April 20th, 2020

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

Re: Docket No. FDA-2019-D-5607: Nonclinical Safety Evaluation of the Immunotoxic Potential of Drugs and Biologics; Draft Guidance for Industry

Dear Sir/Madam:

The Biotechnology Innovation Organization (BIO) thanks the Food and Drug Administration (FDA or Agency) for the opportunity to submit comments on the "Draft Guidance: Nonclinical Safety Evaluation of the Immunotoxic Potential of Drugs and Biologics" (Draft Guidance or Guidance).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.

General Comments:

As noted in the introduction of the Draft Guidance, several guidance documents address, to variable extents, nonclinical immune system safety assessments. While the stated purpose of this Guidance is to supplement the recommendations provided in the existing guidances, as pointed out in the more detailed comments below, the language and organization of the proposed Draft Guidance lacks clarity and/or appears to conflict with existing guidance. In its current form we are concerned that the Draft Guidance will mislead some Sponsors, particularly those who do not have immunotoxicity expertise, and lead to either inadequate safety packages or unnecessary animal studies.

In comparing the proposed Draft Guidance to existing ICH guidance and the withdrawn FDA guidance, it appears that this Draft Guidance attempts to address a limited number of safety topics that are not addressed in other guidances. These topics include immunosuppression and cancer risk, appropriate use of cytokine release assays, autoimmunity, and sensitization. If these are areas where the FDA feels additional guidance is warranted, we suggest this Guidance be more focused on these points. Additionally, we suggest more clearly referring readers to principles of ICH S8 as the primary framework for the assessment of immunotoxic potential and then using this Guidance to cover only those areas not covered in existing guidance.

We note that neither this Guidance nor ICH S8 "Immunotoxicity Studies for Human Pharmaceuticals" contains any text regarding data interpretation or the human translational value (or lack of) of the recommended immunotoxicity testing. We believe it would be very

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

helpful to Sponsors for the Guidance to include some text on this topic such as "there is limited understanding of the extent of reduced or increased immune function required to have significant biological effect, e.g., increased risk of infection, tumor development or autoimmunity in humans. A weight-of-evidence approach where all immunotoxicity data is considered as a whole (and in consideration of the mechanism of action (MoA) of the drug, the predicted extent and duration of human exposure, the clinical population, disease status, concomitant medication etc.) is recommended when interpreting the findings of immunotoxicity assays and in considering the risk of clinically-significant immunotoxicity occurring in humans." BIO believes it is important to add a statement advocating that nonclinical immunotoxicity endpoints, where possible and practicable, should be considered for clinical assessment.

In addition, portions of the Draft Guidance appear to define appropriate strategies to characterize the immunopharmacology of the molecule to enable first-in-man dose selection using MABEL or MABEL-like principles. While we agree that an appropriate set of in vitro and in vivo studies should be conducted to characterize the immunopharmacology, we suggest that inclusion of this information in an immunosafety guidance is not appropriate, as existing guidance and publications outline scientifically-based approaches to first-in-man dose selection. These approaches must be customized based on the nature of the target and are not limited to immunologic targets. As such we suggest sections of the document focused on first-in-man dose selection be removed.

As a general comment, for each section of the document, it would be helpful to provide additional references and or examples to further clarify the topics and issues.

Section III. B – Carcinogenicity and Immunosuppression

BIO suggests that clarification of a few key points in this section is needed. First, not all forms of immunosuppression lead to an increased cancer risk. The suggested revision in the chart attempts to clarify this point as there is now significant clinical experience with a variety of agents impacting the immune system and for only a limited set is there evidence of an increased cancer risk.

Second, despite long-standing efforts (Lebrec et al., 2016. Regul Toxicol Pharmacol 75, 72-80) there remains a lack of predictive animal models to aid quantitative risk assessment in this area. As such, the Guidance needs to focus on hypothesis-driven approaches guided by the mechanism of action of the compound. The Guidance appears to suggest a need to study in vivo models of tumor promotion, growth, and metastasis, and we are unaware of data validating the predictive value of these models for clinical risk.

Third, the ongoing ICH S1 prospective data collection may provide additional insights and Guidance into carcinogenicity assessment practices. As such, the Guidance should not be overly prescriptive and perhaps conflict with future ICH guidance.

Section IV – Assessing the Potential for Products to Increase Activity of the Immune System

In multiple sections in the document, particularly in Section IV, the Guidance suggests that there are no reliable nonclinical and/or validated models for prediction. BIO recommends

that the Agency consider data from investigative (and likely non-GLP) work if scientifically justified in the weight of evidence (WOE) evaluation.

Section V. C - Nonhuman Primate Enhanced Pre- and Postnatal Development

The need for a section on the ePPND study is unclear as NHPs are not a routine species for developmental toxicity testing and these studies are only performed when the risk assessment cannot be completed without data from this model. In addition, ICH S5(R3) and S6(R1) indicate that developmental immunotoxicity endpoints should be incorporated in these studies when appropriate. Therefore, BIO suggests that this section be deleted. As an alternative, the section could be altered to give guidance on the incorporation of immunotoxicity endpoints in both rodents and NHP study designs.

Conclusion:

BIO appreciates this opportunity to comment on the "Draft Guidance: Nonclinical Safety Evaluation of the Immunotoxic Potential of Drugs and Biologics." Specific, detailed comments to both the Core Guideline and the Annex are included in the following charts. 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 (BIO)

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
I. INTRODUCTION		
Pg. 2, 1st paragraph:	The Guidance clearly indicates that it covers new drugs, therapeutic proteins and blood proteins and excludes cell and gene therapies and adjuvanted vaccines. However, the term "other biologics" is not clear. In addition, the applicability to RNA-based therapies (e.g., siRNA, antisense oligonucleotide) is not clear though these are mentioned in Section IV E Innate Immunity page 8 which suggests they are in scope, it would be helpful for it to be included here.	BIO suggests the Guidance include clarification of the intended scope more clearly define "other biologics" and to address RNA therapies.
Pg. 2, 1st paragraph:	BIO finds the statement "Evaluation of all assessments discussed in this guidance may be indication-specific and is not necessarily expected for every product with potential immune effects" to be unclear.	BIO suggests replacing this text with the following: "Evaluation of immune-related effects may be tailored to indication, modality, and mechanistic considerations as well as specific causes for concern".
II. BACKGROUND		
Pg. 2, last paragraph:	We note that the examples of immunity (e.g., innate, adaptive, cell-mediated, and humoral immunity) may imply that they are separate categories, rather than subsets within larger frameworks (i.e., humoral immunity being an adaptive immune response).	We suggest clarification.
Pg. 2, last line:	The Draft Guidance states, "Safety evaluation of these drugs and biological products should include evaluating both the intended (pharmacological) and the unintended (toxicological) actions on the immune system."	BIO believes unintended effect might be present without toxicological significance, and recommends the guidance discuss intended and unintended actions without associating these terms with pharmacological/toxicological. As such we suggest editing the text to read:

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		"Safety evaluation of these drugs and biological products should include evaluating both the intended ~~(pharmacological)~~ and the unintended ~~(toxicological)~~ actions on the immune system." Additionally, a reference to "on-target and off-target effects" in addition to "intended and unintended effects" might help framing the scope of the recommendations.
Pg. 3, 1st paragraph (continuing from page 2):	The Draft Guidance states, "Effects can include both a reduction or an increase in activity, as well as changes in the immune balance (e.g., a shift from Th1 to Th2)."	BIO suggests more examples to illustrate undesired immunostimulatory and immunosuppressive risks. As such, BIO suggests adding "altering Teff:Treg cell balance, M1/M2 macrophages balance, changes in cytokine expression profiles" to the current text.
Pg. 3, 1st paragraph:	The Draft Guidance states, "For drugs that are designed to affect the immune system, the sponsor should provide data from immunological assays to demonstrate the pharmacological effects of the drug".	We ask that FDA recognize that in some cases these assays may be from non-GLP studies or the endpoints may be non-GLP in a GLP study.
Pg. 3, 1st paragraph:	The Draft Guidance states, "In addition, it may be important to evaluate the possibility of off-target or unintended effects on the immune system when results from standard studies suggest unexpected effects."	BIO suggests editing the text as follows for clarity: "In addition, it may be important to evaluate the possibility of off-target or unintended effects on the immune system in targeted immunological assays when results from standard toxicity studies suggest unexpected effects.

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Pg. 3, 3rd paragraph:	The Draft Guidance states, "Data on antigenicity should be included in section 4.2.3.7.1." BIO notes that there is often confusion between antigenicity (i.e., allergenicity) and immunogenicity (ADA). In line with ICH S8, we suggest clarification that "antigenicity" refers to "allergenicity". It would also be helpful to clarify that immunogenicity data should also be discussed within the context of the study for which it was done and not the antigenicity section.	For clarity, BIO suggests editing the text to read: "Data that refer to specific immunotoxicology studies should be included in the eCTD in section 4.2.3.7.2. Data on antigenicity (allergenicity) should be included in section 4.2.3.7.1. Data evaluating the immune system that are part of a general repeated-dose toxicity study (including immunogenicity) should be included with those data in section 4.2.3.2."
Pg. 3, 4th paragraph:	The term immunomodulator is not used in other sections of the document. While we agree that the term immunomodulator does not have a precise definition, this paragraph does not provide guidance or provide a definition that is used consistently throughout the document which could lead to confusion.	BIO suggests that this paragraph be deleted as it does not provide enough clarity to be useful. The general concept that the mechanism of action should inform the design of the safety program has already been covered by prior language. If not deleted, BIO asks FDA to please consider further explaining the purpose of this paragraph and how this terminology applies in the context of the proposed assessments.
Pg. 3, 4th paragraph:	As written, it is unclear what parameters are being referred to from general tox studies since many people won't include much beyond the standard ones in the first tox studies unless there is an expectation of immune effects.	If the entire paragraph is not deleted as recommended, for clarity, BIO suggests editing the text to read: "Alterations in immune system parameters (e.g., hematology, immune phenotype, histopathology) that are detected in general toxicology studies can warrant further investigation, on a case-by-case basis, depending on the characteristics of the specific

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		development program (e.g., indication, patient population, intended pharmacology)."
III. ASSESSING THE POTENTIAL FOR PRODUCTS TO REDUCE THE ACTIVITY OF THE IMMUNE SYSTEM		
A. General Immunotoxicity Assessment		
Pg. 4, subtitle:	"General immunotoxicity assessment" is a very broad term and while this section is dedicated to molecules reducing the activity of the immune system.	BIO suggests revising the title to "General ~~Immunotoxicity~~ Immune Assessment"
Pg. 4:	The intent of this section is not clear. The section starts by referring to endpoints for immunologic safety testing, rather than first defining the overall strategy which would provide a valuable framework to guide the reader.	We suggest this section be refined to clearly describe the general immunotoxicology testing strategy emphasizing the following points: - WOE principles in ICH S8 are relevant to determine the nature and scope of the assessment. - ICH S8 text which indicates that for compounds intended to affect the immune system the Sponsor should provide data from an appropriate set of assays/studies guided by the mechanism of action. After outlining this high-level approach, the Guidance can use subsequent sections to define specific topics that the FDA considers to be inadequately addressed in existing guidances.
Pg. 4, 3rd paragraph:	The Draft Guidance states, "If the WOE approach suggests potential immunotoxicity…" However, BIO notes that this section deals with immunosuppression.	BIO suggests editing the text to read: "If the WOE approach suggests potential ~~immunotoxicity~~ immunosuppression…"

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Pg. 4, 3rd paragraph:	BIO suggests broadening the language covering the WOE approach to include assays other than TDAR as they may be more appropriate based on the cell population of concern. This paragraph also recommends the use of a positive control compound in any TDAR assays. In many cases, these assays are conducted within the repeat-dose toxicity studies in nonhuman primates and a positive control is not needed. The concurrent control values and the historical experience of the laboratory is used to interpret the assay.	BIO suggests deleting the extensive information on TDAR and the requirement for a positive control. We suggest replacing this paragraph with the following: "If the WOE approach suggests potential immunosuppression, but a specific affected part of the immune system is not identified, then a common secondary assay that requires functionality of several key immune cell subtypes (e.g., antigen-presenting cells, T-helper cells, B cells), such as the T-cell-dependent antibody response (TDAR) assay is recommended. When the specific part of the immune system is known, then other functional assays designed to assess the impact on these immune cells/systems (e.g., NK cells, macrophages, CD8+ T cells etc.) can be used for further assessment."
Pg. 4, 3rd paragraph:	The Draft Guidance states, "KLH is a common choice of antigen based on the extensive historical database, growing standardization, and experience across multiple labs."	Although progress has been made, KLH is a very large protein and forms irregular aggregates and standardization is challenging. BIO suggests editing the text as follows: " KLH is a common choice of antigen based on the extensive historical database~~, growing standardization,~~ and experience across multiple labs".
Pg. 4, 3rd paragraph:	The TDAR is described as a "secondary assay".	BIO asks FDA to clarify how primary and secondary are defined as it is currently unclear from the Guidance.

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Pg. 4, 3rd paragraph:	The Draft Guidance discusses "other antigens".	BIO suggests editing the text to read: "(e.g., sheep erythrocytes, tetanus toxoid, HBsAg, or adenoviral vector-expressed antigens). The mechanism of action of the test molecule may influence the choice of antigen and dose. ~~have been used in drug development.~~
B. Carcinogenicity and Immunosuppression		
Section B:	As discussed in the general comments section, BIO believes that a few key points need to be clarified and have offered suggested replacement text for this section. Should this approach not be taken, we also include additional specific edits below.	The following is a suggested revision of this section: Profound immunosuppression is associated with an increased risk of certain tumor types in humans. These tumors are primarily associated with loss of control of chronic/latent pathogen infections, although direct interference with tumor surveillance could also result in an increased risk for tumors. As such, consideration of the effects of a drug or biologic on the immune system should be considered when assessing its carcinogenic potential. Sponsors should follow the recommendations in ICH S1, ICH S6(R1), and ICH S9 in 1) determining the need for an assessment of carcinogenic risk and 2) determining which experimental approaches are warranted. To date, animal models, including rodent bioassays, have not been shown to be helpful in quantitative risk assessment for immune mediated cancer risk. A weight-of-evidence (WOE)-based risk assessment should be conducted which addresses relevant attributes of the drug and drug target. When there is sufficient cause for concern, characterization of the products impact on key components of the

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		immune system thought to be involved in tumor surveillance (e.g. natural killer (NK) cells, T cells, B cells) may be warranted. FDA recommends that sponsors discuss their assessment strategy with the review division prior to embarking on extended studies.
Pg. 4, last paragraph:	The Draft Guidance states, "Standard 2-year carcinogenicity studies are not specifically designed to detect carcinogenicity caused by drug-induced decreases in tumor surveillance, particularly when the increased tumor risk is caused by recrudescence of latent viral oncogenes, infectious agents, or chronic inflammatory states."	BIO suggests the Guidance add further explanation at end of this sentence by adding*:* "...where significant species differences exist, which make translatability to humans challenging".
Pg. 4-5:	The Draft Guidance states, "Therefore, if an assessment is warranted for a product with immunosuppressive potential, sponsors should complete a WOE-based risk assessment in addition to the standard carcinogenicity studies."	BIO suggest deleting "in addition to the standard carcinogenicity studies." as carcinogenicity studies are not required for every product.
Pg. 5:	The Draft Guidance states, "A WOE-based risk assessment is particularly relevant for drugs and biologic products that lack the intended pharmacological activity in rodents and for biologics for which significant formation of anti-product antibodies diminishes interpretability of rodent studies."	BIO suggests editing the text to read: "A WOE-based risk assessment is particularly relevant for drugs and biologic products that lack the intended pharmacological activity in rodents a~~nd for biologics for which significant formation of anti-product antibodies diminishes interpretability of rodent studies~~ and/or when standard carcinogenicity studies are not practical (e.g., significant formation of anti-drug antibodies)."

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Pg. 5, 2nd paragraph:	The Draft Guidance states, "When the product adversely impacts key components of the immune system, such as critical cells involved in tumor surveillance (e.g., natural killer (NK) cells, T cells, B cells), sponsors should consider a functional assessment of these key components."	The sentence implies that there is similar importance of B cells for immune surveillance of tumors in comparison to NK and T cells. BIO suggests deleting B cells from the example and instead referencing other antigen presenting cells. Further, we suggest replacement text for "when the product adversely impacts key components. BIO suggests editing the text to read: "When ~~the~~ a product ~~adversely impacts key components~~ downregulates immune function of the immune system, such as critical cells involved in tumor surveillance (e.g., natural killer (NK) cells, T cells, other antigen presenting cells), sponsors should consider a functional assessment of these key components."
IV. ASSESSING THE POTENTIAL FOR PRODUCTS TO INCREASE ACTIVITY OF THE IMMUNE SYSTEM		
A. Immunostimulation		
Section A:	This section appears to cover both recommendations on when studies are needed to address the potential for cytokine release with the broader topic of what pharmacology assays are warranted to inform first-in-man dose selection. As described in our general comments on the Guidance, we believe that the approaches to informing first-in-man dose selection are covered in existing guidance and publications, are highly specific to the mechanism of action of the product, and are not solely limited to immunologic mechanisms. Should this approach not be taken, we also include additional specific edits below.	We suggest the information on dose selection be deleted and that this section focus on factors to consider in determining the need for, and nature or appropriate format of, cytokine release assays. We note, for instance, that while the plate-bound format was previously considered sufficient for compounds binding surface receptors on T cells (e.g., TGN-1412-like), the Guidance seems to suggest the use of both assays (soluble and plate-bound formats) for this class. Additional clarity on expected cytokine release assay formats is suggested with reference to target, target

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		distribution, mechanism of action, and potential for effector function.
Section A:		BIO suggests including discussion about the importance of the mechanism of action (MoA) in selecting the approach as approaches vary for T cell engaging (i.e., direct activating) molecules, check point inhibitors, and agonists. In addition, the in vitro assays specifically mentioned in this section are more relevant for direct activating molecules (i.e., a T cell engaging therapies) and are not as informative for the other modalities (CPIs and costimulatory agonists).
Pg. 5, 5th paragraph:	Reference 9	BIO suggests deleting the current reference and add the following more relevant publications: 1) Peter J Bugelski, Ram Achuthanandam, Renold J Capocasale, George Treacy & Esther Bouman-Thio (2009) Monoclonal antibody-induced cytokine-release syndrome, Expert Review of Clinical Immunology, 5:5, 499-521, 2) D. Finco, C Grimaldi, M Fort, M Walker, A Kiessling, B Wolf, T Salcedo, R Faggioni, A Schineider, A Ibraghimov, S Scesney, D Serna, R Prellk, R Stebbings, PK Narayanan. Cytokine Release Assays: Current Practices and Future Directions. *Cytokine* April 2014. Vol 6(2): 143-155.
Section A:	This section can be interpreted to indicate that CRAs are required for every biologic (other than CD3 bispecific). Depending on the construct, target, and known information, CRA may not be scientifically	We suggest replacing this section with the following text:

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	warranted. For example, cross-linking is not necessary for stimulation of every receptor and this assay may not be the most sensitive assay or necessary. There is also no clear justification as to why both a substrate bound and soluble assay format is necessary.	"Due to immunological differences in expression and sensitivity between humans and nonclinical test species, additional safety considerations may be needed for therapeutics intended to modulate the immune response, which can lead to adverse reactions such as excessive cytokine release. In addition to biological activity and pharmacological in vitro assessments using human cells, an appropriate hazard identification assessment of the potential for cytokine release syndrome caused by therapeutic proteins using unstimulated human cells should be considered based on the product's mechanism of action and/or binding potential to immune cells. There are several formats discussed in the literature (references included above and below) for assessing cytokine release. The appropriate format for an assay should be based on the biology of the target. For example, an appropriate assay for a therapeutic that binds a receptor on the T cell surface of which is activated through crosslinking, would include a plate (or substrate) bound format. This most sensitive hazard identification format (e.g., plate bound) for therapeutics targeting receptors that require cross linking for activation, is not amenable to deriving a concentration of therapeutic translatable to potential human peripheral exposure; results should be interpreted as a general hazard identification with consideration to the profile of cytokines elicited (Ref, Bugaleski et al (above), Finco et al (above), Stebbing et al 2007 J Immunol.). If the assays used to characterize the primary pharmacology of the product have already

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		demonstrated that the product has a clear potential to directly cause cytokine release (e.g., a CD3 bispecific T cell redirector) or cytokine release has been identified in pivotal toxicity studies, these assays are usually not necessary, as the potential hazard has already been identified. Moreover, when products do not directly bind to surface receptors with recognized involvement in immune system activation, cytokine release assays for hazard identification are generally not warranted. When appropriate to conduct a cytokine release assay for hazard identification, the assays should include assay positive controls (treatment of donor cells with known mitogens [e.g., TGN 1412 biosimilars, PMA, or anti-CD3/CD28 antibodies) to ensure the donor cells are capable of eliciting cytokines under the assay conditions. In addition, negative controls (comparator controls) such as antibody isotype controls with the same Fc tail for antibody therapies are necessary for appropriate interpretation of target-mediated cytokine release. References (listed above)."
Pg. 6, 1st paragraph:	As this section is about immune stimulation, BIO suggests using "enhance" or "increase" instead of "modulate" for clarity as the term "modulate" can be either direction.	We suggest editing the text to read: "Because of immunological differences in expression and sensitivity between humans and nonclinical test species, additional safety considerations may be needed for therapeutics intended to ~~modulate~~ enhance the immune response, which can lead to adverse reactions such as excessive cytokine release."

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Pg. 6, 1st paragraph:	The Guidance has introduced a new term and acronym called pharmacological effect level (PEL) but it is unclear how this differs from other current terms.	BIO asks FDA to clarify how this differs from other acronyms already in use such as Pharmacologically Active Dose (PAD), minimal Pharmacologically Active Dose (mPAD), Minimum Effective Dose (MED), Anticipated Therapeutic Dose (ATD) and Optimum Biological Dose (OBD).
Pg. 6, 2nd bullet:	The section mentions soluble vs. immobilized formats however, industry is using broader modifications of the standard format such as tumor and endothelial cell co-cultures, patient-derived cells, 3D MPS, use of whole blood vs. PBMCs, etc. The section also recommends that both soluble and plate-bound formats should be used but this should be case-by-case dependent on the MoA of the molecule.	BIO suggests removing the statement that "both" formats should be used for hazard identification and replace it with a statement that the selection of the assay format for hazard identification should be driven by the mechanism of action of the drug.
Pg. 6, 2nd bullet:	Reference 10.	It is unclear why reference 10 is listed here. There are multiple references that can be leveraged to help sponsors selecting proper assays and the proposed reference does not seem to be fit for purpose. As such, we suggest deleting it.
Pg. 6, 3rd bullet:	The Draft Guidance states, "When products do not directly bind to surface receptors…"	For clarity regarding which types of products are being referred to in this text, we suggest editing the text to read: "When therapeutic protein products do not directly bind to surface receptors with recognized involvement in immune system activation"
Pg. 6, last paragraph:	The Draft Guidance states, "Although a positive response in a cytokine release assay may not preclude further development of a drug, it could	BIO suggests editing the text to read:

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	impact the selection of the appropriate start dose and inform clinical monitoring, the need for potential interventions, and dose escalation and stopping criteria." BIO suggests adding additional context regarding what a cytokine release profile of concern may be.	"Although a positive response in a cytokine release assay may not preclude further development of a ~~drug~~ pharmaceutical, depending on the magnitude/duration of the effect and/or the number and functions of cytokines affected, it could impact the selection of the appropriate start dose and inform clinical monitoring, the need for potential interventions, and dose escalation and stopping criteria."
B. Non-Target-Related Antibody-Mediated Immune Stimulation		
Title:	BIO suggests changing the title, as the content of this section contains immune stimulation effects that can be mediated by both biologics and small molecule or peptide drugs.	BIO suggests editing the title to: "B. Non-Target-Related and Antibody-Mediated Immune Stimulation"
Section B:	In contrast to the prior guidance which summarized the classical types of hypersensitivity reactions in this type of section, the purpose of this section is not clear, and it does not appear to offer interpretable guidance for designing safety programs.	We suggest either omitting this section or revising to better define "non-target-related antibody-mediated immune stimulation" safety concerns and then provide clear guidance.
Pg. 7, 1st paragraph:	It is unclear what "ELISA, immunoassay, modified TDAR" measures in the context of this section. The value of TDAR to assess enhancement of antigen-specific IgM/G production in the risk assessment is unclear.	BIO asks the FDA to clarify what would be a trigger for TDAR in that context.
Pg. 7, 2nd paragraph:	BIO notes that both mast cells and basophils can contribute to IgE-mediated anaphylactic reactions.	BIO suggests editing the text to read: "Anaphylactic reactions occur when a drug binds to IgE on mast cells or basophils and induces a

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		degranulation reaction. Symptoms may range from mild to fatal."
Pg. 7, 2nd paragraph:	In general, drug-induced anaphylactoid reactions can be induced by the direct activation of mast cell/basophils by a peptide or small molecule drug, or drug-induced complement activation.	BIO suggests editing the text to read: "Anaphylactoid reactions are caused by multiple mechanisms, including the activation of the complement system by anti-product antibodies, or a direct interaction between a peptide or small molecule drug and a receptor on the mast cell or basophil surface."
Pg. 7, 2nd paragraph:	Drug-induced anaphylactic and anaphylactoid reactions can be observed in preclinical species.	BIO suggests editing the text as follows regarding for risk assessment considerations. "~~Overall, no nonclinical models are available to reliably predict either anaphylactic or anaphylactoid reactions.~~ For therapeutic proteins, anti-product antibody driven anaphylactic findings observed in nonclinical species have limited predictive value for humans. For drug-induced anaphylactoid reactions, in vitro assays such as complement activation or mast cell/basophil activation assays can be used for risk assessment, although the ability to adequately predict human risk is still unknown."
Pg. 7, 3rd paragraph:	The value of using the TDAR to assess potential for increased antibody responses and hence risk of antibody-mediated (IgG/IgE) hypersensitivity is speculative and it use is not clear.	BIO suggests deleting the following text: "Although not traditionally considered as a means to understand the potential risks associated with increased IgM/G production, an antigen-based model (e.g., the TDAR assay) can be modified to detect increased antibody production to address specific

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		concerns. This may be especially concerning for products with the potential for long-term effects, including significant enhancement of secondary or memory responses."
Pg. 7, 4th paragraph:	The Draft Guidance references the Guidance for Industry Immunogenicity Assessment for Therapeutic Protein Products. This guidance provides a nice summary for consequences of ADA, however, the assessment of ADA that is described is specific for clinical immunogenicity. Since the purpose of assessing ADA in nonclinical animal models is to aid in interpretation of the nonclinical study, the same approach should not be required for nonclinical studies.	BIO suggests deleting this or provide clarity of intention of its inclusion.
C. Autoimmune-Type Reactions		
Section C:	While we agree that available nonclinical models are not predictive for autoimmune reactions, it would be helpful to expand on the examples provided in this section. The focus on skin reactions is unclear as is the lack of discussion on the spectrum of autoimmune syndromes that accompany immunostimulatory therapies (i.e., immune-oncology therapeutics) in humans.	BIO suggests extra consideration be given to the examples provided in this section. For instance, the autoimmune diseases (lupus and myasthenia gravis) used as apparent examples of T cell-mediated hypersensitivity are complex, multifactorial diseases that are not solely driven by T cells.
D. Dermal Sensitization		
Pg. 7, last paragraph:	This section discusses FDA's recommendations for dermal sensitization for topical drugs.	BIO suggests that the selection of the species for topical drug products should be made case-by-case with a strong rationale considering the nature of administration and the formulation used.

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		Considering the 3Rs aspect highlighted in this draft by FDA the integrated in vitro testing strategy according to OECD TG 442 C, D, E should be the preferred approach (with murine LLNA -OECD TG 429 - as a second option) to evaluate the skin sensitization potential. Finally, it is unclear why "FDA no longer recommends that sponsors conduct the murine local lymph node assay to assess the sensitization potential of topical drug products due to the limitations of the assay". BIO requests additional information regarding the basis of this recommendation.
E. Innate Immunity		
V. DEVELOPMENTAL AND JUVENILE STUDIES		
A. Overview		
Pg. 8:	We note that the guidance here is generally consistent with current practice and is covered in existing guidance.	We suggest that cross-referencing appropriate guidances (including the upcoming final ICH S11 guidance) would be sufficient for the purposes of this document. Should this approach not be taken, we also include additional specific edits below.
Pg. 8:	The section focuses on assessing the impact on the immune system of the developing fetus and neonate/juvenile but makes no mention of immunomodulation of the maternal immune system.	BIO suggests adding a section on the impact of immunomodulatory drugs on the maternal immune system and pregnancy maintenance.
Pg. 8, 4th paragraph:	The Draft Guidance states, "Juvenile and pre- and postnatal development studies are not typically	For consistency with ICH S9, we suggest editing the sentence to read:

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	warranted for products intended to treat patients with cancer."	"Juvenile and pre- and postnatal development studies are not typically warranted for products intended to treat patients with advanced cancer."
B. Developmental Animal Studies		
Pg. 9, 1st paragraph:	As written, it is unclear what is meant by "follow-up assessments".	For clarity, we suggest replacing "Follow-up assessments may be necessary in the following circumstances" with "Such cases include:" followed by the existing bullet points.
Pg. 9, 3rd bullet:	As written, it is unclear if this refers to direct effects on adult or on the developing immune system.	BIO asks FDA to clarify intent.
C. Nonhuman Primate Enhanced Pre- and Postnatal Development		
	The need for a section on the ePPND study is unclear as NHPs are not a routine species for developmental toxicity testing and these studies are only performed when the risk assessment cannot be completed without data from this model. In addition, ICH S5(R3) and S6(R1) indicate that developmental immunotoxicity endpoints should be incorporated in these studies when appropriate.	BIO suggests that this section be deleted. As an alternative, the section could be altered to give guidance on the incorporation of immunotoxicity endpoints in both rodents and NHP study designs.
Pg. 9, 1st bullet:	The Draft Guidance specifically references specialized IHC.	BIO asks FDA to provide more context or rationale for noting specialized IHC including examples.
Pg. 9, 2nd bullet:	It is unclear whether specialized endpoints are to be included in pregnant dams or offspring.	For clarity, BIO suggests editing the text to read: "Sponsors can include specialized endpoints for immunotoxicity in the offspring if there is a concern to the developing immune system."

SECTION	ISSUE	PROPOSED CHANGE
D. Juvenile Animal Studies		
Pg. 10, 1st paragraph:	In addition to findings in nonclinical toxicity studies, target biology may drive the concern for potential effects on development and should also be included as a reason to consider a juvenile toxicity study. Additionally, we find the text "for products being developed in some indications" unclear.	BIO suggests editing the text to read: "If an evaluation of target biology or existing nonclinical toxicity studies…" Additionally, we ask FDA to clarity "some indications".