Biotechnology Industry Organization

May 9, 2013

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

Re: Docket No. FDA–2013–D–0576: Draft Guidance for Industry on Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products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Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the "Draft Guidance for Industry on Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products."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:

BIO commends FDA on the release of this Draft Guidance, which will help to increase the efficiency of early clinical research for, and ultimately facilitate the development of, cellular and gene therapy (CGT) products. In general, the Draft Guidance is very well written and provides a useful review of the numerous factors to consider during the design of early-phase trials for CGT products.

Because many CGT products currently in development target rare diseases, BIO believes that it would be beneficial for FDA to cross-reference, where possible, appropriate guidance documents that address considerations for developing therapeutic products for indications with limited patient populations. BIO would also welcome in the Draft Guidance a discussion of FDA's views on any unique considerations for CGT products that target rare diseases.

CONCLUSION:

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BIO appreciates this opportunity to comment on the "Draft Guidance for Industry on Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products."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)

SPECIFIC COMMENTS

SECTION	ISSUE	PROPOSED CHANGE
IV. CLINICAL TRIAL DESIGN		
Pages 6-18:	In Section III of the draft guidance, features of cell therapies (CT) or gene therapies (GT) that uniquely influence clinical trial design are outlined separately. In Section IV, however, the trial designs for these classes were melded together. BIO believes that separate discussion of these classes, as was done in the recent draft *Guidance for Industry on Preclinical Assessment of Investigational Cellular and Gene Therapy Products*, would add clarity to this guidance.	BIO suggests that FDA offer separate discussion of unique clinical trial design considerations for cell therapies and gene therapies in this section of the guidance, in order to provide more clarity for developers working in those specific areas.
B. CHOOSING A STUDY POPULATION		
Page 7:	BIO believes that FDA should include the option to offer justifications of when particular biomarkers may not be appropriate or potentially unable to be measured. BIO believes these justifications would be product-dependent.	BIO recommends that FDA revise to read: "For example, a biomarker that may be indicative of risk or benefit might be more sensitive, meaningful, or interpretable in one population versus another. Conversely, some established biomarkers may be less sensitive, meaningful, or interpretable, and in these cases, Sponsors may then offer justification of when biomarkers may not be appropriate or informative."
Page 8-9:	BIO believes that initial studies may offer an opportunity to develop an "all comers" type of protocol, wherein Sponsors may investigate various indications (*e.g.*, tumor	While BIO agrees with FDA's interpretation that the target population does not need to be that with the most advanced state of disease, BIO also believes the opportunity to develop an "all comers" type of protocol may

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	types). BIO therefore believes this approach may offer an opportunity to expand the potential clinical knowledge for future later stage trials.	enable Sponsors to expand the potential clinical knowledge for future later stage trials. BIO recommends, therefore, that FDA include an additional section to provide guidance on the design and conduct of "all comers" types of protocols, particularly in the context of oncology.
D. DOSE SELECTION		
Pages 11-12:	BIO believes that expanding the section on dose selection to include more discussion on factors to consider when selecting the starting dose [*e.g.,* safety margin below No Observed Adverse Effect Level (NOAEL), Minimal Erythema Dose (MED), *etc.*] and dose escalation scheme would add value to the guidance. As suggested above, separate discussion of cell therapy and gene therapy product specific issues in starting dose selection would contribute to document clarity and flow. Considerations to highlight include impact of immune response on potential for product re-administration to study subject, manufacturing constraints (*e.g.,* variability in yield, transduction efficiency, *etc.*).	BIO requests that FDA expand the section on setting a starting dose to include discussion of factors to consider when selecting the starting dose [*e.g.,* safety margin below No Observed Adverse Effect Level (NOAEL), Minimal Erythema Dose (MED), *etc.*] and dose escalation scheme. Distinction between CT and GT-specific considerations, with examples that highlight various aspects of these complex therapies which warrant considerations different from those used for small molecule drugs (*e.g.,* potential for re-administration, manufacturing variability, *etc.*) should be included.
E. TREATMENT PLAN		
Page 12:	The draft guidance states, "Many CGT products can persist in the subject or have an extended duration of activity, so that repeated dosing might not be an	BIO requests that FDA provide an additional section with preliminary guidance on re-dosing viral vector-based gene therapies, particularly on issues related to immunogenicity.

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	acceptable risk until there is a preliminary understanding of the product's toxicity and duration of activity. Therefore, most first-in-human CGT trials use a single administration or one-time dosing regimen." However, BIO believes that guidance on re-dosing viral vector-based gene therapies, particularly on issues related to immunogenicity, would be valuable to Sponsors.	
F. MONITORING AND FOLLOW-UP		
Page 16:	The second bullet point introduces the need to evaluate "the potential for viral shedding," yet cites the 2006 *Guidance for Industry: Supplemental Guidance on Testing for Replication Competent Retrovirus in Retroviral Vector Based Gene Therapy Products and During Follow-up of Patients in Clinical Trials Using Retroviral Vectors*, which does not provide guidance on monitoring viral shedding BIO believes that guidance on the design and timing of shedding studies would be useful for Sponsors.	BIO suggests that FDA remove the current citation and requests that FDA develop guidance on the design and timing of shedding studies for viral GT products.
Page 16:	FDA has developed clear guidance on determining need for and design of long-term follow-up for GT products. BIO believes that the addition of similar clear	BIO requests that FDA provide guidance on long-term follow-up for CT products. Recommendations should include criteria for evaluating CT products to determine the need for long-term follow-up as well as guidance on observation

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	criteria for determining the need for and design of long-term follow-up for CT products would provide additional clarity to Sponsors.	elements, frequency and study duration.
Page 17:	The second paragraph states that long-term follow-up should be part of the original proof-of-concept trial. However, due to the logistics of carrying a proof-of-concept trial protocol forward for up to 5 years, BIO requests that Sponsors retain the option of setting up separate trial protocols for long-term follow-up. In addition, the terms "monitoring" and "follow-up" are used seemingly interchangeably in the paragraph. BIO suggests revising to avoid any confusion associated with the varying terms.	BIO recommends FDA revise to read: "~~Sponsors sometimes propose to have one protocol for a CGT study of safety or efficacy, and a separate protocol for long-term monitoring. However, long-term follow-up is sometimes necessary for the trial to have an acceptable balance of risks and benefits. In that case, long-term monitoring should be included as an integral part of the CGT trial, and not designed as a separate protocol.~~ Long-term follow up can be included as part of the original proof-of-concept trial – in the same protocol or designed as a separate protocol."