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

DATE: August 17, 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: **Roland Herzog, PhD.**

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. Roland Herzog, 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 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. No specific marketing applications 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. Herzog is a Professor of Pediatrics, Riley Children's Foundation Professor of Immunology, and Director of the Gene and Cell Therapy Program at the Indiana University, School of Medicine. He has several current related interests with NIH/NHLBI, NIH/NIAID, and (b) (4) for principal

investigator (PI) and consulting roles. The matter before the upcoming CTGTAC will have a direct and predictable effects on these interests. Dr. Herzog is the PI or Project Leader for unaffected entities NIH/NHLBI & NIH/NIAID. The NIH grants are as follows:

1. NIH/NHLBI - Grant R01 HL131093 (5/5/2021-04/30/2025)
   Topic: Focused on enhancing immune regulation in gene therapy for hemophilia,
   Magnitude: $1,000,000 -- $1,100,000 per year to Indiana University.

2. NIH/NHLBI - Grant 1 U54HL142012-01 (3/01/2018/-02/28/2023)
   Topic: Molecular and cellular mechanisms of the Factor VIII immune response
   Magnitude: $250,000 -- $300,000 per year to Indiana University.

3. NIH/NIAID - Grant R01 A151390 (12/01/2017-11/30/2022)
   Topic: Focused on Immunology of factor IX gene transfer to liver
   Magnitude: $350,000 -- $400,000 per year to Indiana University.

4. NIH/NHLBI - Grant R01 HL133191 (4/1/2017 -3/30/2022)
   Topic: Oral Tolerance for hemophilia
   Magnitude: $1,000,000 -- $1,100,000 per year to Indiana University.

Dr. Herzog also reported that he has been involved in a contract under negotiation with the affected entity (b) (4) regarding a consulting/advisor position pertaining to (b) (4) AAV gene transfer. An amount is not available with respect to the magnitude of the contract under negotiation.

Basis for Granting the Waiver:

Dr. Roland Herzog has unique qualifications and specialized expertise needed for this particular matter.

Dr. Herzog has a degree in biology from the University of Kaiserslautern, Germany, and received a Ph.D. in microbiology from Auburn University. He is a Professor of Pediatrics, Riley Children's Foundation Professor of Immunology, and Director of the Gene and Cell Therapy Program at the Indiana University, School of Medicine. He also serves as the editor-in-chief of the scientific journal *Molecular Therapy* and is on the board of the American Society of Gene and Cell Therapy, a leading scientific organization in the field of gene therapy. His long-standing research focus is on defining the mechanisms that drive immune responses to AAV vectors. He has experience in evaluating AAV vectors in both rodent and nonrodent species/models of disease such as hemophilia, which is germane to the discussion topic of this CTGTAC meeting. Dr. Herzog is an authority in the field of AAV vector immunobiology. He has authored several key reviews, with 50+ publications, on this topic within the context of AAV gene therapy development and immune-mediated toxicities. He has also participated in numerous conferences and workshops focused on this class of products over several years, more recently, for example, in the *Virtual Workshop on Systemic Immunogenicity Considerations for AAV-mediated Gene Therapy* at the National Institutes of Health in 2020. He has received numerous awards for his seminal research including awards from the American Society of Gene and Cell Therapy, the National Hemophilia Foundation, the Bayer Hemophilia Program, and the University of Florida Research Foundation.

Dr Herzog's expertise is directly relevant to multiple sessions on AAV vector associated toxicities to be held at this CTGTAC meeting because many of these toxicities are thought to be immune response-mediated. As the only AAV vector immunologist on the panel, he brings unique expertise to the committee and his participation would allow for comprehensive discussions on this topic so that the questions put forth by FDA in these sessions are addressed. As a result, his expertise in this particular subject matter and his contribution to the committee's discussion will be highly valued and is necessary 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 individuals without a disqualifying financial interest. This is because most academic scientists are involved in product development given that AAV vector-based gene therapy products show great promise in the clinic and the technology is rapidly developing towards translation. Dr. Herzog's expertise is very unique and given previous multiple recusals of invited participants for this meeting, it will not be possible to replace Dr. Herzog, 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. Herzog's expertise in this particular matter is necessary in the interest of public health.

Dr. Herzog is an authority in the field of AAV vector immunobiology with experience with different animal species/models of disease. Given his exceptional scientific and public health 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. Herzog's expertise in this matter.

The strong need for Dr. Herzog'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. Roland Herzog, 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):

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_____ Denied – The individual may not participate.

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Russell Fortney
Director, Advisory Committee Oversight and Management Staff
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