May 6, 2022

Dockets Management Staff (HFA-305)
Food and Drug Administration (FDA)
5630 Fishers Lane
Room 1061
Rockville, MD 20852
Attn: Docket No. FDA-2021-D-1051

Re: Docket No. FDA-2021-D-1051: Clinical Pharmacology Considerations for Antibody-Drug Conjugates Guidance for Industry

Dear FDA Colleagues:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments regarding the Draft Guidance for Industry, **Clinical Pharmacology Considerations for Antibody-Drug Conjugates.**

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's members develop medical products and technologies to treat patients afflicted with serious diseases, to delay the onset of these diseases, or to prevent them in the first place.

BIO greatly appreciates the opportunity to provide feedback to the Agency on its recent draft guidance regarding antibody-drug conjugates (ADCs) as this innovative class of therapeutics has evolved significantly over the last several decades and stands today as a proven treatment option in oncology. In recent years, rapid advancements in ADC development have spurred even greater interest in their refinement and potential to revolutionize the treatment of indications beyond oncology. As a result, there are numerous ADC formulations now in the pipeline with conjugates spanning from "conventional" cytotoxic small molecules to radioactive particles, siRNA, immune modulators, antibiotics, and other macromolecules. The ability of sponsors to finetune chemical linkers and experiment with various payload conjugation and release methods has also expanded the wealth of products under development, not to mention the enhancement of next generation bi- and trispecific antibodies, allowing sponsors to bridge multiple target cells and/or engage multiple targets on a singular target cell, and their impact on ADC development.

Given the diversity and complexities of ADCs today, BIO recognizes the challenge FDA faces in creating a regulatory guidance that is comprehensive yet adaptable. However, we believe there are certain aspects of the draft guidance that could be improved to provide more clarity to sponsors regarding the Agency's expectations.

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Clarification on Antibody-Drug Conjugate Products

As written, it is unclear if FDA intends this guidance to apply *only* to "conventional" ADCs that use antibodies to deliver cytotoxic, small molecule drugs selectively to target cells where the payload is internalized and released intracellularly, or whether certain aspects could be applied more broadly. BIO suggests that the guidance either be revised to account for the diversity of ADCs that exist today, or explicitly describe the products for which it would apply to. Specifically, it would be helpful if the revised definition of ADCs incorporates/responds to the following points:

1) It is unclear if the guidance applies to ADCs with mechanisms that expand beyond internalization and lysosomal release of the payload. Incorporation of non-internalizing MOAs and potential implications would be beneficial.
2) While ADCs *may* be derived from mAbs or antibody fragments, this is not exclusively the case. Clarification is needed on whether the guidance applies to ADCs derived from other therapeutic proteins as well.
3) The guidance currently generalizes that all ADC payloads are cytotoxic, however there are many ADCs under development where this is not the case. Clarification is needed on whether the guidance applies to products with non-cytotoxic payloads.
4) Similarly, it is unclear whether the guidance applies *only* to ADCs with small molecule conjugates or whether it covers products where macromolecules or other substances such as radioactive particles are linked to antibodies as well.
5) As written, the guidance does not mention any differences in the requirements for known, well-characterized payloads (e.g., MMAE, DM1) versus those that are newer. It would be helpful if the guidance clarified which requirements, if any, the Agency might consider waiving or modifying based on payload characterization.

Clarity & Consistency of ADC Terminology

In addition to requesting that the Agency consider revising the types of products referred to as antibody-body drug conjugates, BIO also encourages FDA to provide further detail in the definitions provided in the introductory section of the guidance and to ensure terms are used consistently throughout.

In particular, the draft guidance defines "constituent parts" as total antibody and unconjugated payload in the introductory section. As the chemical linker is a vital component of ADCs, it is unclear why it has been omitted from this definition. Additionally, this definition does not account for other potentially active, payload-containing or payload-related products of ADC catabolism as measuring unconjugated payload may be irrelevant for certain ADCs (e.g., a non-cleavable linker that results in a catabolic product containing drug-linker-amino acid). However, in other places throughout the guidance, the term "constituent parts" does seem to incorporate components like "pharmacologically active metabolites" leading to inconsistencies in use of the term. Finally, it would be helpful if FDA specified whether it considers individual DAR measurements to be a

"constituent part" of ADCs and clarified throughout when using the term "ADC" to describe a bioanalytical analyte (DAR ≥ 1) versus describing a therapeutic that is really the sum of its constituent parts, including the unconjugated antibody.

Next, though widely used in small molecule drug development, BIO suggests that the term "pharmacologically active metabolites" is restrictive and somewhat counter to the terminology typically used to describe products derived from the release of the ADC's payload. We suggest FDA use the term "catabolite" when referencing products derived from the release of the ADC's payload as it more accurately reflects the range of potentially relevant species. This would include, for example, payload-containing products released directly from the ADC without degradation of the protein carrier and also payload-containing products formed as a result of catabolism of the ADC. Likewise, we suggest the term "metabolite" be used only when referencing biotransformed ADC-related products resulting from processes more commonly associated with small molecule metabolism (e.g., CYPs). Though nuanced, differentiating between these two terms is important and the use of more specific terminology will greatly assist sponsors in interpreting the implications of this guidance once finalized. For example, none of the eleven currently approved ADCs detected pharmacologically active *metabolites,* only unconjugated payload or payload-containing *catabolites*. Given these differences, we also suggest that FDA replace the term "unconjugated payload" with one of these more specific terms whenever possible to provide additional clarity throughout the guidance. Conversely, when it is not possible or necessary to distinguish between the two, we suggest that more flexible and inclusive language is used, like "pharmacologically and safety relevant species," to maintain accuracy.

Study Design Implications & Agency Expectations

BIO highlights that the strategy laid out in Section II-B (Dosing Strategies) of the draft guidance is currently not feasible for sponsors as regulatory authorities currently request the exclusion of organ impairment patients and patients with potential interacting drugs in dose escalation studies. The general reasoning for doing so is to mitigate any theoretical risk posed to these patients, given the efficacious dose is unknown at the time of dose escalation studies and safety data on the ADC being studied is rather limited per dose level. While sponsors have not included these patients in dose escalation studies in the past, we acknowledge that the level of theoretical risk posed to patients varies and could be quite low based on the ADME properties of the ADC being studied. In these circumstances, when there is a low theoretical risk for patients with organ impairment or interacting concomitant medications, sponsors could include them in regular dose escalation studies as is done in safety and efficacy studies (i.e., no need for dedicated organ impairment or DDI studies). BIO requests additional clarification on whether the Agency's thinking on this particular topic has shifted and if FDA is recommending a new standard. Furthermore, if the Agency's thinking has shifted, it would be helpful if FDA provided a decision-making tool or provided further detail to sponsors on what would qualify as an acceptable level of risk in determining whether to include these patients in dose escalation studies.

BIO also highlights that there are no recommendations provided on DAR or DLD determination. Given this omission, we suggest the inclusion of explicit language in the final guidance stating that this is not required.

Finally, some of the guidance in sections such as Section II-B (Dosing Strategies) and Section III-F (DDIs) appear to be generally applicable to all therapeutic modalities, not just ADCs. BIO recommends that the language be refined to focus on aspects which are unique to ADCs and that more general principles be referred to in other Guidances.

Opportunities to Further Leverage Existing Data & Expand Use of PBPK Modeling

BIO urges FDA to further consider and specify the circumstances where sponsors could leverage existing data on ADCs with the same linker-payload (if available), as these products usually share similar PK and safety profiles. By leveraging existing data, sponsors could use PBPK modelling to project magnitude of DDI and guide dose adjustment for ADCs with payload-mediated DDI. Additionally, while PBPK modeling offers a key alternative approach to assessing and de-risking DDIs of the unconjugated payload ahead of in vivo studies, it could also be used for patients with severe organ impairment based on data in mild/moderate impairment patients with appropriate cautionary language. As certain subsets of patients such as cancer patients with severe organ impairment are almost impossible to recruit, allowing sponsors to leverage existing data and utilize PBPK modeling in these situations would be especially beneficial. Lastly, in addition to assessing organ impairment and DDI potential, BIO suggests the revised guidance include specific language on leveraging existing data from ADCs with the same linker-payload to assess QTc based on pharmacokinetic profile of unconjugated payload as well.

Sincerely,

/s/

Rachel Coe, MSPH, CPH
Manager, Science and Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS:

LINE NUMBER	ISSUE	PROPOSED TEXT CHANGE
I. INTRODUCTION (Lines 17-40)		
Page 1 Footnote 4	"The FDA considers an ADC to be a combination product composed of a biological product constituent part and a drug constituent part (see 21 CFR 3.2(e)(1); 70 FR 49848, 49857-49858 (August 25, 2005; effective November 23, 2005). As explained in Q.II.3 of the guidance for industry, Questions and Answers on Biosimilar Development and the BPCI Act (Revision 1) (December 2018), CDER considers submission of a BLA under section 351 of the PHS Act to provide the more appropriate application type for ADCs."	Clarify the use of "combination product" in this statement, as an ADC is a single molecular entity that is not subject to the requirement of the Combination Product Rule (as per 21 CFR 300.50).
II. BACKGROUND		
Section II-A : ADCs (Lines 45-86)		
Line 47	"Composed of one type of"	Specify whether this would apply to ADCs that carry more than one type of payloads. Suggest removing this phrase to provide flexibility.
Lines 52-54	"…at which point the payload is released either upon exposure to the low pH of the lysosome or by degradation of the antibody/linker by lysosomal enzymes"	Cytotoxic payloads can also be released by reduction (e.g., disulfide bond). Suggest omitting any details regarding the mechanism of payload release as can be diverse. Suggest: "… at which point the payload is released via lysosomal release mechanism (e.g., reduction, pH-dependent hydrolysis, or enzyme-mediated linker cleavage)."
Lines 57-58	"Given that the mechanism of action (MOA) of ADCs aims to deliver the payload directly to a specific site…"	The background information only describes ADCs that deliver the payload to an intracellular site of payload-action following antigen-mediated internalization. In line with overarching comments, BIO suggests either accounting for diverse MOAs

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		or specifying scope more explicitly. If intended application of guidance is "conventional" ADCs only, we suggest revising this line to differentiate cell surface target for the antibody vs. the intracellular site of action for the payload. For example, suggest: Given that the mechanism of action (MOA) of ADCs aims to deliver the payload directly to a specific intracellular site
Lines 73-74	"Unconjugated small-molecule drug or payload – a free small-molecule drug that is not conjugated to an antibody"	Suggest revising this definition to be more inclusive. Suggest: "Unconjugated small molecule drug or payload – a free small-molecule drug that is not conjugated to an antibody or other macro-/bio- molecule."
Line 79	"Constituent parts of the ADC"	In line with overarching comments, suggest clarifying the definition of "constituent parts" to be more inclusive/comprehensive. Additionally, specify whether FDA considers individual DAR measurements to be "constituent parts" of ADCs. The terminology "total antibody" as used here seems to conflict with the definition of "total antibody" above.
Line 82	"Pharmacologically active metabolite – a pharmacologically active metabolite from the metabolism of the unconjugated small molecule drug or payload that contributes to efficacy and safety."	In line with overarching comments, the use of the term "metabolite" seems restrictive in this context and is somewhat counter to the terminology typically used to describe products derived from the release of the ADC's payload (and payload-related products). Depending on payload and chemistry, one may also need to look for catabolites containing payload (amino acid – linker – payload) and linker-payload species. Suggest removing the phrase "pharmacologically active metabolite" altogether or adding the term "catabolite" which is more commonly used and is more accurate. For example, suggest: Pharmacologically active metabolite – a metabolite from the metabolism of the unconjugated small molecule drug or payload and any payload containing catabolites (such as aa-linker-payload, linker-payload) that contributes to…
Section II-B : Key Considerations for ADC Dosing Strategies (Lines 87-151)		

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Line 92	Text states that payloads are cytotoxic.	There are many ADCs under development where this may not be accurate. Guidance should either acknowledge this, and account for it in the recommendations, or explicitly state that scope is for ADC with cytotoxic payloads.
Line 93	Payload refers to unconjugated small molecule.	This sentence as written is not valid for payloads that are very poorly membrane permeable and rely on the antibody to get to the target. In this case, ADC exposure is the relevant exposure. Suggest adding "and/or ADC" after payload. Suggest adding "increased" before adverse reactions.
Lines 102-113	"Broad dose-ranging... and selection of multiple-dose levels..."	Consider clarifying dose levels and/or schedules, and including a discussion of exploration of fractionated dosing regimens as was ultimately used for several ADCs.
Line 107		This line indicates that sponsors should evaluate relationship between exposure and response of ADC and constituent parts. As defined earlier, the term "constituent parts" is total antibody and unconjugated payload, and does not account for other potentially active, payload-containing or payload-related products of ADC catabolism. Suggest the use of more flexible language to account for diversity of ADCs.
Lines 109-112	"Furthermore, exposure-response analyses can be used to select dosing strategies for specific subsets of patients in pivotal studies (e.g., study participants with organ impairment…"	Suggest including the potential effects of target density and the levels of both membrane-bound vs soluble antigen at the tumor site and systemically. Suggest: "(e.g., study participants with organ impairment… "or considerable differences in tumor target density and target mediated drug disposition). When/If a target density- efficacy relationship is established, a target companion diagnostic can be recommended."
Lines 111-112		Prognostic factors may result in a spurious correlation between exposure and response that does not represent a causal E-R relationship and therefore, careful consideration should be given while interpreting these relationships.

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		Suggest adding: "Key considerations for prognostic risk factors are needed due to their potential to confound the exposure-response analysis."
Lines 111-112	"Additional supportive data, such as pharmacodynamic biomarker data and receptor occupancy/target engagement data, should be leveraged…"	Consider adding ADC platform learnings from the same linker-payload as ADCs with the same linker-payload usually share similar PK and safety profiles. Suggest: "Additional supportive data, such as pharmacodynamic biomarker data, receptor occupancy/target engagement data and platform learnings for the ADCs with the same linker-payload (if available), should be leveraged…"
Line 131	"Pharmacokinetic, efficacy, and safety information for recommendations on dose adjustments can be obtained from…"	Suggest the addition of a bullet to leverage available clinical DDI data for the ADCs with the same linker and payload to inform dose adjustment. Suggest: For payload-mediated DDI, leverage the clinical DDI studies from the ADCs with the same linker-payloads. The PBPK modelling that is verified with available clinical DDI data may be used to project the magnitude of DDI and guide the dose adjustment.
Lines 134-141		Suggest revising language in lines 134-141 per overarching comments. Indicate specifically whether a PBPK approach can be used for patients with severe organ impairment based on data in mild/moderate impairment patients with appropriate cautionary language.
Lines 143-148	"Of note, enrollment of patients based on various intrinsic or extrinsic factors in safety and efficacy studies should be based on the absorption, distribution, metabolism, and excretion (ADME) of the payload and the safety/efficacy profile of the ADC in early studies. Also, while human mass balance studies might not be feasible with ADCs, efforts to assess or predict human elimination…"	These recommendations primarily relate to DDI factors impacting payload. Consider mentioning that other intrinsic factors relating to antibody or ADC may also need to be considered (for consistency with lines 408-417).
III. CLINICAL PHARMACOLOGY CONSIDERATIONS		

LINE NUMBER	ISSUE	PROPOSED TEXT CHANGE
Lines 159-216		Clarify bioanalytical assay requirements for quantification of ADC constituents during pivotal study/late-stage development and on assay requirements for quantification of chemical linker during various stages of ADC development.
Line 161	"Beginning with first-in-human studies, the ADC, its constituent parts, and its pharmacologically active metabolites, if any, should be measured."	Provide clarity on whether qualification of the assay is enough and what level of validation is needed for all the ADC constituents
Line 161		The bioanalytical strategy proposed does not allow for flexibility in generating information necessary to create exposure-response relationships or to understand ADC disposition. Measuring ADC, Total antibody, and unconjugated drug may be relevant and informative, but there are other approaches to BA that could provide the necessary information. For example, sponsors have measured antibody-conjugated ADC, which is not mentioned here. Additionally, measurement of catabolic products (particularly active ones) containing the payload is not mentioned. Consistent with overarching comments, suggest that "catabolite" is the more appropriate term to use here, not metabolite.
Lines 161-164	"Later in development, the ADC, its constituent parts, and its pharmacologically active metabolites that are quantifiable in systemic circulation should be measured to inform exposure-response analyses…"	The likelihood of following free payload and "all its pharmacological active metabolites in the systemic circulation" may pose a serious technical hurdle given their expected fast clearance, low and potentially transient levels in the circulation. Suggest: "Later in development, the ADC, its constituent parts, and its major pharmacologically active metabolites that are quantifiable in systemic circulation should be measured to inform exposure-response analyses as described in section III"
Lines 165-177		As early clinical trials are often conducted with low patient numbers, it would be helpful if the Agency provided further detail on the characteristics and/or patient data that would justify the discontinuation of certain measurements. For example, what would indicate enough "preliminary exposure-response data" to justify discontinuation of analyzing unconjugated payload?

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Lines 168-170	"Their pharmacokinetic characteristics from early clinical trials (e.g., the correlation between the total antibody and ADC concentrations, the systemic exposure of the unconjugated payload and pharmacologically active metabolites)."	Consistent with our overarching comments, BIO suggests that the terms used to describe active payload-related products be refined here. Rarely is the unconjugated payload the active moiety that is found in circulation. Examples: MMAE released from Val-Cit linker (cleavable); cysteine linked MMAE (non-cleavable). Suggest: "systemic exposure of any pharmacologically active catabolites or their metabolites" or use "systemic exposure of relevant circulating payload components" instead of unconjugated payload.
Line 172		If sufficient nonclinical data and/or prior clinical experience with a given linker/payload is available, can measurements of any ADC constituents (e.g., total antibody) be excluded from FIH study?
Lines 179-183	"For example, if the unconjugated payload is undetectable with a sufficiently sensitive assay, the FDA may not recommend measuring the unconjugated payload. If the antibody constituent part only serves to selectively deliver the payload (i.e., acts as a carrier), and the total antibody concentrations are highly correlated to the ADC, the FDA may not recommend measuring the unconjugated antibody."	For ADC drugs made using Michael chemistry, the bioanalysis of the unconjugated payload (Michael acceptor) may not be practical, mainly because stability concerns. After spiking into matrix, the unconjugated payload will be immediately grabbed by nucleophiles in the matrix such as GSH, cysteine, or albumin and only a small fraction of the payload will remain in its free form, which make the bioanalysis unreliable. Please clarify the terminology for unconjugated payload here. Suggest: "the feasibility of developing a reliable method for the bioanalysis of the unconjugated payload should be evaluated" and "efforts should be made to assess to the fraction of unconjugated payload in incurred samples"
Lines 179-185	"For example, if the unconjugated payload is undetectable with a sufficiently sensitive assay, the FDA may not recommend measuring the unconjugated payload."	Additionally, the term "sufficiently sensitive" is up to interpretation. While acknowledging the difficulty in assigning a numerical value for sensitivity of a bioanalytical method, it would be helpful if FDA could somehow put this term into context (e.g., percentage of the conjugated antibody levels). Also request further detail regarding the point during trials at which this measurement (and the others mentioned in this section) could be discontinued (e.g., after Phase I).

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Line 180		This text mentions measuring antibody (assuming unconjugated antibody). However, unconjugated antibody is not listed as a Constituent part in the Definition section. Thus, should Sponsors be expected to measure unconjugated antibody, or will Total Antibody suffice? Additionally, one scenario not discussed is that where the unconjugated payload (or any active catabolites) concentrations are highly correlated with ADC concentration. Would it be permissible to measure only ADC?
Lines 180-183	"If the antibody constituent part only serves to selectively deliver the payload (i.e., acts as a carrier), and the total antibody concentrations are highly correlated to the ADC, the FDA may not recommend measuring the unconjugated antibody"	Typically, for ADCs, the two antibody assays are conjugated antibody and total antibody (conjugated + unconjugated). We are unaware of the need for an unconjugated antibody assay. Should this sentence end in "total antibody"? Suggest: "…the FDA may not recommend measuring the total antibody." Additionally, it would be helpful if FDA could elaborate further on which types of assays sponsors can have more confidence about which ones are not needed. Without further guidance from regulators, sponsors perform all assays to mitigate the potential risk that FDA asks for one.
Lines: 185-189		Given the challenges of developing free and bound assays, it would be helpful to understand FDA's thoughts on utilizing total assays for shed target and ADC and using those values along with measures of affinity to calculate the free levels of the ADC in circulation.
Line 186-187 and Lines 231-233	"Focus on the extent of shedding as the significant factor may lead to unnecessary assay development on free mAb-conjugate assays. At clinically relevant concentrations the shed target may lead to significant accumulation of complex relative to baseline. However, the critical factor is to what degree the mAb-conjugate concentration is affected by the presence of circulating target."	Recommend defining significant as the degree to which the total concentration of shed target is relative to that of total drug. For example, if the total target is < 5% of total drug at relevant regimens, the pharmacologically active mAb conjugate can be adequately described by the total drug in most scenarios. When these are closer, model-based approaches may be best employed to estimate the unbound mAb-conjugate rather than develop unbound assay that are challenging to deliver quantitative information.

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		Suggest: "Additionally, if the antibody's target is shed into the systemic circulation to a significant extent relative to the levels of total antibody at clinically relevant doses, bioanalytical assays could be recommended to distinguish the target-unbound ADC from the target-bound ADC"
Lines 186-187	"…significant extent for shed targets"	Revise language regarding "shed targets" as some targets are shed, while other soluble versions of cell surface targets are splice variants that are not shed but are present in serum. Clarify what degree of shedding would qualify as "a significant extent" to trigger the separate testing of bound and unbound ADC.
Lines 195 - 196		This text is not consistent with later text in section III.C.1 where ADC is only measured when relevant. Suggest removing the word "should" and substituting with "may" or "when relevant" to ensure consistency.
Lines 195-197	"For organ impairment studies, the ADC, the unconjugated payload, and pharmacologically active metabolites should be measured. The total antibody should be measured if mechanistically relevant…"	For renal impairment studies, ADC should be measured only if it has a size of <69 KDa (e.g., FDCs) and renal clearance is >30%. While this paragraph states that "the total antibody should be measured if mechanistically relevant," it lists the "ADC" within the same group as the "the unconjugated payload, and pharmacologically active metabolites" that "should be measured." Suggest adding a conditional statement: "For renal impairment studies, ADC should be measured only if it has a size of <69 KDa (e.g., FDCs) and renal clearance is >30%."
Lines 200-203	"For QTc assessments, measuring the unconjugated payload and pharmacologically active metabolites is usually sufficient. If the exposure of the unconjugated payload is low and cannot be quantified, a time-based analysis, where detection	Clarify if the objective is to confirm the payload concentration to determine adequate exposure, but a time-based analysis is the preferred primary methodology.

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	of the ADC will verify administration of the product, should be conducted."	
Line 206-209	For DDI studies, measuring the unconjugated payload and pharmacologically active metabolites could be adequate if the bioanalytical assays exhibit a sensitivity that adequately characterizes the relatively low systemic exposure of the unconjugated payload.	Does this mean that no DDI studies are recommended in cases where a sufficiently sensitive method cannot be developed for the unconjugated payload? The intent of this statement is not clear and can be interpreted several ways. BIO suggests revising this statement to provide more clarity.
Line 214	"For pharmacokinetic comparability studies (e.g., manufacturing process changes, formulation changes), concentrations of the ADC and its constituent parts should be measured."	It would be helpful to indicate how similarity with ADC would be assessed? Would classical criteria for BE apply as for small molecules (payload) or would criteria be used as described in ICHQ5E (Comparability of Biotechnological/Biological Products)?
Section III-B : Dose- and Exposure-Response (Lines 217-243)		
Lines 217-241		Given difficulties associated with measuring free unbound ADC/total antibody concentrations, assessing correlation between free unbound and bound drug may be difficult and/or error prone. Also, the number of bioanalytical assays necessary to develop and the quantity of blood sample collections required would be challenging for patients. We propose using model derived free unbound concentration of ADC/total antibody instead of experimentally measured concentrations for such correlations.
Lines 219-221	In addition to evaluating the dose-response relationship of the ADC, exposure-response analyses should be conducted for safety and efficacy with the ADC, its constituent parts, and pharmacologically active metabolites, if any.	This implies conducting dose- and exposure-response analyses with all components of the ADC during early evaluation. However, if ADC and TAb are found to be highly correlated, is it necessary to conduct these analyses for both ADC and TAb? Please clarify.

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Line 225		As above, would it be permissible to exclude conducting exposure-response analyses for payload or active catabolites bearing the payload if these concentrations are highly correlated with ADC concentrations.
Line 231	"Also, if the antibody target is known to shed into the systemic circulation to a significant extent…"	The impact of shed antigen depends on the binding affinity in addition to the relative amount in various dose levels/populations. Consider either providing further clarity on what a "significant extent" means, for example greater than 30 percent. Otherwise, consider substituting the term "clinically meaningful extent". Suggest: "Also, if the antibody target is known to shed into the systemic circulation to a ~~significant extent~~ clinically meaningful extent…"
Lines 232-233	"…exposure-response analyses should only be conducted with the ADC and/or total antibody that is not bound to the shed target in circulation."	Clarify the implications for listed considerations. For example, it is mentioned that exposure-response analyses should only be conducted with free ADC and/or total antibody if the target is shed in circulation. However, lines 235-239 mention concentrations of target-bound ADC. Please clarify if these considerations are needed or if analyses with free ADC concentrations is sufficient.
Lines 233-241		There are additional considerations when the target antibody of an ADC is shed in circulation, such as the potential PK change of payload molecule due to ADC binding to the shed antibody target. Consider adding additional bullet. Suggest: "Considerations for such analyses can include: • The potential PK change of payload molecule due to ADC binding to shed target"
Line 241	"The potential for the target-bound ADC to retain pharmacological activity"	Suggest adding an example to address "the potential for the target-bound ADC to retain pharmacological activity"
Section III-C : Intrinsic Factors (Lines 243-336)		

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Line 263		Provide additional clarification on reasoning for the specific cut-off at MW of 69 kDa for renal clearance without consideration of hydrodynamic radius or other critical parameters due to safety considerations. For example, Fc-fusions or pegylated-molecules may have smaller MW but equivalent or larger hydrodynamic size than a 69 kDa construct.
Lines 273-275	"A population pharmacokinetic approach can be used to assess the effects of organ impairment on the unconjugated payload, pharmacologically active metabolites, if any, and/or other ADC constituent parts if patients with organ impairment are enrolled in pivotal studies."	If early studies show high correlation between ADC and TAb, and only ADC and payload are qualified in later studies, then PK for TAb will not be available for population pharmacokinetic analyses to assess the effects of organ impairment evaluation. Further clarification needed on whether this is acceptable.
Lines 274 - 275 Line 280 Line 289	"… can be used to assess the effects of organ impairment on the unconjugated payload, pharmacologically active metabolites, if any, and/or other ADC constituent parts if patients with organ impairment are enrolled in pivotal studies..."	Replace phrase 'ADC constituent parts' with 'ADC' or 'total antibody' as the other moieties have already been mentioned. Suggest: "… can be used to assess the effects of organ impairment on the unconjugated payload, pharmacologically active metabolites, if any, and ~~/or other ADC constituent parts~~ total antibody if patients with organ impairment are enrolled in pivotal studies..."
Line 286		Suggest adding an additional bullet after line 285, discussing the limitations of using ADC nonclinical models for PK/effect because of the poor conservation of target binding across species. An antibody that binds to the target in mice may not bind to a similar target in humans.
Line 303		The systemic exposure of active catabolic products bearing the payload would also seem to be in scope here.
Lines 310-311	"…testing a reduced starting dose in a dedicated study without compromising the risk/benefit ratio)"	For completeness, suggest adding: "…without compromising the risk/benefit ratio)**,** or the same dose can be tested if the exposure-safety relationship is shallow."

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Lines 322-326	"For ADCs, a recommendation for a pharmacogenetic evaluation depends on ADME information, the systemic exposure of the unconjugated payload, and the role of the antibody in the MOA of the ADC, for example: … Genetic variants and/or expression of the target for the antibody can affect patient response to the ADC…"	There are additional pharmacogenomic considerations which may relate to genetic variation of enzymes associated with cleavable linkers used for ADC. Suggest adding an additional bullet to guidance: "…Genetic variation of enzymes associated with cleavable linkers used for ADC"
Line 330	" …that impact the metabolism rate (e.g., CYP2D6 or BCRP) …"	Suggest: "…that impact ~~the metabolism~~ the disposition rate (e.g., CYP2D6 or BCRP) …"
Section III-D : QTc Assessment (Lines 337-352)		
Line 340-342	"… outlined by the FDA's guidance *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* (October 2012)."	Suggest that the revised 2015 ICH E14 Q&As guideline be cited here as this is the document that allows for conc-QT analysis to be used for assessing risk of QT prolongation, while the 2012 FDA guidance calls for TQT studies. Suggest: "… outlined by the ~~FDA's guidance~~ ICH E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. Question & Answers (R3). (2015) ~~(October 2012)~~."
Lines 342-343	"…the unconjugated payload is the only constituent part of the ADC considered to have potential risk for QT prolongation."	For consistency, suggest clarifying that this also includes payload-derived pharmacologically active metabolites. Suggest: "…the unconjugated payload and its derived pharmacologically active metabolites are the only constituent parts of the ADC considered to have potential risk for QT prolongation."
Lines 343-345		Clarify whether it is necessary to assess the QT potential of active metabolites. Additionally, for payloads already on the market such as MMAE and the like, could QT assessments be omitted regardless of the antibody target (if systemic concentration is similar or lower than those having no QT effect)?

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Lines 347-349	"Electrocardiogram (ECG) monitoring during early clinical trials coupled with a sufficiently sensitive bioanalytical assay for the unconjugated payload could be deemed a sufficient QT assessment."	In early clinical trials, ADC and TAb concentrations will also be measured. As mentioned above (lines 273-275), does this mean that a concentration-QT analyses for payload only is sufficient and additional analyses are not required with ADC or TAb?
Line 342-351		BIO notes that the term "time-based analysis" seems vague in this context and is not included in the *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs* guidance. If FDA recommends time-based analysis as the primary methodology used, we suggest adding a case example and/or more precise language (e.g., analyses of central tendency and categorical analyses). However, BIO highlights that if exposure of the unconjugated payload is so low that it cannot be quantified with a sensitive assay, using total antibody or ADC concentration for concentration-QT analysis could be more valuable, as time-based analysis does not have the power that exposure-response has. The argument could be made that a BQL serum measurement indicates lack of systemic exposure, and therefore by definition, there is no clinically relevant exposure at the level of the myocardium. In line with this logic, we suggest the following: In general, the unconjugated payload and its derived pharmacologically active metabolites are the only constituent parts of the ADC considered to have potential risk for QT prolongation. Therefore, ~~the QT assessment plan for an ADC development program should consider all the factors that would be part of an QT assessment for a small-molecule drug. Any analysis recommended for the QT assessment should be determined using information about the payload's ADME characteristics. Of note, electrocardiogram (ECG)monitoring during early clinical trials coupled with a sufficiently sensitive bioanalytical assay for the unconjugated payload could be deemed a sufficient QT assessment~~ if a concentration-response analysis is conducted, the concentration should correspond to the concentration of the unconjugated payload and/or its pharmacologically active metabolites measured with a sufficiently sensitive bioanalytical assay. If exposure of the

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		unconjugated payload is low and cannot be quantified, ~~a time-based analysis, where detection of the ADC will verify administration of the product, should be conducted~~ total antibody or ADC concentrations may be used.
Section III-E : Immunogenicity (Lines 353-366)		
Line 357		Revise statement that ADCs have a relatively narrow therapeutic window as this is somewhat of a generalization and may not apply to all ADCs, particularly non-oncology ADCs.
Section III-F : DDIs (Lines 367-420)		
Lines 367-420		Consistent with our overarching comments, BIO suggests that the terms used to describe active payload-related products be refined here. For some ADCs, the payload containing, or payload-related products (i.e., catabolites) may be active and worth measuring. However, in other situations, the catabolites such as those containing part of the linker may be further metabolized resulting in active, circulating, and therefore relevant payload-derived metabolite(s). The ADME and DDI strategy should take into consideration the nature of these catabolic products, and the language here should be flexible enough to account for various forms of payload-related products being formed by catabolism of the ADC. Suggest: The sponsors should assess which payload-derived molecules are present in circulation and should focus in their DDI assessment on these components. Additionally, if there are no detectable pharmacologically active metabolites derived from unconjugated payload, we suggest the Agency consider adding a sentence on inducers, as inducers will decrease the concentration of unconjugated payload. For example, suggest: A study evaluating the effect of strong inducers may not be warranted as systemic concentrations of circulating payload are usually lower and it does not appear to contribute to efficacy.

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Lines 369-373	ADC development programs should include an in vitro DDI risk assessment for the unconjugated payload and pharmacologically active metabolites, if any, as both a perpetrator and a victim using both CYP enzyme- and transporter-related assays...	Perpetrator DDI assessment may not be relevant for payload-derived components with very low plasma concentrations (in the nM range). BIO suggests providing a threshold value for plasma concentrations which warrant perpetrator DDI assessment, (e.g. 0.1 µM).
Lines 376-377	"…the FDA could recommend that the sponsor conduct an in vivo DDI evaluation of the unconjugated payload as a victim."	Specify that an ADC DDI evaluation (not payload) could be recommended. Suggest: "…the FDA could recommend that the sponsor conduct an in vivo ADC DDI study to evaluate the unconjugated payload as a victim."
Line 378	"relatively low …for determining its DDI as a perpetrator"	Since the payload is mostly released in the tumor site, drug-drug interaction (DDI) potential as a perpetrator is low. Suggest: "~~though possibly relatively low~~ if the systemic exposure is significant to cause DDI"
Lines 385-387		Clarify position and language around the use of PBPK modelling for payload DDI assessment of known linker-payload. There are several publications now that support the value and predictive capability of PBPK in this space.[1] Suggest: "Additionally, PBPK modeling could be appropriate for payload DDI assessment of known linker-payload already in marketed ADCs and as outlined in the…."
Lines 390-406	Adequate in vivo DDI characterization could be achieved from the pivotal efficacy study when prospectively designed with the following considerations"	While DDI risk characteristic for ADC as a victim could be assessed in the pivotal efficacy study when prospectively designed. It will be very challenging and not practical to evaluate ADC as a perpetrator in the pivotal efficacy study due to the diverse co-medications that may be used and complexity of different time to administer the medications. This will pose significant operational burden and cause many errors and PK sampling for different co-medications will be different.

[1] Li, Chunze et al. "Impact of Physiologically Based Pharmacokinetics, Population Pharmacokinetics and Pharmacokinetics/Pharmacodynamics in the Development of Antibody-Drug Conjugates." Journal of clinical pharmacology vol. 60 Suppl 1,Suppl 1 (2020): S105-S119. doi:10.1002/jcph.1720

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Line 393		Suggest removing the component to evaluate the ADC as a perpetrator: ~~"as sensitive substrates (if the unconjugated payload and/or pharmacologically active metabolites have the potential as a perpetrator based on in vitro risk evaluation)"~~
Lines 405	"Adequate pharmacokinetic sampling and measurement of the victim concomitant medications"	Suggest: "Adequate pharmacokinetic sampling and measurement of ~~the victim~~ the unconjugated payload"
Lines 408-417		It would be helpful if FDA clarified the three scenario recommendations by providing actual case examples of potential DDI with antibody components of ADC.

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