November 28th, 2018

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

Re: Docket No. FDA-2018-D-3124: Adaptive Designs for Clinical Trials of Drugs and Biologics; Draft Guidance for Industry

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments to the Draft Guidance on Adaptive Designs for Clinical Trials of Drugs and Biologics.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.

This important Draft Guidance was well written and provides important information to allow companies to use adaptive trial designs. Of note, the draft guidance suggests in several places that applicability of trial adaptations that could allow earlier stopping for efficacy may be limited by the need to collect adequate safety data. The Draft Guidance would benefit from additional discussion as to the feasibility to trigger early submission based on reaching the primary efficacy endpoint, while also having additional enrolment and/or follow up to generate the requisite amount of safety data. We have also provided additional specific, detailed comments to improve the clarity of the Draft Guidance in the following chart.

BIO appreciates this opportunity to submit comments on the Draft Guidance on Adaptive Designs for Clinical Trials of Drugs and Biologics. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

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SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION AND SCOPE		
II. DESCRIPTION OF AND MOTIVATION FOR ADAPTIVE DESIGNS		
A. Definition		
Lines 52-56	This definition of *interim analysis* is overly broad, as it includes common monitoring activity such as baseline data, safety monitoring, PKPD or biomarker data and not intended for formal comparison between treatment groups. This proposed definition goes beyond the definition in ICH-E9 which defined an interim analysis as "any analysis intended to compare treatment arms with respect to efficacy or safety…"	FDA should distinguish that these safety monitoring activities are not considered "interim analysis" in this context. We suggest to keep the same definition of interim analysis as ICH E9 "Statistical Principles for Clinical Trials".
Lines 59-62	The scope of the definition of *comparative analysis* is not clear.	FDA should clarify whether this definition includes unblinded safety analyses conducted in compliance with the draft Guidance for Industry "Safety Assessment for IND Safety Reporting".
Line 66	This definition for interim analysis uses a broader range of the concept than the use of the term in ICH E9, potentially causing confusion.	FDA should consider either harmonizing and defining the term here, to ensure consistency with ICH E9, or should use a more general term than "interim analysis" if the intended reference is a different and more general one.
B. Important Concepts		
Lines 71-75	This paragraph appears to assume that there will be no protocol amendments.	FDA should clarify how it will handle clinical trials in which adaptive designs are considered to be added via protocol amendment.
Line 78	A distinction is made between trials that are a) intended to provide substantial evidence of safety and effectiveness, and 2) trials intended for exploratory purposes. However, it is not clear whether Footnote	Clarify what is meant by the information in Footnote 4. And consider providing a definition or explanation of exploratory trials.

SECTION	ISSUE	PROPOSED CHANGE
	4 applies to a) or b) or both	
Lines 83-87	The terms *fixed sample trial* and *non-adaptive trial* are generally used interchangeably.	Please clarify why the distinction, if any, made in this draft guidance.
Lines 93-94	Overall the guidance makes a point about bias in estimates and error rates. This statement reads as focused on uncertainty in estimation.	FDA should consider broadening this statement to include the reliability of hypothesis testing / error rates.
C. Motivation and Examples		
General	There are limited number of examples in this section.	FDA should include Dulaglutide trials as example of trial with adaptive design that illustrates the potential advantages.
D. Limitations		
General	There are limited number of examples in this section.	An additional subsection/paragraph with few detailed examples on some of these constraints would facilitate deeper understanding for the readers.
Lines 214-216	The draft guidance does not mention that clinical trial simulation could be used to evaluate the chance of erroneous conclusion and introducing bias in estimates.	FDA should consider including language highlighting that clinical trial simulation could be used to evaluate the chance of erroneous conclusion and introducing bias in estimates.
Line 220-221	A Phase 2/3 design combining both the dose-ranging portion and the confirmatory portion is a good example. Such a design may clearly speed drug development. But on the other hand the design requires pre-specified decision rules at interim to choose a dose for the Phase 3 portion. There is a risk that the decision rules may not cover all the relevant data needed to determine the Phase 3 dose. Thus a step-wise approach to drug development—separate Phase 2 and Phase 3 studies—may be preferred.	BIO suggests an added sentence "Further, there is a risk that preplanned adaptive design modifications may not foresee all the circumstances and data needed to make an adaptive change in the trial."

SECTION	ISSUE	PROPOSED CHANGE
Lines 233-235	It is not very clear why results after the adaption maybe not sufficiently similar to those before the adaption and therefore lead to challenges in interpretability. Does it refer to a trial population change resulting in potential treatment effect difference from the original population?	BIO suggests an example be given for further clarity.
III. PRINCIPLES FOR ADAPTIVE DESIGNS		
A. Controlling the Chance of Erroneous Conclusions		
Lines 266-275	It is well known among statistical community that overall type I error needs to be controlled if adaptive design leads to multiple hypothesis tests. So the type I inflation here actually is related to multiplicity, which is not limited to adaptive design. It may be clearer to point out that some adaptive design will lead to multiple tests. Therefore multiplicity should be considered.	BIO suggested edit: "~~The most obvious examples of this are cases in which multiple statistical hypothesis tests are performed.~~ The most obvious examples of this are cases in which the adaptive design introduces multiple statistical hypothesis tests, e.g. a group sequential design in which a preliminary test to potentially stop the trial for efficacy is performed during interim"
Line 278-283	This paragraph cautions against a "naïve" approach to adaptive patient population selection in which the final analysis includes the same data that were used to choose the patient population. But Lines 569-570 in V.C (adaptive enrichment) highlights that the data before and after interim analysis may be combined.	BIO suggests a sentence be added in Line 283 that says 'Adaptive enrichment designs that preserve Type I error are further discussed in V.C"
B. Estimating Treatment Effects		
Lines 313-317	The adjustment methods on effect estimation are not known for many other adaptations, and FDA rightly asks for cautions in interpretation. However, it is unclear what is the expectation to demonstrate the extent of bias or over-estimation	FDA should provide clarification as well as examples

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C. Trial Planning		
Lines 326-328	It is not clear whether this applies specifically to unblinded adaptive decision-making. An unplanned adaptation that is based on the blinded aggregated data or external information could be allowed here.	FDA should clarify whether this applies specifically to unblinded adaptive decision-making.
IV. ADAPTIVE DESIGNS BASED ON NON-COMPARATIVE DATA		
V. ADAPTIVE DESIGNS BASED ON COMPARATIVE DATA		
A. Group Sequential Designs		
Lines 456-458	Note that, if the interim analysis is not conclusive and the trial continues, sponsors (particularly those involved in trial logistics) should not be informed of the details of interim results.	FDA should consider incorporating this recommendation into the draft guidance.
Lines 486-494	While we agree that trial terminated early for efficacy may have a limited sample size for purposes of evaluating safety and potentially important safety efficacy points, early stopping/ need for interim analysis for evaluation of safety (or other endpoints) may be able to be anticipated before start of the trial by power calculations, in some instances. For vaccine efficacy studies, note that, sample size is generally largely greater than the population used for a safety evaluation. As a result, a detailed safety evaluation can be done for a subset of the first subjects. Where a disease is uncommon, the first interim evaluation of vaccine efficacy may be done using a large sample of included subjects.	FDA should consider revising the guidance to incorporate these points, as well as inclusion of more detailed recommendations around the preventive vaccine trial example.

SECTION	ISSUE	PROPOSED CHANGE
Lines 487-491	It is unclear what the recommended information fraction needed for early stopping for efficacy.	FDA should provide additional information on the recommended information fraction needed for early stopping for efficacy.
B. Adaptations to the Sample Size		
Lines 525-526	Multiplicity adjustment is not always needed, therefore text should reflect this approach	BIO suggested edit: "~~Indiscriminately modifying the sample size of a trial without proper adjustment can inflate the Type I error probability.~~ Proper modification of the sample size of a trial may not inflate the Type I error probability even without adjustment (e.g., Chen et al. 2018a), but indiscriminate modification without proper adjustment can". Chen C, Anderson K, Mehrotra DV, Rubin EH and Tse A. A 2-in-1 Adaptive Phase 2/3 Design for Expedited Oncology Drug Development. Contemporary Clinical Trials 2018a; 64:238-242. Chen C, Li X, Li W, Beckman RA. Adaptive Expansion of Biomarker Populations in Phase 3 Clinical Trials. Contemporary Clinical Trials 2018b; 71: 181-185
C. Adaptations to the Patient Population (e.g., Adaptive Enrichment)		

SECTION	ISSUE	PROPOSED CHANGE
Lines 580-581	Multiplicity adjustment is not always needed, therefore text should be adjusted.	BIO suggested edit: "~~Therefore, statistical hypothesis testing methods should account for both sources of multiplicity~~ While multiplicity adjustment may not be needed for some designs (e.g., Chen et al. 2018b), statistical hypothesis testing methods should account for both sources of multiplicity for other designs." Chen C, Anderson K, Mehrotra DV, Rubin EH and Tse A. A 2-in-1 Adaptive Phase 2/3 Design for Expedited Oncology Drug Development. Contemporary Clinical Trials 2018a; 64:238-242. Chen C, Li X, Li W, Beckman RA. Adaptive Expansion of Biomarker Populations in Phase 3 Clinical Trials. Contemporary Clinical Trials 2018b; 71: 181-185
D. Adaptations to Treatment Arm Selection		
Lines 593-595	Often in biomarker-based adaptive designs the optimal threshold to define an enriched subpopulation may not be known in advance. This is becoming more and more common as biomarkers are introduced into the clinic. Adaptive designs to choose a threshold that at the same time preserve Type I error have been proposed (e.g. N. Simon "Adaptive enrichment designs for clinical trials" 2013).	BIO suggests that the guidance explicitly address the use of biomarker-based adaptive designs to choose an optimal threshold for an enriched population. Current language suggests that the threshold used to define subpopulation needs to be pre-specified and "should be motivated by results from previous trials and/or strong biologic plausibility."

SECTION	ISSUE	PROPOSED CHANGE
Lines 641-648	There is a lack of clarity around adaptive treatment arm selection in the context of adaptive platform trials designs. For example, it can be difficult to enroll populations, and there might be ethical issues with enrolling placebo group. In addition, the current draft guidance provides limited information as to other issues such as how to count placebo for each drug or addressing changing standard of care. Although BIO recognizes these decisions and discussion would be addressed in a case-by-case basis, FDA should consider providing a general framework for sponsors in this Draft Guidance.	FDA should consider providing a general framework for sponsors in this Draft Guidance on how to address the previously described challenges of adaptive treatment arm selection in the context of adaptive platform trials designs.
E. Adaptations to Patient Allocation		
Lines 650	Basket designs can be adaptive and may be viewed as special cases of patient allocation which are not covered by this guidance. For example in Oncology such designs may incorporate dropping specific tumor types. It may be worth providing reference to "Draft Guidance on Developing Targeted Therapies in Low-Frequency Molecular Subsets of a Disease"	BIO suggests that basket designs in which one treatment targets multiple disease subgroups (e.g. tumor types) might be an important example to cite in V.E.
Lines 678-681	Additional reference should be included.	FDA should reference: J. Lin, V. Bunn. (2017) "Comparison of multi-arm multi-stage design and adaptive randomization in platform clinical trials". *Contemporary Clinical Trials*, Volume 54, 48-59.
Lines 683-684	Additional detail regarding the "appropriate statistical analysis techniques" for type I error control in the RAR design.	FDA should consider providing more details or references

SECTION	ISSUE	PROPOSED CHANGE
Lines 683	There is not broad clarity on what would be done in analysis to look at the response-adaptive randomization. AS in previous sections of this draft guidance, examples should be provided	FDA should provide an example reference.
VI. SPECIAL CONSIDERATIONS AND TOPICS		
A. Simulations in Adaptive Design Planning		
Lines 782-783	We disagree with the statement that "[t]ypically, this is too complex an issue to address in clinical trial simulation." This simulation/ analysis could be done without issue using current modeling software tools (e.g., SAS and R). Please see, for example: Patterson S and Jones B. (2016) Bioequivalence and Statistics in Clinical Pharmacology 2ed, Ch. 5.3, Simulation (Chapman & Hall/CRC Press, London) and the code on the website accompanying the book.	BIO suggested edit: "~~Typically, this is too complex an issue to address in clinical trial simulation.~~ Accurate and precise understanding of the analysis of such multiple correlated endpoints presents additional challenges and would require simulations based on the within-subject correlation structure. In some cases, ~~however,~~ it can be….'
Lines 804-808	There is a bit of discussion on having enough iterations to prove type I error control truly is 5%, but there is only a brief mention of bias. Is the consideration of the potential for some small bias acceptable if type I error rate is maintained at 5%?	FDA should provide further clarity.
B. Bayesian Adaptive Designs		
Lines 821-823	Borrowing could also be used within a trial, for example, in a basket trial.	BIO suggested edit: "e.g., previous trials, basket trials, natural history studies, and registries, via informative prior distributions to improve the efficiency of a trial"

SECTION	ISSUE	PROPOSED CHANGE
Lines 832-834	With advances in Bayesian computation and availability of some Bayesian adaptive design software, it is not always advised to use conjugate priors or less burdensome approaches	FDA should consider eliminating this language.
Lines 836-850	Regarding the Type I error considerations under Bayesian Adaptive Designs, it is not clear what the Type I error consideration under null hypothesis of prior information would add, when we also incorporate the prior information when the null was rejected (meaning successful trials). Given the challenges and debate around controlling Type I error under Bayesian framework, it would be useful to specifically clarify FDA's interpretation of Type I error under Bayesian framework.	FDA should clarify its interpretation of Type I error under Bayesian framework as type I error is a frequentist concept.

SECTION	ISSUE	PROPOSED CHANGE
Lines 838-839	When simulating the null for a trial it is not necessary to assume that the prior data come from the null. This issue is whether the type 1 error probability is controlled even when borrowing is incorporated the trial (and the null is true in the current trial). Often borrowing is done across indications, or drugs, from adults to pediatrics, and may take the form of mixture priors that explicitly build in a probability of the null hypothesis. Priors themselves on treatment effects therefore provide some probability of the null (highlighting the expectation that the null may be true). Borrowing from control also influences the null hypothesis differentially across the range of potential true control effects. The point being made is that borrowing prior data is not expected to result in strong control of the null across all scenarios. If it did there would be little to no benefit. Perhaps it is generalized to indicate that when borrowing is agreed the sponsor should assess the impact on null probabilities across a range of null hypotheses. The degree of departure should be within reasonable bounds to ensure that the decision arising from the trial is reliable.	FDA should consider deleting: "Type I error probability simulations need to assume that the prior data were generated under the null hypothesis."
Lines 846-849	In general, this relatively small section on Bayesian adaptive design is not sufficient as Bayesian methods/models are natural choices for many adaptive designs.	The FDA should consider developing another guidance on use of Bayesian methods in drug trials as here it states that a comprehensive discussion of Bayesian approaches is beyond the scope of this document.
C. Adaptations in Time-to-Event Settings		
D. Adaptations Based on a Potential Surrogate or Intermediate Endpoint		
E. Secondary Endpoints		

SECTION	ISSUE	PROPOSED CHANGE
F. Safety Considerations		
Lines 909-911	Further detail regarding other adaptive techniques would be useful.	In addition to CRM, FDA should provide examples of other adaptive techniques in early phase dose-ranging trials.
G. Adaptive Design in Early-Phase Exploratory Trials		
Lines 951-953	The statement, "Thus, exploratory trials that incorporate adaptions should still follow good principles of adaptive trial design so that the risk of adversely affecting the development program is minimized" is unnecessarily broad and does not reflect the reality that sponsors have to take increasing risks with PK, PD, and efficacy evaluations in exploratory development to aid in later confirmatory development, given finite resources. Kept as is, the likely outcome of the language will result in both CDER and CBER being involved in extensive early phase discussions, and may be viewed by sponsors as an implied mandate for DMCs and Steering Cmts in Phase 1-2a.	BIO suggested change: "Thus, exploratory trials that incorporate adaptions should first ensure subject safety, and sponsors should understand and agree with the increased risks of adversely affecting the development program. Although many of the principles discussed in this guidance apply to exploratory trials, FDA does not expect that the same degree of rigor will be applied as that which is expected with confirmatory studies. ~~still follow good principles of adaptive trial design so that the risk of adversely affecting the development program is minimized"~~
H. Unplanned Design Changes Based on Comparative Interim Results		
I. Design Changes Based on Information From a Source External to the Trial		
VII. MAINTAINING TRIAL INTEGRITY		
Lines 993-994	The implication is that no sponsor personnel, including those specified as unblinded, can access comparative results.	BIO suggested edit: "Ensuring that patients, investigators and their staff, and ~~sponsor personnel~~ blinded study team members do not have access to comparative interim results serves two important purposes."

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Lines 1014, 1031, 1055	The distinctions between the "dedicated independent adaption body" (line 1014), the adaption committee (line 1031), and the "trial steering committee" (line 1055), including the relevant roles and memberships of each, are not clear. Sponsors often have members on the trial steering committee as this committee implements design changes (e.g., stopping for futility and efficacy) – see Ellenberg, Fleming, and DeMets (2002) Data Monitoring Committees in Clinical Trials: A Practical Perspective. Wiley. The number of "independent" personnel available for participation on such committees is in steady decline and is also somewhat of a misnomer (they are paid for their work by the sponsor).	Please clarify in the final version of the guidance, in light of the relatively small group of independent experts available for participation on these committees.
Lines 1046-1047	Clarity regarding sponsor access to comparative interim results is needed.	Clarify whether comparative interim results include unblinded safety results. If so, this statement is difficult to reconcile with the requirements of the draft Guidance for Industry "Safety Assessment for IND Safety Reporting".
Lines 1055-1056	Section VII places a high bar on sponsors to document who had access to interim comparative data to ensure they were not utilized for unplanned adaptations. This would be particularly challenging for an open-label phase 3 trial conducted entirely with internal sponsor resource where access to data are typically unrestricted for data management and medical monitoring, and therefore it could be an excessive burden to document access to interim comparative data and it is not feasible to completely restrict sponsor access.	It would be informative if the draft guidance could comment on whether it is credible for a sponsor to conduct such a trial with preservation of trial integrity under these conditions.

SECTION	ISSUE	PROPOSED CHANGE
Lines 1069	This paragraph would be clearer if the general recommendations were stated first and the sample size re-estimation example was provided at the end. In addition, the langue refers to an example of sample size re-estimation is shown however the recommendations don't seem sample size re-estimation specific. Therefore, clarification is needed.	Clarification is needed, specially as to the examples used.
Line 1072	Additional recommendations to limit back-calculation would be useful.	Please provide examples (e.g., symmetric adaptation rule) that can be used to limit the back-calculation.
Lines 1079-1081	Recommendation not to provide specific targeted final sample size should have some flexibility.	BIO suggest FDA allows an exception for providing the final sample size to IRBs and other ethics committees.
VIII. REGULATORY CONSIDERATIONS		
General	With regard to documentation requirements, this section should clarify that its focus is mainly on registration trials, and that more limited information may be sufficient for earlier-phase trials. Such clarification is provided at the end of section C for that section, but similar language would be good for B as well.	Clarifying langue on documentation requirement should be added to section B to match language used in other sections.
A. Interactions With FDA		
Line 1099	When discussing questions about adaptive design elements in an early-phase exploratory trial, the drat guidance states that "Discussion of the plans for an adaptive trial can be the basis for requesting a Type C meeting." However, for an early-phase exploratory trials, we think such discussions also could take place in the pre-IND meeting or in the EOP1 meeting.	FDA should allow for discussions of early-phase exploratory trials to be the basis for either a Type C, pre-IND, or EOP1 meeting.

SECTION	ISSUE	PROPOSED CHANGE
Lines 1113-1119	It is unclear if the complex adaptive designs discussion could only be requested through SPAs or would a request for a Type C, EOP2A or EOP2 meeting also be acceptable.	FDA should provide additional clarity.
Lines 1115-1119	It is not clear what FDA necessarily means by 'complex' (e.g., is an informative prior considered complex?).	FDA should provide additional clarity over the definition of "complex" design.
Lines 1179-1205	Often in conducting simulations external data and analyses conducted on such data are used to inform parameter choices, such as priors in Bayesian designs or correlation structures in the case of multiple endpoints. Examples of external data such as data from other studies, from literature, or real-world data should be cited in justifying some of the design and parameter choices. The need to document such data is not mentioned in VIII.B.	BIO suggests that in Lines 1186-87 the following sentence be added. "Such justification may include data and analyses from external sources such as other clinical trials and real-world data."
Lines 1246-1251	No considerations are included specific to Bayesian analyses.	Please clarify if there are any specific considerations for Bayesian analyses.
B. Documentation Prior to Conducting an Adaptive Trial		
Lines 1139-1224	The level of documentation requested before study initiation is quite burdensome. This has the potential to substantially delay the study and is a deterrent to using adaptive designs.	It may be appropriate for some documentation to be provided after study initiation, and this should be clarified.
Lines 1164-1166	This is a particularly burdensome requirement, and it may be possible to specify the analysis by other means.	BIO suggested edit: "(…) FDA before the trial, unless the analysis can be sufficiently pre-specified by other means."

SECTION	ISSUE	PROPOSED CHANGE
Lines 290-292	The statement "it can be shown that performing analyses at the conventional .025 significance level has a negligible effect on the Type I error probability (Kieser and Friede 2003)" is confusing.	The statement should make it clear whether this is for interim analyses or for final analyses.
Lines 315-317	Lack of details in the recommendations and lack of implementable approaches for sponsors	It would be more helpful if additional details of how to evaluate bias in estimate, such as performing sensitivity analyses, applying penalization in estimate, performing subgroup analyses, etc., can be added
Line 322	There are scenarios that the trial is a fixed design but later changed to an adaptive design before study unblinding, rather than being adaptive from the beginning.	If this is allowed, can agency add it to the written guidance?