Waiver to Allow Participation in a Food and Drug Administration Advisory Committee

DATE: August 18, 2021

TO: Russell Fortney
Director, Advisory Committee Oversight and Management Staff
Office of the Chief Scientist

FROM: Prabhakara Atreya, Ph.D.
Director, Division of Scientific Advisors and Consultants
Center for Biologics, Evaluation, and Research (CBER)

Name of Advisory Committee Meeting member: **Barry Byrne, M.D., Ph.D.**

Committee: Cellular Tissue and Gene Therapies Advisory Committee (CTGTAC)

Meeting dates: September 2-3, 2021

Description of the Particular Matter to Which the Waiver Applies:

Dr. Barry Byrne, a special government employee, has been invited to participate in the September 2-3, 2021, CTGTAC meeting as a temporary voting member (TVM). The committee will meet in open session to discuss the evaluation of the toxicity risks in the context of vector design and quality, non-clinical and clinical studies, and the long-term monitoring of human recipients of adeno-associated virus (AAV) gene therapies. The committee will hear presentations and discuss topics on genotoxicity, hepatotoxicity, thrombotic microangiopathy, dorsal root ganglion (DRG) toxicity, and magnetic resonance imaging (MRI) findings in the brain.

The topic of this meeting is a particular matter of general applicability (PMGA). The CTGTAC will discuss more than one general scientific topic and many invited speakers from the field will give presentations. There is no specific sponsor, and no marketing application will be discussed. The discussion will not focus on approval, ongoing approval, or conditions of approval of any specific product, and it is a non-voting meeting. The particular matter will affect entities that make, or are seeking to make, AAV vector-based gene therapy products.

Type, Nature, and Magnitude of the Financial Interests:

Dr. Barry Byrne is the Director, Child Health Research Institute, Professor, Associate Chairman of the Department of Pediatrics at University of Florida (UF). He has several current and future personal and imputed financial interests related to the topic coming before the CTGTAC. Dr. Byrne is the principal investigator (PI) for (b) (4) The University of Florida has received between $1,500,000 to $2,000,000 to date for conducting this clinical trial and has estimated it will receive between approximately (b) (4) per year thereafter. The SGE receives no personal renumeration for the study.

Additionally, there are two pending clinical trials currently under negotiation by the University of Florida; the study period/dates and magnitude of funding to be received by the University of Florida are not available at this time:

(b) (4)

Additionally, Dr. Byrne is a paid consultant-advisor for three entities involving products that may be directly and predictably affected by the particular matter before the committee:

1. Advisor to (b) (4) regarding AAV gene therapy since January 2021. Payment: between $45,000 to $50,000
2. Member of (b) (4) Rare Disease Advisory Board since January 2021. Payment: between $10,000 to $15,000
3. Member of (b) (4) Scientific Advisory Board since January 2021. Payment: between $5,000 to $10,000

Finally, Dr. Byrne owns stock worth between $25,000 and $50,000 each of (b) (4) Each of these entities may be directly and predictably affected by the particular matter before the committee because they are developing, or funding the development of, AAV vector-based gene therapies.

Further, Dr. Byrne's conflicts of interest were made known to FDA on August 6, 2021, which is less than 30 days from the date of the CTGTAC meeting (see Dr. Byrne's signed FDA Form 3410). Accordingly, pursuant to 21 U.S.C. § 379d–1(c)(2), FDA is exempted from posting this waiver at least 15 days before the upcoming CTGTAC meeting (see 21 U.S.C. § 379d–1(c)(1)).

Basis for Granting the Waiver:

Dr. Barry Byrne has unique qualifications and specialized expertise needed for this particular matter.

Dr. Barry Byrne is a pediatric cardiologist and a leading scientist in the development of gene therapies for inherited muscle disease. He earned his B.S. in Chemistry from Denison University, and both his M.D. and Ph.D. in Microbiology from the University of Illinois. He completed his Residency in Pediatrics and Fellowship in Pediatric Cardiology at Johns Hopkins University. While at Johns Hopkins, he also was a Postdoctoral Fellow in Biological Chemistry. Dr. Byrne is the Associate Chair of Pediatrics and Director of the University of Florida Powell Center for Rare Disease Research and Therapy and the Earl and Christy Powell University Chair in Genetics. Dr. Byrne has made several key contributions to the field of gene therapy and has extensive knowledge, not only in the field of clinical development but also in the field of AAV vectorology, product development and manufacturing. His research focus is on conditions that lead to skeletal muscle weakness and abnormalities in heart and respiratory function. Over the years his group has made significant contributions to the understanding and treatment of neuromuscular diseases using AAV vectors. His group at the Powell Center has also established a series of new methods for large-scale AAV clinical manufacturing.

Dr Byrne's expertise is directly relevant to multiple sessions on AAV vector-associated toxicities to be held at this CTGTAC meeting. He has authored over 60 peer-reviewed original and review articles on AAV-based gene therapy. He has remained a key opinion leader in the field of gene therapy, as noted by recent reviews he has authored, notably, 'Considerations for the Systemic Use of Gene Therapy' [Mol Therapy (2021) 29:422], and 'Management of Neuroinflammatory Responses to AAV-Mediated Gene Therapies for Neurogenerative diseases' [Brain Science (2020) 10:119]. These reviews cover topics relevant to the anticipated discussions by the CTGTAC committee. Also, Dr. Byrne has served as the acting chair of the 67th CTGTAC meeting on October 12, 2017 to discuss the safety and efficacy of Biologics License Application (BLA) 125610, voretigene neparvovec, sponsored by Spark Therapeutics, for the treatment of patients with vision loss due to confirmed biallelic RPE65 mutation-associated retinal dystrophy. Voretigene neparvovec was a first-in-class product approval for an AAV-based gene therapy.

As a result, his expertise and depth of experience in this particular subject matter and his contribution to the committee's discussion, specifically on Day 2 of the meeting, is highly valued and greatly outweighs the above-described financial conflicts of interest, and his participation is in the interest of public health.

There is limited expertise available, and it is difficult to locate similarly qualified individuals without a disqualifying financial interest.

It has been challenging to identify similarly qualified clinician scientists without a disqualifying financial interest. This is because most academic scientists with the necessary level of expertise are also involved in product development, as these novel AAV vector-based gene therapy

products have shown promise especially in treatment of rare and life-threatening genetic disorders. Dr. Byrne's expertise is unique and given previous multiple recusals of invited participants for this meeting, it will not be possible to replace Dr. Byrne, especially given the short timeframe before the scheduled meeting date.

The particular matter is not sensitive.

The meeting topic for this session is not sensitive; however, the meeting may still receive significant public interest or (non-trade) press interest due to the discussions involving various toxicity risks noted in the preclinical and clinical studies, and the long-term monitoring of human recipients of AAV gene therapies.

Dr. Byrne's expertise in this particular matter is necessary in the interest of public health.

Dr. Byrne is an authority in the field of AAV vector gene therapy for treatment of rare, inherited diseases with both clinical experience in treatment of muscular dystrophies, as well as manufacturing and development of such therapies. Given his exceptional scientific and clinical background, his participation in this meeting will bring the benefit of his unique expertise that is critical to the CTGTAC's deliberations.

Any potential for a conflict of interest is greatly outweighed by the strong need for Dr. Byrne's expertise in this matter.

The strong need for Dr. Byrne's demonstrated expertise and diverse perspective that he can bring to this matter before the committee greatly outweighs any potential for a conflict of interest.

Accordingly, I recommend that you grant Dr. Barry Byrne, a temporary voting member of the Cellular Tissue and Gene Therapies Advisory Committee, a waiver from the conflict-of-interest prohibitions of 18 U.S.C. § 208(a).

Certification:

___✓___ The individual may participate, pursuant to 18 U.S.C. 208(b)(3) – The need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved.

Limitations on the Regular Government Employee's or Special Government Employee's Ability to Act:

_____ Non-voting

_____ Other (specify):

_____

_____

_____ Denied – The individual may not participate.

s

_____ August 31, 2021

Russell Fortney Date
Director, Advisory Committee Oversight and Management Staff
Office of the Chief Scientist