November 9, 2020

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

Re: Docket No. FDA–2020-D-1480: FDA Draft Guidance, Drug-Drug Interaction Assessment for Therapeutic Proteins.

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments regarding the Draft Guidance *Drug-Drug Interaction Assessment for Therapeutic Proteins* (Draft Guidance or Guidance).

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BIO believes the Draft Guidance provides helpful information to sponsors regarding assessing drug-drug interactions for therapeutic proteins. The opportunity for sponsors to consider the specifics of their particular therapeutic proteins in the context of specific indications and concomitant medications and propose a fit-for-purpose development strategy in consultation with the Agency is appreciated. In addition, the recognition of the potential contribution and value of model-based analyses, such as PBPK modeling, affords additional tools to interrogate the potential for DDIs and make informed decisions or scientific justifications.

More generally, BIO suggests that the Guidance include a discussion on the potential of generalizing information between ADCs that share the same payload. It would be helpful to understand, from FDA's perspective, under what conditions it would be possible to apply information from a DDI study conducted using an ADC to another ADC that had the same payload.

While the Guidance focuses on CYP-related DDIs, we suggest clarifying when there should be assessments for potential transporter related DDIs with TPs[1,2]. If FDA decides to include

[1] Fardel O, Le Vée M. Regulation of human hepatic drug transporter expression by pro-inflammatory cytokines. Expert Opin Drug Metab Toxicol. 2009 Dec;5(12):1469-81. doi: 10.1517/17425250903304056. PMID: 19785515.
[2] Le Vee M, Lecureur V, Stieger B, Fardel O. Regulation of drug transporter expression in human hepatocytes exposed to the proinflammatory cytokines tumor necrosis factor-alpha or interleukin-6. Drug Metab Dispos. 2009 Mar;37(3):685-93. doi: 10.1124/dmd.108.023630. Epub 2008 Dec 15. PMID: 19074973.

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such a discussion, potentially as part of Section III.B (pages 5-6; starting at line 196), endogenous CYP/drug transporter substrates may help define the potential for clinically significant DDIs.

BIO appreciates this opportunity to submit comments regarding FDA's Draft Guidance *Drug-Drug Interaction Assessment for Therapeutic Proteins.* Specific, detailed comments to both the are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/
Victoria A. Dohnal, RAC
Director, Science and Regulatory Affairs
Biotechnology Innovation Organization

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Line 20-23:	The Guidance states that it applies to therapeutic proteins, but that the general concepts within could be applied to other biological products including CBER-regulated products such as cellular and gene therapies.	BIO asks that FDA further clarify what other biological products are covered/not covered by the Guidance document, and specifically mention T-cell redirecting bispecific antibodies since they are also mentioned in a later section of the Guidance. As the Guidance also mentions that the general concepts could be applied to other biological products, including cell and gene therapies, it would be helpful if FDA either expand this Guidance or addresses considerations specific to cell and gene therapies in targeted guidance.
II. CONSIDERATION FOR ASSESSING DDIs FOR TPs		
Lines 37-47:	To highlight the complexity of the task for developers, it should be mentioned in this section that although TPs are not metabolized by CYP450 enzymes, do not interact with cell membrane transporters and as such are not expected to suffer from interaction with small molecules, their clearance may be affected by modulation of patient's inflammatory status, immune response (ADAs) to treatment, and modulation of target expression,. All of these, and the list is probably not exhaustive, are potential sources of DDIs.	BIO requests that FDA modify the Guidance text accordingly.
Lines 39-42:	The Draft Guidance states "When evaluating the potential for a DDI between a TP and small molecules or between TPs, sponsors should consider the mechanisms of a potential DDI, taking into account	As such, BIO suggests editing the text to read: "When evaluating the potential for a DDI between a TP and small molecules or between TPs, sponsors should consider

SECTION	ISSUE	PROPOSED CHANGE
	the pharmacology and clearance of the TP as well as any co-administered medications in the patient population." BIO finds the text regarding "mechanisms" unclear and believes this refers to endogenous activity and impact of TP on such activity as well as the disease state. There are many examples where TP-DDIs are explained by modulation of the disease state by a therapeutic protein (e.g., rheumatoid arthritis). In those cases, normalization of drug metabolizing enzymes and transporters could occur. Further, we suggest adding patient population to the list of items that should be taken into account when evaluating the potential for a DDI between a TP and small molecules or between TPs.	the mechanisms of a potential DDI, taking into account endogenous target biology impacting the pharmacology and clearance of the TP, disease states, the makeup of the patient population as well as any co-administered medications in the patient population."
Lines 40-41:	In addition to the pharmacology and clearance of co-administered medications, the target indication and/or comorbidities in the target patient population should also be considered carefully. For conditions where the inflammatory status of patients is compromised, the expression of CYPs and transporters could be affected. A treatment with a TP affecting cytokines levels (e.g., IL-6, IFNs, TNFa, IL1-B) may modify the bioavailability of small molecules via a modulation of CYP and/or transporter expression. A TP that would significantly affect immune cell count may also affect the elimination of IgG and mAbs.	BIO requests that FDA modify the Guidance accordingly to take into account the suggestion that sponsors also consider the target indication and/or comorbidities in the target patient population.
Line 52:	The Draft Guidance focuses on changes in CYP activities.	BIO suggests adding "drug transporters" to this section of the Guidance. This change would also make this section

SECTION	ISSUE	PROPOSED CHANGE
		consistent with the Figure in the Appendix, which mentions transporters.
Lines 57-58:	The Draft Guidance states "Of note therapies such as T-cell redirecting bispecific antibodies as well as certain cellular and gene therapies can cause cytokine release syndrome." We suggest adding a reference describing cytokine release syndrome.	BIO suggests adding the following reference: Shimabukuro-Vornhagen et al. Journal for ImmunoTherapy of Cancer (2018) 6:56 https://doi.org/10.1186/s40425-018-0343-9
Line 64:	The Draft Guidance notes that "Sponsors should evaluate the DDI potential for therapeutic proteins that are proinflammatory cytokines". BIO suggests that it may not be necessary to evaluate DDI potential for proinflammatory cytokines in some cases, as for pro-inflammatory cytokine modulators. For example, recent trials to simulate the effect of IL-6 on CYP enzyme activities have been conducted with the aid of PBPK modeling.[3] Further, it has been shown that the risk for TP-DDIs is very low for mAbs that block receptors for proinflammatory cytokines that are not expressed on hepatocytes or immune cells such as Kupffer cells. A clinical trial with an anti-IL-23 mAb, tildrakizumab,	As such, we suggest replacing the text with the following: "The sponsor should evaluate the DDI potential consistent with section 2.a." The figure in the appendix seems to suggest that sponsors always need to conduct a DDI study for TPs that are pro-inflammatory cytokines without giving an option to provide justification for low/no DDI potential should also be revised accordingly. Please also see comments regarding the decision tree in Section V. Appendix. Further, we believe it would be helpful to provide specific recommendations on "***how***" DDI potential should be evaluated or which metric should be used to assess DDI potential or from what threshold value sponsor will decide on conducting DDI study.

[3] Y Xu, Y Hijazi, A Wolf. "Physiologically Based Pharmacokinetic Model to Assess the Influence of Blinatumomab-Mediated Cytokine Elevations on Cytochrome P450 Enzyme Activity." *CPT Pharmacometrics Syst Pharmacol*. 2015 Sep; 4(9): 507–515.

SECTION	ISSUE	PROPOSED CHANGE
	has confirmed that in such a case no clinically significant DDIs with CYP substrates are found[4,5,6]. Finally, BIO finds the statement "Evaluate the DDI potential" unclear as it could mean either: to assess the necessity/relevance of performing a TP DDI study-- or--to conduct a study.	Several factors determine the need for a clinical DDI study, and such studies may not be always required for TPs that are pro-inflammatory cytokines. Therefore, we recommend the addition of text to clarify that sponsors have an option to provide justification for no interaction potential and lack of need to conduct a DDI study. Finally, the Guidance should include additional details that the sponsor can provide justification why a study may not be needed in certain cases.
Line 66:	This section header is "The TP is a Cytokine Modulator".	We suggest renaming the title of this section "The TP is a Proinflammatory Cytokine Modulator" to be consistent with the subsection titles and content.
Lines 77 – 80:	The Draft Guidance states "b. the TP modulates proinflammatory cytokines in conditions associated with elevated cytokine levels…" This sub-category should be made clearer, as it could be interpreted in more than one way. One way this type of DDI risk could be interpreted is that the TP directly modulates a proinflammatory cytokine that is known to effect CYP expression (e.g., IL-6 or TNF-α). Another way is that a moderate-to-severe inflammatory disease state or severe medical condition itself increases proinflammatory cytokines and decreases CYP expression, and effective	We suggest editing the text to read: b. the TP modulates proinflammatory cytokines in conditions associated with elevated cytokine levels. There are two ways in which this may occur. First, the TP could directly block proinflammatory cytokines (i.e., an IL-6 antagonist or TNF-inhibitor) in disease states associated with elevated cytokine levels (e.g., rheumatoid arthritis). Second, a moderate-to severe inflammatory disease state or condition (e.g., such as influenza B, HIV infection, critical illness, bone marrow transplant, sepsis, moderate-to-severe rheumatoid arthritis, and patients with active and moderate-to-sever Crohn's disease) can cause an increase in

[4] Dallas et al., 2013, DMD 41, 689-693
[5] Nguyen et al., 2015, DMD 43, 774-785
[6] Khalilieh et al., 2018, Br J Clin Pharmacol 84, 2292-2302

SECTION	ISSUE	PROPOSED CHANGE
	treatment by a TP in turn causes an indirect normalization of CYP expression. An important note is that most disease states are of insufficient severity to cause a meaningful (≥ 2-fold) change in exposure of concomitant medicines, even those that are sensitive CYP substrates. Disease states of low- to moderate-systemic inflammation do not result in a meaningful (>2-fold) drug interaction. Psoriasis, for instance, is a disease state with insufficient systemic inflammation to cause meaningful changes in CYP-mediated drug exposure. For this reason, and also as multiple TP drug-drug interaction (DDI) studies of different TPs in psoriasis patients have failed to see any meaningful difference in CYP exposure[7], we do believe further TP DDI studies in psoriasis patients are not warranted.	proinflammatory cytokines that in turn results in decreased expression of CYP enzymes and/or drug transporters. Effective treatment by the TP would then indirectly normalize CYP or transporter expression. In these conditions, a DDI will only be observed if: • The victim drug is predominantly cleared by the affected CYP enzyme(s) and/or drug transporter(s) • Administration of the TP effectively normalizes CYP and/or transporter expression. • The therapeutic window of the victim drug is narrow (close to 2-fold). An important note is that most disease states are of insufficient severity to cause a meaningful (≥ 2-fold) change in exposure of concomitant medicines, even those that are sensitive CYP substrate. For instance, it appears that psoriasis is a disease state that does not cause meaningful indirect drug interactions (see ref on left).
Lines 80-96:	The Guidance gives the sponsors some flexibility in different scenarios where designing a DDI study could be challenging: 1. To include language in the label to indicate DDI potential 2. To provide justification for why such language will not be included in the label and they provide some guidance for what that	It would be helpful if the Guidance provides specific examples (e.g., transient elevation of cytokines may not lead to a clinically-relevant interaction).

[7] Y Zhu et al. Clin Transl. Sci. 2020. May 14. Online ahead of print; S Kalilieh et al, Br J Clin Pharmacol. 2018 Oct 84(10) 2292-2302; G Bruin et al. Clin Pharmacol Ther. 2019. 106(6); G Bruin et al. *Clin Pharmacol Ther.* 2019. 106(6); Brodalumab (Siliq) drug label; Ixekizumab (Taltz) clinical trial results at ClinicalTrials.gov

SECTION	ISSUE	PROPOSED CHANGE
	justification should include but no examples were provided	
Lines 93-94:	The statement of "Differences in exposure levels of sensitive CYP substrates in healthy subjects versus the indicated population" is not a good justification for not including the labelling language as mentioned in line 86.	BIO requests clarification from the Agency on how differences in exposure levels of sensitive CYP substrates in HV versus patient population may justify not including the labelling language should be provided. Alternatively, this language should be struck from the Guidance document.
Line 96:	The Draft Guidance states "The magnitude of the drug effect or the extent of cytokine modulation by the TP." BIO notes that the magnitude of drug effect and extent of cytokine modulation can vary and may not be of clinical importance. We believe the Guidance would be more helpful if it was clearer about the magnitude or extent that would warrant inclusion in labeling.	As such, we suggest including an example of a justification for not including labelling language based on the "magnitude of drug effect".
Line 98:	It is mentioned that "Alternatively, the sponsor can perform a DDI study…" However, conducting a stand-alone DDI study in healthy volunteers or patients is not always possible (e.g., in case patients demonstrate a different PK than healthy volunteers due to target expression differences or in case of rare/serious diseases, respectively). For those situations, DDI studies can be nested within larger Phase 2 or 3 studies. Although, the latter option has been adequately described in section IIIC, this nested	We suggest replacing "Alternatively, the sponsor can perform a DDI study" with the following: "Alternatively, the sponsor can assess the clinical DDI potential either in a stand-alone DDI study or by conducting a nested DDI study as part of a larger Phase 2 or 3 study whose primary objective is not to evaluate DDI"

SECTION	ISSUE	PROPOSED CHANGE
	approach should be introduced here with a reference to section IIIC.	
Lines 98-101:	The Draft Guidance suggests: 1. Conducting a DDI study in the relevant population to further inform labeling 2. If a TP is being developed for multiple indications, the potential for DDIs can be evaluated in the disease with the most severe inflammatory burden.	We request FDA clarify what is meant by "severe inflammatory burden". It is unclear whether this refers to specific cytokines (e.g., CRP, IL-6).
Lines 100-101:	The Draft Guidance states "Therefore, if a TP is being developed for multiple indications, the potential for DDIs can be evaluated in the disease with the most severe inflammatory burden." However, we note that cytokine levels differ by disease type and severity of disease and the Guidance should reflect this concept.	We recommend that FDA include the option to conduct a TP DDI study in the disease with the most severe inflammatory burden, or in patients with various disease types manifesting a severe inflammatory burden. As such, we suggest editing the text to read: "Therefore, if a TP is being developed for multiple indications, the potential for DDIs can be evaluated in the disease with the most severe inflammatory burden or in patients with various disease indications manifesting a severe inflammatory burden."
Lines 103-130:	This section provides scenarios unrelated to proinflammatory cytokines in which DDI evaluations should be considered.	BIO suggests that the FDA note that characterization of elimination pathways might be informative as to whether DDI evaluations are needed.
Lines 105-106:	The Draft Guidance states "Mechanisms unrelated to proinflammatory cytokines have been observed or postulated where the TP acts as a perpetrator (e.g., an inhibitor or inducer) or a victim of a small molecule or other TP..."	BIO suggests editing the text to read: "Mechanisms unrelated to proinflammatory cytokines have been observed or postulated where the TP acts as a perpetrator ~~(e.g., an inhibitor or inducer)~~ or a victim of a small molecule or other TP..."

SECTION	ISSUE	PROPOSED CHANGE
	BIO notes that cytokines have been shown to affect CYP transcription. The use of the term "inhibitor" could be confusing, as it could imply a small molecule CYP enzyme inhibitor. "Perpetrator" and "victim" are likely clear enough terms already used in the Guidance that we would recommend be used here, instead of "inhibitor".	
Lines 115-117:	The Draft Guidance states "Co-administered medications that impact the TP target or target-mediated disposition.[10,11] In these cases, depending on the role of the TP in the DDI, the sponsor should evaluate the DDI potential of the TP either as a perpetrator or as a victim." We note that reference 10 and 11 are about angiogenesis inhibitors influencing the access of a mAb to a tumor, which seems to be a physiological mechanism, rather than a change in the target levels. In addition, it is unclear how a TP could act as a perpetrator in a scenario such as the one described.	We ask the Agency to please clarify how a TP in this scenario would be a perpetrator. Further, BIO believes these references would be better suited for the bullet above this one regarding physiological effects. Additionally, BIO suggests using a reference that includes changes in target levels such as the following: S.M. Lavezzi et al. Systemic exposure of rituximab increased by Ibrutinib: pharmacokinetic results and Modeling based on the HELIOS trial, Pharm. Res. 36 (7) (2019) 93.
Lines 124-125:	The Draft Guidance states "Co-administration of immunosuppressors with a TP whose pharmacokinetics are affected by immunogenicity (e.g., methotrexate on the clearance of adalimumab).[5]" However, the given reference appears to be incorrect.	We suggest referencing: Pouw, C.L. et al., Key findings towards optimising adalimumab treatment: the concentration-effect curve, Ann. Rheum. Dis. 74 (3) (2015) 513–518.
Lines 125-130:	The Draft Guidance states "Since immunogenicity (i.e., the formation of antibodies to TPs) can alter the clearance of some TPs, drugs that suppress	As such, BIO suggests editing the text to read:

SECTION	ISSUE	PROPOSED CHANGE
	immunogenicity can change the clearance of a TP. In these cases, the sponsor should evaluate the DDI potential of the TP as a victim. This type of DDI evaluation can be difficult to prospectively design, in which case a descriptive analysis can often be considered adequate." Approved dose of drugs like anti-TNF are based on efficacy and safety information predominantly from individuals who had sustained drug exposures in the absence of ADA. If administration of immunosuppressors decreases immunogenicity incidence, then individuals predisposed to immunogenicity will approach efficacious and safe exposures consistent with the drug label. Although this is an example of DDI, the clinical relevance in terms of efficacy or safety is unclear. Further, we believe that the text regarding evaluating the DDI potential of the TP as a victim is too prescriptive based on historical examples.	"Since immunogenicity (i.e., the formation of antibodies to TPs) can alter the clearance of some TPs, drugs that suppress immunogenicity can change the clearance of a TP. ~~In these cases, the sponsor should evaluate the DDI potential of the TP as a victim.~~ This type of DDI evaluation can be difficult to prospectively design, in which case a descriptive analysis can often be considered adequate. The sponsor may evaluate the exposure of the TP in the presence and absence of the immunosuppressant in subjects negative and positive for antidrug antibodies."
Lines 134-135:	The Draft Guidance states "For antibody-drug conjugates (ADCs), the small molecule drug component conjugated to the antibody component can be released into unconjugated form." The Guidance does not give a definition for ADC, we suggest defining before this text.	We suggest adding the following text: "Antibody drug conjugates (ADC) are the product of covalently linking a monoclonal antibody or antibody fragment with a small molecule (payload)." Reference: Beaumont, M., Tomazela, D., Hodges, D. et al. Antibody-drug conjugates: integrated bioanalytical and biodisposition assessments in lead optimization and selection. AAPS Open 4, 6 (2018). https://doi.org/10.1186/s41120-018-0026-0

SECTION	ISSUE	PROPOSED CHANGE
Line 142:	The Draft Guidance states "For the small molecule drug component, follow the considerations described in the final FDA guidances for industry entitled…"	We suggest the following language for clarification purposes: "For the small molecule drug and payload containing moieties component, follow the considerations described in the final FDA guidances for industry entitled…."
III. TYPES OF DDI ASSESSMENTS AND STUDY DESIGN CONSIDERATIONS		
Lines 171-216:	This section of the Guidance discusses the types of DDI assessments and various study design considerations but does not include any discussion about phase-appropriateness of these assessments.	We ask the Agency to provide clarification on the phase of drug development where each methodology should be used. This should be clarified in the Guidance as in early stage of drug development, DDI studies are frequently performed in healthy subjects and thus may not adequately assess the true magnitude of the effect in the population of interest and the Dose in Phase 3 could be different from dose in Phase 1.
Lines 173-178:	This section discusses in vitro and animal studies.	We suggest including or referencing acceptable methods to assess *in vitro* risk of cytokine modulation.
Lines 192- 194:	The Draft Guidance states "The sponsor should determine the time course for cytokine modulation by the TP in the specific disease state to guide the timing and duration of administration of substrate and TP in the study". This statement implies that DDI study will be conducted after the drug is already given to patients.	As the intent of this language is unclear, we request that FDA please provide additional guidance in cases of modulation of multiple cytokines with different time profiles. This could include examples of cytokines where non-transient elevation was observed and a clinical DDI study was needed. Further, the sponsor should determine the time course for cytokine modulation by the TP in the specific disease state to guide the timing and duration of administration of substrate and TP in the study either in healthy subjects or patients before Phase III study.

SECTION	ISSUE	PROPOSED CHANGE
Lines 198-216:	These sections discuss population PK modeling and physiologically based PK modeling. BIO believes these sections are relevant and informative but can be expanded.	Besides highlighting "Population PK Modeling (Nested DDI Studies)" and "Physiologically Based PK Modeling", a separate paragraph can be added to consider other methods such as "Mechanism-based PK/PD modeling" to aid DDI assessment and study design that is beyond PK interactions. This will also link nicely with examples mentioned earlier in the document (e.g., "Mechanisms of DDIs Unrelated to Proinflammatory Cytokines").
Lines 212-216:	This section discusses physiologically based PK modeling.	We suggest that the Agency expand on the utility of using *in vitro data* and PBPK approaches. For example, there is the example of blinatumomab conducted a PBPK model assessing the effect of IL-6 levels on CYP enzymes[8]. If possible, we suggest expanding what would be the features that would improve the utility of this type of model in labeling. It would also be helpful for the Guidance to provide specific examples of PBPK use in evaluating DDI potential of TPs.
IV. LABELING RECOMMENDATIONS		
Lines 219:	This section discusses labeling.	We suggest FDA include examples and/or refer to relevant FDA publications[9] that provide more details on labelling for TP DDIs.
V. APPENDIX. TP-DDI DECISION TREE		

[8] Xu, et al. PT Pharmacometrics Syst Pharmacol. 2015; 4(9):507 – 15
[9] X Jing et al. Clin Pharmacokinetics 2020

SECTION	ISSUE	PROPOSED CHANGE
	The decision tree notes the potential need for labeling language indicating potential for transporter mediated drug interactions.	The transporter-mediated DDI in the decision tree has not been reflected in main text. We suggest that any concerns about the transporter mediated DDI can be stated in Section II (Consideration for assessing DDIs for TPs.)
	The decision tree does not include the category of antibody-drug conjugates which is discussed in main text.	We suggest that DDI potential evaluation for the large molecule components could be applicable to the decision tree, and that of the small molecule drug components should be evaluated according to the final DDI Guidances for industry (Jan 2020). This could be stated in the figure legend.
	This diagram suggests that if the justification for no interaction potential is not adequate, the sponsor should include labeling language highlighting potential for DDI. This diagram suggests that for pro-inflammatory cytokine TPs, a DDI study must be conducted.	If the justification for no interaction potential is not adequate, the sponsor could then conduct DDI evaluation OR include labeling language highlighting potential for DDI. There could be an option to provide a scientific justification for no interaction potential. The body of the guidance indicates a justification can be provided. This figure should be aligned.
	Even if the known or suspected mechanisms for DDI have been identified, the opportunity not to conduct a formal DDI clinical study based on relevant scientific- and/or PBPK-based justification should be offered. This option does not appear on the current decision tree.	We request that FDA modify the decision tree to discuss the ability to provide a justification to not conduct a formal DDI study.
	The box titled: "Pro-inflammatory cytokine modulator TPs" defaults to the diamond-shaped decision box: "Include labeling language indicating potential for CYP/transporter mediated drug interaction."	We suggest adding a new diamond-shaped decision box titled "Known or suspected mechanisms for DDI (see section IIa)"--prior to the existing diamond-shaped decision box.

SECTION	ISSUE	PROPOSED CHANGE
	The decision tree seems to indicate that FDA sees labeling as the default option, but without requiring the sponsor to conduct any of the assessments outlined in Section IIA.	
	The sub-category "Pro-inflammatory cytokine modulator TPs" should be made clearer. As suggested at Line 77-80, there are 2 ways in which this may occur.	We suggest adding "Direct pro-inflammatory cytokine modulator TPs" and "Indirect pro-inflammatory cytokine modulator TPs in select diseases" instead of "Pro-inflammatory cytokine modulator TPs".
	The box titled: Pro-inflammatory cytokine TPs" defaults to "Conduct DDI evaluation" (See section IIIB)" box. We find the current position to be overly prescriptive and defaults to having sponsors conduct clinical DDI studies for all proinflammatory cytokine TPs.	Pro-inflammatory cytokine TPs also should be given the option to include labeling language (i.e., the arrow should be directed towards the decision box stating: "Include labeling language indicating potential for CYP/transporter mediated drug interaction)." As such, we ask for the decision tree to be updated accordingly. Additionally, see our prior comments to Line 64: "The sponsor should evaluate the DDI potential for TPs that are proinflammatory cytokines."
	"Conduct DDI evaluation (see Section IIIB)" -> section IIIB only refers to clinical studies, although in-vitro, Pop-PK studies and PBPK studies are also mentioned and may provide a systematic, science-driven approach to evaluate the DDI potential as well.	We suggest the box should state "Conduct DDI evaluation (See Section III), method to be discussed with agency"
	This decision tree, along with Section II.A, indicates the possibility of scientific justification for no interaction potential only for the case of cytokine modulating TPs. The possibility of scientific justification for no interaction potential should be	Please revise relevant portions of the Guidance accordingly.

SECTION	ISSUE	PROPOSED CHANGE
	expanded to include the other categories of TPs (Section II.B) with well understood and quantitatively tractable underlying DDI mechanisms by allowing discussion of effects seen with other or similar agents for which the relevant mechanism (e.g., FcRn blocking, TMD, receptor agonism, etc.) occurs to a similar or greater degree.	