



December 10, 2018

Peter Marks, M.D., Ph.D.
Director
Center for Biologics Evaluation and Research
U.S. Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

Sent electronically

Re: Docket No. FDA-2018-D-2173: Draft Guidance on Long-Term Follow-Up After Administration of Human Gene Therapy Products

Dear Dr. Marks:

The Personalized Medicine Coalition (PMC), a multi-stakeholder group comprising more than 230 institutions and individuals across the health care spectrum, appreciates the opportunity to submit comments on the Food and Drug Administration (FDA)'s draft guidance titled *Long Term Follow-Up After Administration of Human Gene Therapy Products*.ⁱ

We applaud the agency's effort with this draft guidance to establish regulatory approaches suitable for an era in which biopharmaceutical companies are increasingly developing therapies that can treat disease in just a few doses by permanently changing the genes in patients' own cells. These gene therapies pose different challenges than traditional treatment approaches, most of which are effective only when they are administered on an ongoing basis. With some minor modifications, we believe this guidance will be better able to assist industry sponsors in developing human gene therapy products and determining their long-term follow-up strategies after gene therapy administration.

PMC and its members recognize personalized medicine as a rapidly evolving field that uses diagnostic tools to identify specific biological markers to help determine which interventions will be best for each patient. By combining this information with an individual's medical history, circumstances, and values, personalized medicine allows doctors and patients to develop targeted prevention and treatment plans.

Earlier this year, PMC released *Personalized Medicine at FDA: 2017 Progress Report*.ⁱⁱ This annual report documented a record number of new personalized medicine approvals by the agency, including the first three gene therapies to correct specific genetic disorders or modulate specific cellular reactions. These innovations

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resulted from groundbreaking scientific discoveries, industry's commitment to bringing novel products to market, and FDA's receptivity to evaluating new treatment approaches.

Some patients are fortunate to have access to approved gene therapies now, but many are not. A recent report estimates that there are nearly 300 cell and gene therapy products for a broad range of diseases in development.ⁱⁱⁱ We hope that FDA's continued work to refine a regulatory path for gene therapy products will provide more patients with the option when it is appropriate for treatment of their specific diseases or conditions in the future.

Statement of Neutrality

Many of PMC's members will present their own responses to FDA and will actively advocate for those positions. PMC's comments are designed to provide feedback so that the general concept of personalized medicine can advance, and are not intended to impact adversely the ability of individual PMC members, alone or in combination, to pursue separate comments on the *Long Term Follow-Up After Administration of Human Gene Therapy Products* draft guidance for industry or other associated documents.

Overall, we agree with the direction of this draft guidance and believe that it is consistent with what product sponsors and FDA have encountered in assessing the safety of gene therapy products. PMC respectfully asks FDA to consider the following comments as the agency finalizes this document.

I.) Future Applicability of Final Guidance

In the current environment, viral vectors are the most common tools used to deliver gene therapies. The draft guidance assumes that the delivery system for gene therapy products will continue to be viral vectors. We are therefore concerned that as non-viral delivery systems are developed, some topics in this draft guidance may not be applicable and the recommendations will be less useful for sponsors of gene therapies employing non-viral delivery systems. FDA should address how the final guidance would apply to gene therapy products with non-viral delivery systems. We would also suggest that FDA outline a plan for providing additional guidance as science advances and new gene therapy delivery tools are made available.

II.) General Characterization of Risk

Other stakeholders have expressed to FDA that this draft guidance may overstate the risk of gene therapy products by implying that long-term persistence of a gene therapy product inherently increases its safety risk. PMC agrees with their assessment. Section III of the draft guidance appropriately describes the primary rationale of gene therapy product development being the offering of therapeutic effect through permanent or long-acting changes in the human body. We believe the safety risks, however, will be different between a carrier and a protein encoded by a transgene.

The draft guidance would be improved if it highlighted the challenges associated with viral vector persistence and associated safety risks. In instances where a viral vector does not persist, a gene therapy's efficacy may wane, requiring the re-administration of the viral vector. This re-administration introduces the added risk of immune-mediated toxicities. Since repeated administration of a gene therapy product

that has limited persistence may result in a prolonged duration of exposure to a gene therapy product, it does not seem appropriate to emphasize the risk of the gene therapy product alone after a single administration.

The presence or absence of a genome in the viral vector through immune-mediated mechanisms could impact safety risks, and gene therapy products often utilize naturally occurring viruses. It is possible that safety concerns may be the result of an infection with a naturally occurring virus. It is likely that the long-term safety risks of a gene therapy viral vector are no greater than the safety risks posed by a naturally occurring infection with a source vector. PMC believes these important distinctions are worth noting in the final guidance.

III.) Flexibility of Long Term Follow-up Protocol

The draft guidance lays out recommendations for the duration of long-term follow-up periods based on product type and other elements detailed in Section VI of the document and PMC appreciates FDA's consideration of unique situations. FDA and product sponsors cannot anticipate all challenges posed by changes in individual patient circumstances over a 5 - 15-year follow-up period. In addition to allowing sponsors the flexibility to discuss with the agency individual clinical experiences and their need to adjust long-term follow-up protocols, PMC encourages FDA to work with individual sponsors on proposed follow-up periods for their products. We believe this approach will minimize the burden on patients and sponsors and ensure that the appropriate number of patients can be effectively tracked when lengthy follow-up timeframes are necessary.

Conclusion

Thank you for considering our comments. PMC welcomes the opportunity to serve as a resource to FDA as this guidance on gene therapy is finalized. If you have any questions about the content of this letter, please contact me at 202-589-1769 or cbens@personalizedmedicinecoalition.org.

Sincerely,



Cynthia A. Bens
Senior Vice President, Public Policy

ⁱ Food and Drug Administration. *Long Term Follow-Up After Administration of Human Gene Therapy Products. Draft Guidance for Industry*. July 2018
<https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM610797.pdf> Last accessed: December 5, 2018

ⁱⁱ Personalized Medicine Coalition. *Personalized Medicine at FDA Progress Report 2017*. January 30, 2018.
http://www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/PM_at_FDA_2017_Progress_Report.pdf Last accessed: December 5, 2018

ⁱⁱⁱ Pharmaceutical Researchers and Manufacturers of America. *Medicines in Development for Cell and Gene Therapy*. December 2018. http://phrma-docs.phrma.org/files/dmfile/MID_Cell_and_Gene_Therapy_2018_FINAL.pdf Last accessed: December 6, 2018