December 10, 2018

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

Re: Docket No. FDA-2018-D-2173: Long Term Follow-Up After Administration of Human Gene Therapy Products; Draft Guidance for Industry

Submitted via www.regulations.gov

Dear Sir/Madam:

Biocom is the largest, most experienced leader and advocate for California's life science sector, which includes biotechnology, pharmaceutical, medical device, genomics and diagnostics companies of all sizes, as well as research universities and institutes, clinical research organizations, investors and service providers. With more than 1,100 members dedicated to improving health and quality of life, Biocom drives public policy initiatives to positively influence the state's life science community in the research, development, and delivery of innovative products.

In our mission of providing feedback and communication between regulators and industry, we are writing in response to the Food and Drug Administration's (FDA) request for comments on the draft guidance entitled "Long Term Follow-Up After Administration of Human Gene Therapy Products" (the "LTFU Draft Guidance" or "Draft Guidance").

Biocom commends the agency on its efforts to develop a comprehensive gene therapy framework to spur innovation and access to potentially life-saving treatments while ensuring safety and efficacy. Biocom supports the Agency's decision to issue this important Draft Guidance as it will aid gene therapy ("GT") product sponsors with their understanding of the scientific, medical, and legal issues they may face during the FDA gene therapy product development and review process.

In an effort to enhance the LTFU Draft Guidance before FDA finalizes it, we offer comments on specific sections of the LTFU Draft Guidance. Please find below an executive summary highlighting our core observations, followed by chronological section-by-section comments.

Executive Summary

- **Continuity**: LTFU studies require an extremely long commitment from both investigators and subjects. Patients may decide they do not want to continue further with an LTFU study or investigators are unable to follow-up with patients. Investigators may also decide to change institutions or retire. Additionally, changes in healthcare providers over the span of 15 years can lead to inconsistent subject outcomes reporting. Biocom recommends the agency explain how this may impact the sponsor's legal requirement to conduct a LTFU study and provide further clarification of a sponsor's commitments in these specific scenarios.

- **Clarity**: Biocom recommends the agency to provide more clarity on several key terms in the guidance. We recommend that FDA distinguish "transient" gene expression from "permanent" gene expression more clearly, as those terms impact whether or not an adverse event is considered "delayed." In FDA's discussion of "genome editing activity" on Page 3, we recommend that FDA distinguish whether the agency is referring to an *intentional* gene editing process or result (*e.g.*, CRISPR), or whether it is referring to an *unintentional* result of a gene therapy protocol. Lastly, FDA provides examples of what it considers to be a "similar GT product." However, the examples listed fall short of providing clarity about the level of and criteria for similarity.

- **Study Design & Considerations**: Biocom asks that the agency provide a discussion of what FDA considers to be the appropriate time points and/or milestones during development that should prompt sponsors to seek FDA guidance on the need for LTFU studies and how they should be designed.

Section-by-Section Comments

I. Introduction

- We recommend that FDA clearly state in the Introduction that LTFU studies can occur either as part of a Phase 3 clinical trial or a Phase 4 post-marketing requirement. The LTFU Draft Guidance states this element later in the document, but discussion in the introduction would provide sponsors with clarity when reviewing the sections that follow.

- FDA notes later in the Guidance (Section III.B., Page 4) that an LTFU study could extend as long as 15 years. We recommend raising this issue in the introduction so that sponsors are alerted early in the guidance document about the time period for LTFU studies that is at stake.

- We also recommend that FDA include examples of the types of technologies in addition to gene therapy mediated by viral vectors that fall within the scope of the LTFU Draft Guidance in the Introduction section. These examples will facilitate sponsor understanding regarding the scope and applicability of the Guidance to a sponsor's development program.

II. Scope

- We recommend that FDA distinguish "transient" gene expression from "permanent" gene expression more clearly, as those terms impact whether or not an adverse event is considered "delayed." Some genes may be functional for a lifetime, while others may not be. However, it is not clear that an event occurring at year 14 of a 15-year LTFU study, for example, should be treated any differently than an event occurring at year 16 post-treatment (*i.e.,* one year following completion of a 15-year LTFU study) when deciding whether that event does or does not require adverse event reporting to the agency.

III. Background

- (Page 3) In FDA's discussion of "genome editing activity" on Page 3, we recommend that FDA distinguish whether the agency is referring to an *intentional* gene editing process or result (*e.g.,* CRISPR), or whether it is referring to an *unintentional* result of a gene therapy protocol. Some genome editing is performed deliberately or intentionally to produce a therapeutic result, while some genome editing/genetic modifications may occur unintentionally if a gene therapy product integrates at multiple places in the genome, for example. Therefore, we recommend that FDA be clear here and throughout the Guidance when discussing "genome editing activity" as to whether the agency is referring to an intentional activity or an unintentional event.

- (Page 4) It is important for the FDA to clarify what is meant by "off-target changes in the genome." If the off target changes are referring to a safety issue, it would be of value to summarize what may be anticipated from off-target gene expression and it is determined.

IV. Preclinical Data Used for Assessment of Delayed Risks in Gene Therapy Clinical Trials

- (Page 5) It is not clear whether FDA intends to meet with sponsors to help sponsors assess (and reassess) the risk of delayed adverse events and to offer guidance on this matter. If so, we recommend that FDA clarify whether there are particular time points during the development process when such a meeting would be encouraged to take place (*e.g.,* end of phase ("EOP") 2 or pre-biological license application (BLA)).

- (Page 5) There may be occasions when sponsors may not be able to follow-up with study subjects, particularly if a LTFU study was not initially required but the sponsor's continuous risk assessment indicates that such a study should be initiated later. The sponsor may not be able to remain in contact with the subject at the end of the Phase 3 trial, for example, or a subject may not want to be further followed (because they assumed that their study participation was completed for example). In any of these cases, FDA should clarify how such an event will impact the sponsor's legal requirement to conduct a LTFU study.

- (Page 6, Figure 1) The framework set forth in Figure 1 is a valuable decision-making tool. However, Question 1 should be clarified to convey that, in this case, FDA is referring to *intentional* genome-editing technology and not *unintentional* gene editing effect. For example, Question 1 may be reworded as: "Does your GT product utilize intentional genome-editing technology?"

- (Page 6, Figure 1 and Footnote 1) It is not clear how Question 4 differs from Question 1. Moreover, neither Footnote 1 on Page 6 nor the discussion on Page 7 clarifies the issue. It appears that there would be overlap in these questions. For example, we interpret the integration of a vector sequence (Question 4) as also referring, in part, to genome-editing technology (Question 1). Furthermore, it is unclear how genome-editing technology, a product that "may integrate," and a product that "was intentionally designed to facilitate integration" are the same or different. As a result, we recommend additional clarification about how Questions 1 and 4 differ.

- (Page 8) FDA provides examples of what it considers to be a "similar GT product." However, the examples listed fall short of providing clarity about the level of and criteria for similarity. To illustrate, with respect to example 1, different coding sequences for the therapeutic gene product may or may not be impactful once the gene is translated into a protein. Furthermore, similar sequences can produce different results depending upon the locus of insertion of the gene. It is also not clear how "similar" the plasmid must be to be considered a "similar GT product." Additional clarity on these points is welcomed.

- (Page 8) We suggest that the FDA provide more details related to the lack of requirement to assess LTFU. It will be important for the inserted gene to be expressed for a specified duration to assess safety.

- (Page 9) We are concerned that, if clinical hold is a possibility when FDA disagrees with a sponsor's assessment of the need for an LTFU study, most sponsors may automatically plan for an LTFU study and let FDA decide whether or not such a study is required. This approach does not take into account the additional time and resources that both sponsors and FDA will need to invest – even in marginal cases where the need for an LTFU study is not clear. We hope that FDA will comment on whether it believes this will be the case, as well as how sponsors can most appropriately address the need for an LTFU with FDA well in advance of any contemplated LTFU study submission.

- (Page 9) As an example of evidence that may warrant an LTFU study for delayed adverse events, FDA lists a preclinical toxicology study showing that gene expression is associated with delayed toxicity. It is not clear how long FDA envisions that such a pre-clinical toxicology study should be conducted to identify "delayed" toxicity. It is also unclear if FDA expects that the pre-clinical toxicology study will need to last for a longer period of time than would otherwise be necessary in a traditional pre-clinical toxicology study so that a potential "delayed" effect can be identified.

- (Page 9) The third and fourth bullet points on Page 9 reference "data collected in a clinical study." However, this Section IV of the Guidance addresses pre-clinical studies. These bullet points therefore appear to be misplaced in the Preclinical section. Alternatively, FDA should clarify why they are listed here.

- (Page 9) We recommend that FDA provide a general range for the length of time for the pre-clinical pharmacokinetic/toxicology studies that it will require, instead of stating "the duration of the preclinical studies will vary depending on the animal model employed." While we understand that the period of time will vary, it is unclear if FDA envisions a six-month period, a one-year period, or even longer.

- (Page 10) To determine the design of the toxicology studies, the FDA should include appropriate end points, such as an evaluation of the gene product(s).

- (Page 11) FDA states that it encourages sponsors to discuss the study design for a GT product with Office of Tissues and Advanced Therapies (OTAT). It would be beneficial for FDA to clarify when it expects such discussions to take place (*e.g.,* during a pre-investigational new drug (IND) meeting).

- (Page 12) It is suggested that a qualification of the LTFU studies include an evaluation of a gene that is not integrated into the genome and therefore not functional. If the gene is not integrated in the genome, or if the mechanism has not been determined, the FDA should provide clear criteria for what delayed adverse events the sponsor should be responsible for.

- (Page 13) We encourage FDA to include a separate discussion in the Guidance of what FDA considers to be the appropriate time points and/or milestones during development that should prompt sponsors to seek FDA guidance on the need for LTFU studies and how they should be designed. For example, sponsors would find it beneficial if FDA stated whether these consultations should occur in the form of a pre-IND, EOP2, or pre-BLA meeting, or if OTAT is open to other less formal dialogue and correspondence outside of the formal meeting context to answer specific sponsor questions.

- (Page 15) We also suggest that a quantitative polymerase chain reaction (qPCR) evaluation be included to determine the site of insertion of the gene and the potential impact of linkage to potentially harmful adjacent genes.

V. Recommendations for Protocols for Long Term Follow-Up Observations: Clinical Considerations

- (Page 15) FDA states that LTFU observations are typically conducted under an LTFU protocol that is "separate from the main study protocol." FDA should address why this is the case, and whether a sponsor can integrate an LTFU protocol into the main protocol as an extension of the main protocol study. If a sponsor has already concluded that an LTFU study will be required, that sponsor may want to eliminate a separate Institutional Review Board (IRB) approval that may delay the investigation.

- (Page 16) As FDA acknowledges, LTFU observations may have reduced utility in certain cases, including when there remains a short life expectancy even after GT treatment. Therefore, if a GT product is intended to treat a disease or condition that will not dramatically increase the life expectancy of patients, it is not clear if FDA will still require an LTFU study – particularly if the typical LTFU study lasts anywhere from 5-15 years. If an LTFU study is still required, then we recommend that FDA clarify if there will be a particular expected duration, or if the decision will be made on a case-by-case basis.

- (Page 16) FDA states that its current recommendations for duration of an LTFU study are 5 or 15 years. Page 4 of the Guidance notes that, in 2006, FDA had recommended these 5/15 year periods. However, no rationale is provided in the LTFU Draft

Guidance. We therefore recommend that FDA provide its rationale for selecting 5/15 years as its general recommendation.

- (Page 17) FDA states that amendments can be submitted to INDs. However, as FDA states in the Guidance, some of these LTFU studies can persist past BLA approval into Phase 4. Therefore, FDA should clarify here (and throughout the Guidance, where appropriate) that amendments may be required to either the sponsor's IND or BLA.

- (Page 17) In general, Section V.D. assumes a number of parameters, which FDA may not have considered, that will make LTFU observations potentially very different for both study subjects and sponsors. First, an LTFU study requires an extremely long commitment from both investigators and subjects. It is not at all clear that either investigators or subjects will be willing to participate for this lengthy period of time. Subjects may wish to be done with their formal study commitments and withdraw their informed consent, and investigators may change institutions or retire. Second, subjects may change their healthcare providers ("HCPs") several times over the LTFU study period, making consistency of subject outcomes reporting potentially difficult to achieve. Although there may be scientific and medical reasons for a sponsor to provide LTFU data for up to 15 years after treatment, it is clear that sponsors will actually be able to obtain data over this time period. We therefore recommend that FDA consider these points and provide further clarification of a sponsor's commitments in these specific scenarios.

- (Page 19) In point 1.a., FDA states that it recommends identification of "suitable HCPs" in the LTFU protocol. FDA should clarify whether it is expecting names of particular physicians, or rather broad categories of HCPs (*e.g.*, primary care physician; oncologist). Providing specific names will prove difficult if not impossible because of changes in HCPs. Moreover, LTFU protocols could require constant updating and FDA notification. It is not clear if FDA intends that its recommendations have these potential impacts.

- (Page 21) We recommend that FDA acknowledge that subjects may withdraw their informed consent at any time, making it more difficult to complete an LTFU study as the period of time required by FDA increases (*e.g.*, 5 years vs. 15 years). We further recommend that FDA state whether it will modify its expectations for completion of, or release sponsors from their commitment to complete, LTFU studies if they become impossible for the various reasons noted above.

- (Page 23) FDA states in point c. that the sponsor should test for vector sequences for up to 15 years "or until such time that no vector sequences are detectable." FDA should clarify whether this vector sequence testing could extend even beyond the 15 year period discussed in this Guidance.

- (Page 24) Point 2 states that data reporting should be done via submission of an annual report to an IND. However, because an LTFU study can extend post-approval into Phase 4, FDA should clarify that the reporting can be done to either the IND or the BLA.

- (Page 25) FDA provides a list of recommended information and language in the informed consent document for a study involving a retroviral vector. We would appreciate FDA acknowledgment that an IRB may request or require different phrasing or different elements in the informed consent document for such a study, and that sponsors will not be bound by the suggested information and language.

VI. General Considerations for Post-Marketing Monitoring Plans for Gene Therapy Products

- (Page 26) FDA states that it recommends that a BLA submission include a pharmacovigilance plan ("PVP") for continuing LTFU observations. We recommend that FDA clarify whether an LTFU protocol that extends into Phase 4 can be used as the basis for, or converted into, a PVP. As written, it is not clear whether FDA considers a PVP to be an obligation in addition to and ongoing LTFU study, or whether ongoing LTFU studies are one element of a PVP.

VII. Long Term Follow-Up Under Special Circumstances

- (Page 27) In general, we recommend that FDA address in this section other possible "special circumstances" that could occur during the pre-approval/IND period or during the post-approval/BLA period. For example, a clinical investigator may no longer be available or wish to participate for an extended period of time to complete an LTFU study; moreover, study subjects may become unavailable, refuse to participate in the entire LTFU study period, or withdraw their informed consent. These additional types of special circumstances may occur even after BLA approval, and FDA should note these possible situations here and how FDA will help sponsors address them.

Appendices

- (Page 32, Appendix 1) We recommend that FDA clarify whether the reference to "annual report" refers to an IND annual report, a BLA annual report, or both. Moreover, if the information required in either annual report differs, we recommend that FDA be specific and clear about how the information differs.

Thank you again for the opportunity to provide these comments. We look forward to a continued dialogue with the FDA on the development of the gene therapy framework. If you have any questions about these comments, please contact Brittany Blocker, Manager of Regulatory Affairs at bblocker@biocom.org.

Sincerely,

Joe Panetta
President and CEO
Biocom