Biotechnology Innovation Organization

October 12, 2018

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

Re: Docket No. FDA-2018-D-2777: Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the draft guidance titled "Expansion Cohorts: Use in First-In-Human Clinical Trials to Expedite Development of Oncology Drugs and Biologics."

BIO is the world's largest trade association representing 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.

BIO welcomes FDA's efforts to provide clear guidance on the regulatory and scientific framework for product developers designing and conducting adaptive trial designs in which different aspects of a drug can be assessed in a single clinical trial while enrolling the minimum number of study participants necessary to obtain this information. BIO has provided below comments for the Agency to consider as it finalizes the Guidance.

General Comments:

- For safety reasons, Section V places a limit on sample sizes. However, depending on the study design and potential effect size of a therapeutic agent as well as safety profile, sample size numbers may unnecessarily limit expansion of cohort trials that do not pose unexpected safety issues and ultimately would lead to registration. FDA should reconsider providing prescriptive recommendations on sample size and permit science-based flexibility by Sponsors.

- In general, the Draft Guidance should focus on design features that are desirable for a First-in-Human (FIH) cohort and not on specific types of designs or specific sample-sizes for study cohorts. This is particularly relevant as we make advances in statistical techniques and changing standards of care.

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- In particular, the guidance should avoid mentioning specific statistical approaches (e.g., Simon 2-stage design[1]) for FIH expansion cohorts and instead suggest relevant design principles sponsors could address in the methodology they select. While we acknowledge that Simon 2-stage design is a widely accepted and well-validated method, it should not preclude the use of other scientifically-accepted analytical approaches (e.g., using a Bayesian framework) that potentially offer greater flexibility while still maintaining rigor.

- Although Simon's design has been widely used, critical drawbacks of the approach have been noted in the literature[2,3]. When the presence or lack of an efficacy signal is the primary phase II design consideration, there are a number of other options[4,5,6,7,8] available that provide several advantages over Simon's design. Furthermore, the guidance treats a study with multiple expansion cohorts simply as an operationally convenient "many protocols in one" basket trial where futility or efficacy in any one cohort is determined independently of another. However, basket designs come in several other varieties[5] and designs based on Bayesian hierarchical models[6-7] can achieve far greater inferential efficiency through thoughtful information borrowing across cohorts. Historical borrowing is another approach that can provide substantial inferential advantages and efficiency in go/no-go decision-making over traditional approaches, especially where randomization is contemplated. One should also consider statistical approaches that can address the primary safety concern of "increased risk involved in exposing large numbers of patients to drugs with minimally characterized toxicity profiles in FIH trial with multiple concurrently accruing expansion cohorts", as outlined in Section II of the draft guidance. Several phase II design options[9] are available that attempt to balance safety and efficacy and bear discussion in the guidance.

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[1] Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials, 1989, 10:1-10
[2] Ratain MJ and Karrison TG. Testing the wrong hypothesis in phase II oncology trials: There is a better alternative. Clin Cancer Res, 2007, 13(3):781-2
[3] Englert S and Kieser M. Improving the flexibility and efficiency of phase II designs for oncology trials. Biometrics, 2012, 68, 886-92
[4] Cunanan KM, Gonen M, Shen R, et al. Basket Trials in Oncology: A Trade-Off Between Complexity and Efficiency. J Clin Oncol, 2017, 35(3):271-3
[5] Thall PF, Wathen JK, Bekele BN, et al. Hierarchical Bayesian approaches to phase II trials in diseases with multiple subtypes. Stat Med, 2003, 22(5):763-80
[6] Berry SM, Broglio KR, Groshen S and Berry D. A Bayesian hierarchical modeling of patient subpopulations: Efficient designs of phase II oncology clinical trials. Clin Trials, 2013, 10(5):720-34
[7] Pulkstenis E, Patra K and Zhang J. A Bayesian paradigm for decision-making in proof-of-concept trials, Journal of Biopharmaceutical Statistics, 2017, 27:3, 442-56
[8] Conaway MR and Petroni GR. Designs for phase II trials allowing for a trade-off between response and toxicity. Biometric, 1996, 52(4):1375-86
[9] Thall PF and Russell KE. A strategy for dose-finding and safety monitoring based on efficacy and adverse outcomes in phase I/II clinical trials. Biometrics, 1998, 54(1):251-64

- Thus, the references to Simon 2-stage method should be followed by the text, "or an equivalent statistical method".[10] [11] This is also in keeping with the Agency's current efforts to encourage the use of innovative approaches including innovative statistical approaches in novel clinical trial designs via the Complex Innovative Trial Designs (CID) pilot program.

- BIO encourages the Agency to consider expanding the use of this Guidance Document beyond Oncology.

BIO appreciates this opportunity to submit comments regarding FDA's draft guidance titled "Expansion Cohorts: Use in First-In-Human Clinical Trials To Expedite Development of Oncology Drugs and Biologics". More detailed comments are provided in the table below. BIO would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Sesquile Ramon, Ph.D.
Director, Science & Regulatory Affairs
Biotechnology Innovation Organization

[10] Ratain MJ and Karrison TG. Testing the wrong hypothesis in phase II oncology trials: There is a better alternative. Clin Cancer Res, 2007, 13(3):781-2
[11] Berry SM, Broglio KR, Groshen S and Berry D. A Bayesian hierarchical modeling of patient subpopulations: Efficient designs of phase II oncology clinical trials. Clin Trials, 2013, 10(5):720-34

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Lines 27-28	Language should be clarified	BIO suggested edit: "(3) when to interact with FDA on planning and conduct of multiple expansion cohorts **depending on the objectives of the expansion cohort(s)"**
II. BACKGROUND		
Lines 48-49	Phase 1 clinical trials are designed to evaluate the safety, tolerability, pharmacokinetics and pharmacologic activity.	BIO suggested edit: "**Phase 1 clinical trials are designed to evaluate the safety, tolerability, pharmacokinetics** ~~**determine the metabolism**~~ **and pharmacologic activity** ~~**actions**~~ of an investigational drug in humans"
Lines 49-50	The scope of the guidance seems very specific to FIH studies. However, expansion cohorts may also be useful in Phase 1b protocols post-FIH.	FDA should clarify if the Draft Guidance would also be applicable to any early-phase protocol that intends to include or add expansion cohorts. In addition, if the FDA intends for references to "FIH" and all "Phase 1", including "Phase 1b", studies to all be used synonymously, then we recommend the FDA to state this clearly in the document.
Lines 53-54	The total number of patients included in phase 1 studies may be above the suggested range.	BIO suggested edit: "**In general,** the total number of patients included in phase 1 studies is anticipated to be in the range of 20 to 80 patients; **multiple expansion cohorts with phase 1 objectives may exceed 80 depending on the number of cohorts and the cohort-specific objectives**."
Lines 62-67	Some expansion cohorts do not involve exceptionally large numbers of patients	BIO suggested edit: "Because of the rapid enrollment and evolving nature of the information obtained in these trials, ~~**large numbers of**~~ patients ~~**are**~~ **may be** exposed to drugs with unknown efficacy and minimally characterized toxicity profiles. To mitigate such risks and to protect patients, it is

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		imperative that sponsors establish an infrastructure to streamline trial logistics, facilitate data collection, and incorporate plans to rapidly assess emerging data in real time and to disseminate interim results to investigators, institutional review boards (IRBs), and regulators."
Lines 63-66	In regard to risk mitigation to patients it is unclear what the Agency would consider appropriate in regard to "facilitating data collection" and assessment of data in real time	FDA should provide clarity on the expectation for affiliating data collection as well as to what timeframe is expected for "real time" data entry. Delayed data entry is an auditable finding at clinical trial sites.
III. FIH EXPANSION COHORT DEFINITION AND POTENTIAL OPPORTUNITIES AND CHALLENGES		
A. Definition of FIH Multiple Expansion Cohort Trials		
Lines 82-83	It is unclear if comparison of activity between cohorts would be allowed if one cohort (for example a cohort in which the drug under investigation is administered with another oncology drug) shows increased toxicity relative to another cohort (in this case the cohort in which the drug is administered alone), prompting the pausing or closing of the combination cohort, and if the other cohort(s) will be allowed to proceed with enrollment.	FDA should provide clarity.
B. Potential Opportunities and Challenges Posed by FIH Multiple Expansion Cohort Trials		
Line 92	This text is written in a way that the reader will interpret the bullets below as a comprehensive list of challenges.	BIO suggested edit: "FIH multiple expansion cohort studies pose several challenges and risks, ~~**including**~~ examples include:"
IV. DRUG PRODUCT AND PATIENT CONSIDERATIONS		
Lines 118-119	It is unclear what the FDA means by "robust rationale".	FDA should provide additional information as to what it is meant by "robust rationale,", and it means a rationale that extends beyond what is laid out in Section III A.
Lines 116-122	The language used can be limiting. For example, referencing "no curative therapies" can be limiting to patients. In addition, focusing only on BTD ignores	BIO suggested edit: "To ensure that potential benefits outweigh the risks to patients, the patient population should be limited to patients with serious diseases ~~**for which no**~~

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	other important regulatory categories that have the potential to meet unmet medical needs such as RMAT and fast track.	~~curative therapies are available~~. Sponsors should provide a robust rationale for use of an expansion cohort trial. As drug product development progresses, FDA expects that the investigational drug has the potential to ~~meet the criteria for breakthrough therapy designation to~~ support **a marketing application such that the potential benefits outweigh the risks**. ~~continuation of the expedited clinical development program, such that the potential benefits of enrollment in these complex clinical protocols continue to outweigh the potential for the increased risks to patients."~~
Lines 127-128	The guidance references example of biopharmaceuticals classification system class, but it is unclear if classes 2, 3, and 4 are excluded from multiple expansion trials.	The Agency should provide clarity regarding if biopharmaceuticals classification system class 2, 3, and 4 are excluded from multiple expansion trials.
Line 131-135	Language is limiting and is written as a comprehensive list rather than providing examples.	BIO suggested edit: "Characteristics of investigational drugs that ~~are~~ **may** not **be** suitable for study in clinical trials with multiple expansion cohorts because of increased risks of drug-related toxicity. **Examples could** include steep toxicity indices and large inter- and intra-patient variability (i.e., co-efficient of variability greater than or equal to 100 percent), ~~in~~ pharmacokinetics ~~indicative of~~ **should be evaluated on case by case (for example,** polymorphic enzyme mediated drug clearance for small molecules **where consideration should be focused on enzyme phenotyping and allowing poor metabolizers to receive lower dose than extensive/ultra metabolizers)."**
V. CONSIDERATIONS BASED ON COHORT OBJECTIVES		
A. Confirming Safety of Recommended Phase 2 Dose		
B. Evaluating Preliminary Anti-Tumor Activity		
Lines 173-174	In FIH Multiple Expansion Cohort studies, protocols are typically written to start expansion after safety is confirmed in dose-finding portion, without requiring an amendment or formal reporting of safety from	BIO requests that expansion could proceed seamlessly after dose-finding portion provided safety data from dose-finding portion is reported in the next agreed upon safety reporting period.

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	dose-finding. Investigators are typically informed through calls/updates on the safety experience from dose finding before expansion starts.	
Lines 176-179	Language suggest that an IND should be submitted to the appropriate review division, however we note that the IND may already be submitted to the appropriate review division at this point.	BIO suggested edit: "In general, based on the results observed in a disease-specific expansion cohort, a sponsor intending to continue development of a drug for that indication ~~**should**~~ **may** submit a new IND to the appropriate review division to facilitate direct communication on the adequacy of the development program for that indication."
Lines 176-179	It is unclear if the expansion cohort study already resides in the appropriate FDA review division, opening a new IND for the expansion cohort indication that the sponsor plans to develop would not be warranted. The spirit of the guidance is to expedite drug development as well as enable a more efficient clinical trial. From a sponsor perspective, if development of a cohort indication leads to a new IND for further study, it would result in a sizable delay and would put into question the value of an expansion cohort study.	FDA should provide clarity on this issue. From a sponsor perspective, if development of a cohort indication leads to a new IND for further study, it would result in a sizable delay and would put into question the value of an expansion cohort study.
C. Evaluating Specific PK and Pharmacodynamic Aspects		
Lines 194-200	Since a food effect may be dependent on the formulation, food effect studies should only be conducted with formulations that are used in Phase 2 or Phase 3; not with the powder in capsule formulation as they are abandoned after the FIH trial.	FDA should clarify that food effect studies should only be conducted with formulations that are used in Phase 2 or Phase 3.
Line 202	The Draft Guidance would benefit from providing additional thinking on special populations section and include organ dysfunction, elderly, pediatrics, among others.	FDA should consider creating a "Special Populations" Section of the guidance to contain "organ dysfunction" "elderly" "pediatrics" expansion cohort guidance subsections.
D. Further Dose/Schedule Exploration		

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Lines 220-236	The Draft Guidance could benefit from discussion of dose escalation. Maximum Tolerated Dose (MTD) can be identified in the dose escalation phase using innovative design methodologies such as Bayesian Logistic Regression Model (BLRM) that warrants more efficient dose expansion phase (i.e., less dose modifications), which in turn could efficiently expediate the clinical development of drugs.	Suggest the Agency provide language on Dose escalation and appropriate methods to identify the Maximum Tolerated Dose, including BLRM.
Lines 225-226	There are cases where the expansion cohort has one dose regimen rather than two or more dosage regimens for reasons of safety and/or PK/PD.	BIO suggested edit: "Randomization to two or more dosage regimens to increase the confidence that any differences between treatment arms are not due to chance alone, **except where safety, PK and PD data provide clear support for a single dose/dosing regimen to be used in the expansion cohort."**
E. Biomarker Development		
Lines 240-244	This section should align with FDA draft guidance on co-development.	Suggest FDA add footnote to this guidance due to relevance, as the importance of conducting analytical performance testing is described and emphasized in this guidance.
Lines 247	The guidance document referenced in footnote 14 is incorrect. The concepts described are not mentioned in the draft guidance, "In Vitro Companion Diagnostic Devices."	BIO suggests the addition of the reference to the draft guidance "Principles for Codevelopment of an IVD CDx with a Therapeutic Product" as many of the concepts referenced are elaborated in great detail in it.
Lines 251-254	BIO notes that the approach described in lines 251 through 254 is not consistent with the approach outlined in the cited draft guidance (see footnote 15). The draft guidance, Investigational In Vitro Diagnostics in Oncology Trials: Streamlined Submission Process for Study Risk Determination," recommends that Sponsors include the request for "significant risk determination" in the IND for maximum efficiency.	BIO recommends the following: "**For efficiency, the significant risk assessment for the investigational IVD can be included as part as the IND as suggested in recent draft guidance (footnote 15).** If further assistance with the IVD is required, FDA recommends that sponsors contact the appropriate IVD review center (Center for Devices and Radiological Health or Center for Biologics Evaluation and Research)."
F. Evaluating Drug Product Changes		

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Lines 256-281	Evaluating Drug Product Changes	The guidance should note that the data needed to support an early stage formulation change may differ from data to support a change to a commercial formulation
Lines 262-264	The draft guidance would benefit from including examples of "major manufacturing changes".	BIO proposed edit: "The sponsor should prominently identify in the cover letter of a protocol amendment any change that introduces into an ongoing trial a new formulation or presentation of a drug or major manufacturing changes **(e.g., change in the downstream purification steps).**
Lines 265-266	The FDA should specify that the bridging study should be based on the same route of administration and that bridging could include device delivery systems.	BIO suggested edit: "In such amendments, the sponsor should identify changes in drug product quality attributes that may require bridging to earlier clinical trial drug products that differ in their formulations, **(based on the same route of administration), device delivery system,** packaging configurations, manufacturing processes and impurity profile to allow comparison of the clinical data across cohorts. ~~**using different formulations**~~"
Lines 268-269	It is unclear whether bridging new and older formulations applies to pediatric formulation	FDA should clarify if "bridge new and older formulations" applies to pediatric formulations
Line 268-269	It is unclear whether adjustments to the CMC/formulation/presentation of a drug may be introduced with the intention of altering the safety/efficacy profile of a new drug within the context of a multiple expansion cohort trial, rather than to bridge to earlier clinical results.	FDA should provide clarity on whether adjustments to the CMC/formulation/presentation of a drug may be introduced with the intention of altering the safety/efficacy profile of a new drug within the context of a multiple expansion cohort trial, rather than to bridge to earlier clinical results.
Lines 270-271	The draft guidance would benefit from including an example of when changes in presentation would require human factors studies	Suggested example to include: "When changes in presentation result in significant modifications to dose preparation **(e.g., changing from IV to SC self-injection)"**
Line 280-282	It is unclear what FDA means by "pool key clinical data"	BIO suggested change: "In the absence of such bridging information, it may ~~**not be scientifically valid to pool key clinical data and may**~~ significantly delay marketing approval."

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G. Evaluating More Than One Therapeutic Drug		
Lines 284-291	FDA states that expansion cohort studies with an investigational drug and a second drug are appropriate only after "preliminary safety" has been characterized for both compounds. It would be helpful if FDA could expand on the meaning of "preliminary safety".	FDA should provide further clarity on the concept of "preliminary safety" as it is used in this context. For example, where an investigational agent is not expected to demonstrate efficacy when used as monotherapy, would preliminary safety data derived from a trial design consisting of a "monotherapy lead-in phase" followed by combination therapy with another (fixed dose) therapeutic drug be viewed as adequate?
Lines 284-296	There are some situations where establishing the preliminary safety profile and activity for each investigational drug as a single agent prior to initiating expansion cohort studies with drug combinations is not the optimal approach. This would be the case in settings where preclinical data demonstrates efficacy in combination with a second mechanistically synergistic agent or clinical data with certain drugs have clearly demonstrated synergistic efficacy in combination with a second agent with the same molecular target. In addition, there are certain situations where the second agent is expected to mitigate the toxicity of the single agent.	Suggest the Agency provide guidance on when it is appropriate to initiate combination drug testing prior to establishing the preliminary safety and activity profile for each investigational drugs as a single agent.
Lines 286-291	It is unclear if a staggered approach is acceptable. For example, in cases of a combination of investigational drug A with a fixed dose of approved or investigational drug B (e.g., the established recommended phase 2 dose of drug B), that initiation of a combination with drug B may begin once 1 or 2 dose levels for monotherapy drug A have been cleared for tolerability.	FDA should provide clarity as to whether a staggered approach would be acceptable.
H. Evaluating PK, Tolerability, and Initial Evidence of Activity in the Pediatric Population		
Lines 306-309	The document would benefit from additional information on age group to be studied considering that the minimum information on the safety available	The FDA should consider including additional information on the age group to be studied, considering that the minimum information on the safety available at this point of the

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	at this point of the development may not be appropriate for age < 2 years. In addition, an important and challenging aspect of inclusion of pediatrics in clinical studies are the determination of the appropriate (starting) dose.	development may not be appropriate for age < 2 years. In addition, given the expected limited PK/PD information available at the stage of FIH expansion, the FDA should d provide further guidance on the initial dose selection for pediatrics in these trials and/or clarify the applicability of recent draft guidance "Considerations for the Inclusion of Adolescent Patients in Adult Oncology Clinical Trials".
Lines 307-309	The pediatric expansion cohort can be included as spart of the iPSP. However, it is unclear if the iPSP needs to be agreed upon before initiating the pediatric expansion cohort	BIO suggests that FDA provide clarity on the timing of the iPSP in relation to initiation of the pediatric expansion cohort.
Lines 320-324	The document specifies that, to support inclusion of pediatric expansion cohorts, we need detailed safety monitoring, plans for assessing PK and PD study objectives (i.e., preliminary efficacy). BIO believes that if evaluated as part of an expansion cohort the pediatric expansion cohort *should* meet our requirement under FDARA 504. Any further development (or indication seeking protocols), based on the information generated from such an expansion cohort(s) would not be *required* but could be the subject of a WR (obviously the sponsor can choose to do this without a WR. The point is that an indication seeking trial is not one that the law allows FDA to require in this case and the way it is written right now gives the opposite impression).	BIO suggested edit: "Information to support expansion cohorts for pediatric patients should include detailed toxicity monitoring plans, plans for PK assessment, and, when appropriate, pharmacodynamic study objectives to guide further pediatric development, **which if evaluated as part of an expansion cohort *should* meet the requirement under FDARA 504**."
Lines 326-327/ 182-185	If the new treatment tested in a pediatric expansion cohort demonstrates substantial improvement over the available therapy in a pediatric population with a high unmet medical need, the expansion cohort data should be considered to support a marketing application (to benefit children early), like the recommendation for adults in Line 182-185.	BIO suggested edit: "Further development of the drug for one or more pediatric cancer-specific indications should be pursued as a separate protocol. **In the exceptional situation where data from an expansion cohort may support a marketing application, the protocol should contain provisions ensuring adequate data quality, independent review of tumor-based endpoints, and**

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		optimal dose selection, as well as a prespecified plan ensuring statistical rigor."
VI. STATISTICAL CONSIDERATIONS		
Lines 338-340	As noted in the more general comments above, reference to specific statistical approaches is not be broadly relevant or helpful, given that determination of product activity could be assessed using other approaches such as Bayesian statistical framework, which is especially attractive in expansion cohort with low sample size. Moreover, Bayesian paradigm lends itself naturally to the implementation of interim analysis to trigger, for example, early stopping of the trial due to lack of activity. In addition, we note that even if hypothesis testing is planned in multiple cohorts, FDA should consider mentioning that multiplicity adjustment is generally not needed across cohorts, as decisions are done independently in each cohort, as they are in separate studies, based on all relevant data (activity, safety, PK).	BIO suggested change: "In a nonrandomized cohort, assessment of anti-tumor activity is generally determined using ~~**a Simon 2-stage design**~~ **multi-stage designs with early stopping for futility that** limit exposure of additional patients to an ineffective drug. **(e.g., Simon 2-stage or Bayesian statistical approach). If hypothesis testing is performed in different cohorts, multiplicity adjustment is generally not necessary across cohorts."**
Lines 332-335	Some studies will enrol rapidly and an assessment for efficacy/futility may not be feasible. Some studies may include small cohorts that do not allow for such an analysis.	BIO suggested edit: "The background information for each expansion cohort should contain the scientific rationale for that individual cohort. **Where feasible based on the enrolment rate and the size of the cohort**, individual expansion cohorts should describe the prespecified stopping rules for that cohort, based on insufficient anti-tumor activity or unacceptable level of toxicity for that population."
Lines 344-346	Assumes that for a randomized design, in all cases, one will be performing a hypothesis test. While often true, this is overly limiting in cases where one wants to estimate the treatment effect with a desired precision or to weigh evidence, using Bayesian methods or otherwise. The sample-size in a	BIO suggested deleting the following sentence: "In a cohort with a randomized design, the sample size and the inference that can be made will be based on the prespecified null and alternative hypotheses to be tested, the level of significance, and the power of the test."

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	randomized setting may therefore be justified from an estimation rather than testing perspective. Also, given the typical size of FIH expansion cohorts, the power for formal statistical comparisons would typically be very low under reasonable assumptions of effect-sizes. Randomization may then be performed for purposes of signal calibration (for either efficacy or safety) or measuring "assay sensitivity" where no formal comparison is planned.	
VII. SAFETY CONSIDERATION		
General comment	The safety recommendations proposed in the guidance are reasonable and consistent with expected/appropriate pharmacovigilance practices/activities with regard to IDMC/ISAC trial monitoring and cumulative safety reporting to IRBs and regulatory authorities.	It would be helpful to better understand what the format of cumulative safety reports required "more frequently" than annually (lines 363-364) would consist of; we presume this format could be negotiated with the FDA.
A. Safety Monitoring and Reporting Plans		
Lines 352-373	Reference 22 (21 CFR 312.30(b)) suggests that a protocol amendment is needed to provide an update on the safety experience.	BIO suggests that a protocol amendment is not needed to provide an update on the safety experience.
Line 368	It is unclear what the threshold recommended for safety stopping rules in expansion cohorts.	It would be helpful if the Agency could provide clarity on the threshold recommended for safety stopping rules in expansion cohorts.
Line 369	The Draft Guidance should indicate what would be the Agency's preferred mechanism of reaching such an agreement, especially when multiple expansion cohorts are introduced after the initial IND approval.	The Draft Guidance should indicate what would be the Agency's preferred mechanism of reaching such an agreement.
B. Independent Safety Assessment Committee		
Line 375	The section refers to both forms of committees and should allow an internal committee as long as the processes are in-place for an independent assessment.	BIO suggested edit: "B. Independent Safety Assessment Committee **and Independent Data Monitoring Committee (internal/external)"**

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Lines 377-389	BIO understand the importance of safety data monitoring, especially in the context FIH trials with expansion cohorts given their complexity. However, these trials can generate an enormous amount of safety data which can pose many challenges in interpretation.	BIO requests the Agency to consider flexibility in establishing Independent Safety Assessment Committees (ISACs) and Independent Data Monitoring Committees (IDMCs) for all FIH studies with expansion cohorts, especially considering the resource and time burden to all parties involved in these small FIH trials. Instead, we suggest to consider the possibility of including, in such committees, experts internal to the sponsor organization as they may be better positioned to monitor, understand, integrate and interpret the many safety signals that can rise from such complex trials. While prespecified safety and efficacy assessments of an IDMC may be rather generic d/t the limited number of data available at this stage in development, participating investigators and sponsor medics may be better positioned to judge emerging safety and efficacy signals.
Lines 377-386	Historically, FIH oncology studies have included multiple dose cohorts and often more than one histology-specific expansion cohort. These studies are performed with rigorous safety monitoring, typically involving weekly meetings with the sponsor and investigators, and are designed with dose escalation approaches to ensure that few patients at any time are exposed initially to a given dose. Given this rigorous safety monitoring and the historical success of this approach, it is not clear why an independent data monitoring committee (IDMC) is suggested for all phase 1 studies that have 3 or more expansion cohorts (defined as a "FIH multiple expansion cohort trial" on page 3). IDMCs are typically used for phase 3 studies, where the sponsor is blinded, and where safety monitoring is not performed as rigorously as in a phase 1 study. Furthermore, with use of Simon 2-stage designs, enrollment of a large number of patients without some evidence of efficacy is avoided. Given the rigorous safety monitoring in phase 1	Suggested Edit: **Establishment of an** ~~**An**~~ independent safety assessment committee (ISAC) or an independent data monitoring committee (IDMC) structured to assess **aggregate** safety **data** in addition to efficacy should be **considered** ~~**established**~~ for ~~**all**~~ FIH ~~**multiple**~~ expansion cohort protocols, ~~**given that**~~ based on the **study design** complexity of these trials, **including: therapeutic index** ~~**with regards to different cohort objectives**~~**; size of the** trial population**(s); the number of different cohort objectives;** and **number** of dosages evaluated simultaneously~~**. can lead to potential increased risks to patients.**~~ **The ISAC or IDMC may be comprised of internal or external members, or a mixture of both.** Responsibilities of the ISAC/IDMC should include, but not be limited to, ~~**analysis of incoming expedited safety reports**~~**, review of** aggregate safety data **(including SUSARs and SAEs),** ~~**development**~~ review of cumulative summaries of ~~**all**~~ adverse events, and **providing** ~~**making**~~ recommendations to the IND sponsor regarding protocol modifications to ~~**reduce**~~ **minimize** risks to patients enrolled in the trial. The ISAC/ IDMC should ~~**be charged with the**~~

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	oncology studies, and with the use of Simon 2-stage designs, the role of an IDMC is questionable. Therefore, it is suggested that an IDMC should only be required for some trials, based on their complexity including: therapeutic index; the number of different cohort objectives; size of trial populations; and number of dosages evaluated simultaneously. It should also be noted that a recent analysis suggests 3-5 as an optimal number of histology-specific expansion cohorts (with 15-30 patients in each cohort) for phase 1 studies that involve drugs with potential broad anti-tumor activity (Chen et al, 2017). Thus, it seems likely that many phase 1 oncology studies, particularly involving immunotherapy, may employ 3-5 expansion cohorts, and requiring all of these studies to employ an IDMC seems overly burdensome and again of questionable value	~~**real-time review of all serious adverse events and**~~ meet periodically to assess the totality of safety information **(as noted above)** ~~**in**~~ **as part of** the development program.(…)
Lines 382-383	Suggested clarification	BIO suggested edit: "~~**development**~~ **review** of cumulative summaries of all adverse events"
C. Institution Review Board/ Independent Ethics Committee		
Lines 433-435	It is unclear from the guidance whether the decision to formulate a specially board is up to the IRB or the Sponsor.	Provide clarity on who would decide (IRB or Sponsor) if a separate, specialty IRB needs to be established and the scope of their work separate or in concert with the activities of the main IRB.
D. Informed Consent Document		
Lines 455-456	Suggested change to align with Line 447	**BIO suggested edit: "**~~**The updated consent document should be submitted in each IND amendment containing clinically important protocol modifications.**~~ **FDA may request submission of updated ICFs for IND amendments containing clinically important protocol modifications.**"
VIII. PROTOCOL CONTENT		

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A. Initial Protocol		
Lines 487	The guidance recommends a schema for data flow (data collection, analysis, and dissemination in real time) in the protocol. It is unclear if this would entail more than outlining a plan for distribution of weekly investigator call minutes or similar, containing highlights of real-time safety data.	Suggest Agency provide more detail on what is meant by data collection, analysis, and dissemination in real time.
B. Protocol Amendments		
Lines 500-501	It should be clarified if this should be understood as a subset of the all-treated population. The definition of "patient that have completed at least one cycle" is problematic, as effectively subjects that discontinued due to an AE before completing the first cycle of treatment would be excluded.	Clarifying revision is needed
Lines 506	Informed consent document should be provided at the request of the FDA	BIO suggested edit: "**FDA may request** an updated informed consent document an updated ICF"
IX. COMMUNICATIONS AND INTERACTIONS WITH THE FDA		
Lines 515-517	A requirement for a pre-IND meeting with FDA may have a significant impact in the ability to open a study in a timely fashion, and thus slow the availability of new medications to patients. The guidance provides ample instruction and should obviate the need for a pre-IND in most cases. Requests for pre-IND meetings could be limited to those instances where the protocol needs to substantively deviate from the proposed guidance but is justified by the available data.	BIO suggested edit: "~~**Sponsors should request a pre-IND meeting to discuss their plans to conduct an FIH multiple expansion cohort trial. When the original IND is submitted, the cover letter should prominently identify it as an FIH multiple expansion cohort trial.**~~ **Sponsors should consider requesting a pre-IND meeting where the study design cannot substantively conform to this guidance**"
Line 523-525	The guidance should be clarified to state that an amended protocol may proceed upon submission to the IND and upon IRB approval.	BIO suggested edit: "Though an amended protocol may proceed upon submission to the IND **and IRB approval**, FDA strongly encourages sponsors to submit amendments at least 30 days before planned activation of the amendment to allow FDA to conduct a safety review."

SECTION	ISSUE	PROPOSED CHANGE
Line 524	It is unclear what is meant by "activation"	Please define "activation".
Line 529	The guidance should be clarified that submission to both FDA and IRB is necessary for urgent protocol amendments intended to eliminate an apparent immediate hazard to subjects.	BIO suggested edit: "(…) should be implemented immediately and submitted as soon as possible **to the FDA and the reviewing IRB.**"
Lines 531-533	It is unclear procedurally how the teleconference should be requested and scheduled.	Please clarify procedurally how the teleconference should be requested and scheduled.