provided.~~55~~,56,57"