Biotechnology Industry Organization

April 12th, 2013

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

Re: Docket No. FDA–2013–D–0092: Draft Guidance for Industry on Immunogenicity Assessment for Therapeutic Protein Products

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Immunogenicity Assessment for Therapeutic Protein Products." BIO commends FDA on the release of this Draft Guidance, which will help Sponsors to identify and mitigate risks of adverse immunological reactions during the development and marketing of therapeutic protein products.

BIO represents more than 1,100 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, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

GENERAL COMMENTS:

In general, the Draft Guidance is very well written and provides a useful review of the numerous factors that can affect immunogenicity. BIO generally agrees with the risk-based approach presented in the Draft Guidance but recommends that FDA set a minimum level of required immunogenicity testing for all therapeutic protein products to provide clarity for potential Sponsors and to ensure safety and efficacy for patients.

A. Improving Organization and Flow by Aligning with International Guidelines for Risk Management

BIO encourages FDA to reorganize the Draft Guidance in alignment with the established format of international guidelines for risk management, including International Organization for Standardization (ISO) 31000 – *Risk Management Guidelines and*

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Principles[1] and International Conference on Harmonization (ICH) Q9 – *Quality Risk Management.*[2] This general format can be summarized as[3]:

- ***Risk Assessment***
  - Risk Identification
  - Risk Analysis
  - Risk Evaluation
- ***Risk Control***
  - Risk Reduction
  - Risk Acceptance
- ***Risk Review***
  - Review Events

This could be achieved simply by moving *Section V. Patient- and Product-Specific Factors That Affect Immunogenicity* ahead of *Section III. Clinical Consequences,* to be followed by *Section IV*. *Recommendations for Immunogenicity Risk Mitigation in the Clinical Phase of Development of Therapeutic Protein Products.*

B. Improving Utility by Providing Further Recommendations and Examples from Literature

BIO encourages FDA to add greater detail to the recommendations sections to provide Sponsors with meaningful advice on how to identify and address the risk factors for potential immunological reactions, which would greatly improve the utility of the Draft Guidance. For example, the Draft Guidance briefly mentions in Section V.A.2 the potential impact of prior exposure to a therapeutic protein, but the accompanying recommendation in this section does not provide any suggestions as to how Sponsors should assess this factor in their development programs.

Additionally, BIO believes that further citation of updated examples from the relevant literature would support the requested expansion of the recommendations sections and provide important clarity to potential Sponsors.

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[1] International Organization for Standardization (2009) *ISO 31000:2009 Risk Management – Principles and Guidelines*

[2] FDA Guidance for Industry on *Q9 Quality Risk Management*, http://www.fda.gov/downloads/Drugs/.../Guidances/ucm073511.pdf

[3] Claycamp, HG (2006) *ICH Q9: Quality Risk Management*. CDER Advisory Committee for Pharmaceutical Science (ACPS). October, http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4241s1_3.ppt

C. Addressing Variations Between Specific Classes of Therapeutic Protein Products

BIO requests that FDA provide additional details for the recommendations made within the Draft Guidance to address the specific issues associated with certain therapeutic protein product classes, where appropriate. While well-understood therapeutic product classes may likely present little challenge when conducting immunogenicity assessment, the less familiar or more structurally complex therapeutic protein product classes (such as fusion proteins or monoclonal antibodies, respectively) may require more complex analytical assay methodologies to detect all chemical modifications. Additionally, these novel or more structurally complex product classes may require a more sophisticated clinical monitoring program, in part due to the required prerequisite of maintaining high levels of manufacturing purity and avoidance of chemical degradation.

D. Clarifying Applicability of the Draft Guidance to Biosimilar Development

While BIO recognizes that the topics discussed in the Draft Guidance apply generally to the development of biological products, BIO encourages FDA to address the specific concerns related to immunogenicity assessment for biosimilar biological products in a separate Guidance document that bridges the principles presented in this Draft Guidance with the Draft Guidance on *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product*.[4] Immunogenicity is a critical issue for biosimilar development and marketing because of the potential for differences between the reference product and the biosimilar. Additionally, since biosimilars are expected to have a less robust package of preclinical and clinical testing data, the opportunity to understand the impact of various product characteristics on immunogenicity before marketing will be limited. Therefore, BIO believes the following principles should be considered carefully by FDA regarding immunogenicity testing that will be recommended and/or required for biosimilar biological products:

- *First*, the immunogenicity of therapeutic protein products is unpredictable. As this draft guidance notes, many factors, including a protein's degradation, misfolding, microheterogeneity, and microaggregation, can influence the molecule's immunogenicity.

- *Second*, product differences that are difficult or impossible to detect can lead to differences in immunogenicity. State-of-the-art analytical testing may be capable of showing that two complex protein products are very highly similar in structure, but such testing cannot show that those products will have the same immunogenic responses in humans.

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[4] FDA Draft Guidance on *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product,* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf

- *Third*, similar rates of immunogenicity with an innovator biologic and a potential biosimilar do not necessarily equate to similar immunogenicity profiles. Two similar complex protein products may be immunogenic in different patients and/or elicit antibodies to different epitopes, with different titers or kinetics (time to onset and transient/persistent).

- *Fourth*, differences in immunogenicity can result in differences in safety and efficacy in ways that cannot be predicted without clinical testing.

- *Fifth,* pre-market clinical testing is inadequate to exclude clinically important differences in immunogenicity. Post-market surveillance measures will be necessary.

- *Sixth,* the human immune system is highly sensitive to some types of differences between products (but not others), so differential immunogenicity may be a clue to clinically meaningful product differences not detected by other testing. Therefore, serological cross-reactivity must be taken into consideration, especially for biosimilar biological products seeking an interchangeable designation.

BIO has presented detailed concerns related to immunogenicity of biosimilar products in previous public comments to FDA[5,6,7,8] and looks forward to the opportunity to continue to work with the Agency to address these concerns in the future.

E. Employing Standardized Nomenclature to Replace the Generic Term "Aggregate"

BIO believes that the use of the term "aggregate" throughout the Draft Guidance to refer exclusively to oligomers in the nanometer size range is confusing and that FDA should move to a standard, less ambiguous terminology. For specific species, BIO

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[5] BIO Comments on FDA Approval Pathway for Biosimilar and Interchangeable Biological Products, http://www.bio.org/sites/default/files/20101223.pdf

[6] BIO Comments on FDA Draft Guidance on Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product, http://www.bio.org/sites/default/files/2012-04-16%20Biosimilars%20Quality%20Considerations%20-%20FINAL.pdf

[7] BIO Comments on FDA Draft Guidance on Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, http://www.bio.org/sites/default/files/2012-04-16%20Scientific%20Considerations%20-%20FINAL.pdf

[8] BIO Comments on FDA Draft Guidance on Biosimilars: Questions and Answers Regarding Implementation of the BPCIA of 2009, http://www.bio.org/sites/default/files/2012-04-16%20Biosimilars%20Q&A%20-%20FINAL.pdf

believes that the size being discussed should be used (in this case nanometer-sized aggregates), or alternatively, the nanometer-sized aggregates could simply be referred to as "oligomers." Scientists from industry, academia, and regulatory authorities have extensively reviewed this proposed standardized terminology, which was developed at the meeting of the American Association of Pharmaceutical Scientists (AAPS), co-sponsored by FDA, on Protein Aggregation and Immunogenicity in Breckinridge, Colorado in July 2010.[9]

CONCLUSION:

BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Immunogenicity Assessment for Therapeutic Protein Products." Specific, detailed comments are included in the following chart. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Andrew W. Womack, Ph.D.
Director, Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)

[9] Narhi LO, et al. (2012) Classification of Protein Aggregates. *Journal of Pharmaceutical Sciences*, 101(2): 493-498.

SPECIFIC COMMENTS

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I. INTRODUCTION		
Lines 33-36:	Despite brief sections in the appendix, BIO believes that assessment of immunogenicity in non-clinical studies is largely outside of the scope of this guidance.	BIO recommends that FDA amend the draft guidance to state that, in addition to vaccine development and assay development, the assessment of immunogenicity in non-clinical studies is largely outside of the scope of this guidance.
II. BACKGROUND		
Lines 47-61:	This discussion acknowledges the potential effects of immune responses on safety and efficacy, including adverse events and diminished efficacy due to changes in pharmacokinetics, but does not acknowledge the potential for diminished efficacy due to increased clearance, which may actually be the most common effect.	BIO recommends that FDA acknowledge the potential for diminished efficacy due to increased clearance.
III. CLINICAL CONSEQUENCES		
Lines 74-75:	BIO is concerned that this characterization might imply that transient anti-drug antibodies (ADA) are harmless, and only persistent ADA would be harmful.	BIO recommends revising to read: "…from ~~transient~~ antibody responses with no apparent clinical manifestations to life threatening and catastrophic reactions."
Lines 75-78:	If the terminology "related adverse events" refers specifically to the events detailed in Section III B #1-5 then the guidance document should cross reference this section.	BIO recommends revising to read: "During therapeutic protein product development, elucidation of a specific underlying immunologic mechanism for related adverse events is encouraged (see Section III, B items 1-5), because this information can facilitate the development of strategies to help mitigate the risk of

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		clinically significant immune responses."
Lines 78-81:	During the early stages of drug development, some of these parameters (immune response, target disease indication and population) may not be well defined.	BIO recommends revising to read: "The extent of information required to perform a risk-benefit assessment will vary among individual products, depending on product origin and features, the immune responses of concern, the target disease indication, and the proposed patient population, some of which may not be well-defined during the early stages of drug development."
A. CONSEQUENCES FOR EFFICACY		
Lines 90-99:	Both neutralizing and non-neutralizing antibodies are "binding" antibodies.	BIO recommends revising to read: "Furthermore, although some ~~binding~~ non-neutralizing antibodies may have no apparent effect on clinical safety or efficacy… necessary to determine the clinical relevance of both ~~binding~~ non-neutralizing and neutralizing antibody responses."
Lines 90-92:	For many therapeutic protein products, the FDA-approved labeling does not discuss dose escalation. As a result, the effect of a shortened half-life is more likely to be a lack of, or reduced, efficacy rather than dose modifications. Even where product labeling does discuss dose modifications, physicians often do not know how to modify dosing as a result of an immune response affecting clearance (*e.g.*, a shorter interval, rather than a higher dose, might be needed). Moreover, immune responses are rarely measured in	BIO recommends that FDA clarify that it will often be impractical for Sponsors to develop data sufficient to address dose alteration in the product label and that the issue should be dealt with on a case-by-case basis.

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	clinical practice, so a physician would not necessarily even know to consider dose modifications.	
B. CONSEQUENCES FOR SAFETY		
Line 109:	In order to avoid excluding non-IgE mediated acute (Type 1) hypersensitivity from this discussion, the title of this subsection should refer to "Anaphylaxis and anaphylactoid reactions."	BIO recommends revising to read: "*1. Anaphylaxis and anaphylactoid reactions*"
Lines 131-138:	Cytokine release syndrome is generally not related to ADA, however, there is a theoretical concern for agonistic biologics that ADA could cross-link receptor bound drug molecules and cause super-agonistic reactions, possibly leading to cytokine release syndrome. Additional detail on this topic would provide Sponsors with greater clarity.	BIO requests that FDA provide additional detail on cytokine release syndrome, particularly regarding the concern for agonistic biologics that ADA could cross-link receptor bound drug molecules and cause super-agonistic reactions.
Lines 154-164:	The appendix says that if Type III hypersensitivity is suspected, Sponsors should undertake investigation of immune complexes and suspend administration of the product in that subject, but there is no guidance for how suspected Type III hypersensitivity reactions should affect overall study conduct.	BIO requests that FDA provide guidance on the appropriate response to suspected Type III hypersensitivity reactions in the context of overall study conduct.
Lines 169-173:	A citation from relevant literature would be helpful for this topic.	BIO recommends that FDA provide a citation from relevant literature.
Lines 175-182:	Breast milk has been shown not to contribute meaningfully to antibody exposure for infants; rather, exposure has	BIO recommends revising to read: "…resulting from antibodies to the therapeutic protein

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	been shown to occur *in utero*.[10,11,12]	counterpart may potentially negatively impact fetal or neonatal development when such responses are generated during pregnancy ~~or breast feeding~~. ~~Indeed, the potential transmission of antibodies to developing neonates by breast milk must be considered~~."
IV. RECOMMENDATIONS FOR IMMUNOGENICITY RISK MITIGATION IN THE CLINICAL PHASE OF DEVELOPMENT OF THERAPEUTIC PROTEIN PRODUCTS		
Lines 205-206:	In some cases, assay validation of drug tolerance is sufficient to exclude the necessity of taking concomitant samples for drug level determinations.	BIO recommends revising to read: "Concomitant sampling of therapeutic product levels is recommended to assess potential interference with the assay, unless assay validation obviates this need."
Lines 210-217:	It would be helpful to provide examples or a range of values to consider for sampling frequencies for lower versus higher risk molecules.	BIO requests that FDA provide recommendations for sampling frequencies for lower versus higher risk molecules during post-treatment follow-up period.
Lines 219-221:	BIO believes, in addition to unscheduled samples, samples from early terminations are valuable for immunogenicity assessment.	BIO recommends revising to read: "…unscheduled sampling triggered by suspected immune-related adverse events, including early terminations, is

[10] Vaidyanathan A, et al. (2011) Developmental immunotoxicity assessment of rituximab in cynomolgus monkeys. *Tox Sci,* 119:116-125.

[11] Auyeung-Ki DJ, et al. (2009) Developmental and peri-postnatal study in cynomolgus monkeys with belimumab, a monoclonal antibody directed against B-lymphocyte stimulator. *Reprod Toxicol,* 28:443-455.

[12] Mahadevan U, et al. (2013) Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. Published online: http://dx.doi.org/10.1016/j.cgh.2012.11.011.

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		useful for establishing the clinical relevance of antiproduct antibodies."
Lines 223-224:	The expectations for retention of banked samples from clinical trials are unclear.	BIO requests that FDA clarify typical expectations for sample retention (*e.g.*, through BLA review and/or post-approval).
Lines 227-236:	Although BIO agrees with the considerations presented, dosing for first-in-human trials constitutes general guidance regarding biologics development and is not specifically relevant to the topic of immunogenicity.[13]	BIO recommends removing the following passage: "~~For first-in-human trials, a conservative approach in an appropriate medical setting with staggered dosing among individual patients, dosing cohorts, and different routes of administration is generally appropriate. The trial design should include prespecified dose escalation criteria and adequate time intervals between dosage cohorts and, as appropriate for the pharmacokinetics and pharmacodynamics of the product, between individuals within a dose cohort to assess toxicities prior to administration of subsequent doses or treatment of additional individuals. The need for such an approach will depend on the individual circumstances. As development progresses, dosing strategies and safety parameters can be modified based on clinical experience with the product and related products.~~"
Lines 254-258:	BIO believes that the recommendation to "study the underlying mechanism" of clinically relevant immune responses may interpreted many different ways.	BIO recommends revising to read: "If clinically relevant immune responses are observed, sponsors are encouraged to ~~study the underlying mechanism and~~ identify ~~any~~ critical contributing factors.

[13] FDA Guidance for Industry on *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers,* http://www.fda.gov/downloads/Drugs/Guidances/UCM078932.pdf

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		These investigations can facilitate development of potential mitigation strategies, including modification of product formulation, screening of higher-risk patients, or adoption of risk mitigation strategies (see below). Studying the specific underlying immunologic mechanism for related adverse events can be useful, because this information may facilitate the development of potential mitigation strategies."
Lines 268-272:	BIO believes "pre-specified criteria for acceptable immunogenicity differences" are subjective, and examples are needed. BIO also believes that assays used to measure antibody incidence, titer, or neutralizing activity should be validated/qualified to perform comparably with the use of product before and after the manufacturing change.	BIO recommends that FDA provide examples of pre-specified criteria (and statistical methods) that would be used to determine acceptability. BIO also recommends that FDA specify that assays used to measure antibody incidence, titer, or neutralizing activity for comparison pre- and post-manufacturing changes should be validated/qualified to perform comparably with the use of product before and after the change.
V. PATIENT- AND PRODUCT-SPECIFIC FACTORS THAT AFFECT IMMUNOGENICITY		
A. PATIENT-SPECIFIC FACTORS THAT AFFECT IMMUNOGENICITY		
Lines 339-341:	BIO believes a newer and more widely available reference would be appropriate. BIO also believes that while a therapeutic protein administered subcutaneously at low dosage can indeed be more immunogenic, immunological reactions associated with intravenous (IV) administration can be more severe.	BIO requests that FDA provide an updated reference that leverages the experience gained through the myriad therapeutic proteins that have been studied in the clinic during the last decade. BIO also recommends that FDA acknowledge that while a therapeutic protein administered subcutaneously at low dosage can indeed be more immunogenic, immunological reactions associated with intravenous (IV) administration can be more severe.

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Lines 372-374:	Genotyping of patients in advance of product administration in order to prevent immune responses, or to select other therapies, is exceedingly rare. In fact, in many cases, the scientific link between genetic status and expected immune response is not well-understood.	BIO recommends that FDA clarify that genotyping of patients before product administration for the purposes of predicting immunogenicity is not generally necessary but should be addressed on a case-by-case basis.
Lines 406-408:	BIO believes it would be helpful to illustrate how information on the level of the endogenous protein should be applied by including references to recent risk-assessment publications (*i.e.*, providing context that having lower levels of circulating endogenous protein may carry a higher risk).	BIO recommends that FDA include references to recent risk-assessment publications to illustrate the value to the overall risk assessment of gathering information on the level of the endogenous protein.
B. PRODUCT-SPECIFIC FACTORS THAT AFFECT IMMUNOGENICITY		
Lines 486-489:	BIO believes that it would be helpful to Sponsors for FDA to provide additional references that cite less anomalous fusion proteins and that will be better applicable to the majority of fusion proteins in development.	BIO recommends that FDA provide additional references that cite less anomalous fusion proteins and that will be better applicable to the majority of fusion proteins in development.
Lines 510-514:	BIO believes this paragraph, as currently written, may be misunderstood as a recommendation for an indeterminate number of assays for each potential fragment of a therapeutic protein product. BIO, therefore, believes it would be helpful to clarify that there are alternative methods of assessing the specific reactivity of the ADA without	BIO recommends revising to read: "~~For assessment of immune responses to fusion molecules, or to engineered versions of therapeutic protein products, antibody assays should be developed that enable assessment of responses to the intact protein product, as well as to each of the partner proteins separately or to novel regions~~. The reactivity of the ADA response to fusion molecules or engineered versions of therapeutic protein

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	developing separate assays for each possible component of molecule, such as inhibition of signal in the original screening assay or confirmation assays that inhibit with whole molecule as well as components.	products should utilize assays that are able to assess reactivity to the whole molecule as well as its components. Immune responses directed to the intact protein product, but not reactive with either of the separate partner proteins, may be targeting novel epitopes in the fusion region."
Lines 516-521:	The text implies that such studies are straightforward and can provide useful information regarding the immunogenic potential of therapeutic protein degradation products. However, these experimental protocols would be exceedingly complex to design and perform, and moreover, the results would not be definitely correlated with unwanted immunological consequences (observed "*in vivo*" degradation pathways may not necessarily provide conclusive evidence that the end-products are indeed immunogenic).	BIO recommends removing the following passage: "~~Evaluation of therapeutic protein products in the in vivo milieu in which they function (e.g., in inflammatory environments or at physiologic pH) may reveal susceptibilities to modifications (e.g., aggregation and deamidation) that result in loss of efficacy or induction of immune responses. Such information may facilitate product engineering to withstand undesirable effects. Sponsors should consider this information in early product design and in development of improved products.~~"
Lines 570-583:	While the discussion clearly indicates that the highest risk for immunological response is associated with protein aggregates in the 2-10 micron range, the assays mentioned are only useful for identifying dimers and oligomers in the nanometer range.	BIO recommends removing the following passage: "~~Methods include, but are not limited to the following: size exclusion chromatography, analytical ultracentrifugation (Berkowitz 2006), light scattering techniques (Wyatt Technology n.d.), Fourier transformed infrared spectroscopy (Gross and Zeppezauer 2010), and field flow fractionation (Roda, et al. 2009).~~"

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Lines 592-594:	Glycosylation can shield immunogenic protein epitopes from recognition by humoral immunity; however, cell-mediated immunity involves recognition of processed peptides and, therefore, would not necessarily be inhibited by glycosylation.	BIO recommends revising to read: "…as well as by shielding immunogenic protein epitopes from the humoral immune system…"
Lines 603-605:	BIO believes "does not deviate greatly from the normal glycan repertoire" is clearer than "close to the normal human pattern."	BIO recommends revising to read: "For proteins that are normally glycosylated, use of a cell substrate production system that glycosylates the protein in a nonimmunogenic manner and ~~close to the normal human pattern~~ does not deviate greatly from the normal glycan repertoire is recommended."
Lines 612-626:	BIO believes greater clarity and specificity on how to evaluate innate immune response modulating impurities (IIRMIs) would be beneficial.	BIO requests that FDA offer references that illustrate acceptable/problematic levels of IIRMIs, as well as clarity on the evaluation and reporting of data related to IIRMI levels.
Lines 685-688:	BIO believes alternative wording would be more easily understood.	BIO recommends revising to read: "Thorough analysis of leachables and extractables should be performed to evaluate the capacity of container closure materials to interact with and modify the therapeutic drug protein. ~~An appropriate risk mitigation strategy should be developed, as appropriate, following such an assessment.~~ A risk assessment should be conducted and risk mitigation developed as appropriate."
Lines 706-707:	The container closure considerations appropriately acknowledge that silicone coated syringe plungers can raise immunogenicity issues, however, this	BIO recommends revising to read: "Silicone oil-coated syringe ~~plungers~~ components provide a chemical and structural environment on which proteins can

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	potential issue is not limited to plungers, as syringe barrels can also be coated to improve glide.	denature and aggregate."
Lines 730-733:	It is not possible to obtain detailed description of all raw materials used in the manufacture of the container-closure systems since vendors consider this to be proprietary information. The reference to raw materials is not appropriate. BIO believes the analysis of leachables and extractables is adequate.	BIO recommends revising to read: Sponsors should ~~obtain a detailed description of all raw materials used in manufacture of the container closure systems for their products. Assays based on such techniques as reverse-phase high-performance liquid chromatography should be developed and used to assess the presence of leachables in therapeutic protein products~~ conduct a comprehensive extractables and leachables laboratory assessment using multiple analytical techniques to assess the quality of the container-closure system.
Lines 748-750:	BIO believes that stability studies should be conducted in all cases regardless of the container/closure configuration (vials, cartridges, syringes, etc.) utilized for the product.	BIO recommends revising to read: "Products ~~formulated in prefilled syringes~~ in their intended primary packaging container-closure system should be tested for stability in protocols that include appropriate in-use conditions ~~(e.g., light and temperature)~~ to identify potential causes of ~~conditions and practices that cause~~ product degradation."
Lines 765-766:	BIO believes the two previous sentences (regarding approved patient labeling instructions and storage temperatures) are sufficient to ensure product quality and patient safety. Additionally, this sentence could negatively impact many legacy products that have switched from cold chain shipping to room temperature (RT)	BIO recommends revising to read: "~~Cold chain security should be ensured.~~"

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	storage and transport for Drug & Biologic products.	
VI. APPENDIX		
A. DIAGNOSIS OF ANAPHYLAXIS		
Lines 1049-1057:	The Clinical and Laboratory Standards Institute (CLSI) has published an approved guidance document on Immunoglobulin E (IgE) measurements specific for therapeutic proteins.[14]	BIO requests that FDA cite and discuss the CLSI reference document *Design and Validation of Immunoassays for Assessment of Human Allergenicity of New Biotherapeutic Drugs*.
B. CYTOKINE RELEASE SYNDROME		
Lines 1103-1138:	Cytokine release syndrome generally occurs in response to the first dose of a monoclonal antibody with no pre-exposure by the patient to the relevant product. However, the discussion in this section, as well as the references included, focuses solely on cytokine release caused by the formation of ADAs, which occur with repeated exposure to a monoclonal antibody. It is generally not known whether the mechanism of cytokine release is the same in these two scenarios.	BIO requests that FDA address the different causes of cytokine release syndrome, which may require Sponsors to employ different assay setups and different assay readouts.
C. ANTIBODY RESPONSES TO THERAPEUTIC PROTEINS		
Lines:	Some patients continue to have low levels of antibodies for many years; therefore, it	BIO recommends that FDA specify a risk-adjusted length of time (BIO suggests 6 months to 1 year, depending upon

[14] Hamilton RG, et al (2011) *Design and Validation of Immunoassays for Assessment of Human Allergenicity of New Biotherapeutic Drugs; Approved Guideline, I/LA34AE.* Clinical and Laboratory Standards Institute.

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	may be unrealistic to serially follow them until their levels return to baseline.	product class and risk factors) to follow subjects that are antibody positive in cases where they never return to baseline.
D. UTILITY OF ANIMAL STUDIES		
Lines 1248-1249:	Please see comment above for lines 175-182.	BIO recommends revising to read: "~~As in human studies, consideration should be given to the potential transmission of antibodies to developing neonates by breast milk,~~"
E. COMPARATIVE IMMUNOGENICITY STUDIES		
Lines 1265-1269:	It is unclear which specific factors (or their relative importance) Sponsors should consider when assessing whether the clinical consequence of a manufacturing change has the potential to be "severe."	BIO recommends that FDA more thoroughly identify the factors that Sponsors should consider when assessing whether the clinical consequence of a manufacturing change has the potential to be "severe."