DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Silver Spring MD 20993

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

DATE: September 28, 2016

TO: Janice M. Soreth, M.D.
Associate Commissioner for Special Medical Programs (Acting)
Office of Medical Products and Tobacco
Office of the Commissioner, FDA

THROUGH: Michael F. Ortwerth, Ph.D.
Director, Advisory Committee Oversight and Management Staff
Office of Special Medical Programs

FROM: Danyiel D'Antonio
Acting Chief, Committee Management Branch
Division of Workforce Management, OM
Center for Devices and Radiological Health CDRH)

Name of Advisory Committee Member: Randall T. Hayden, M.D.

Committee: Microbiology Devices Panel of the Medical Devices Advisory Committee

Meeting date: November 9-10, 2016

Description of the Particular Matter to Which the Waiver Applies:

The Division of Microbiology Devices Panel will meet on November 9, 2016, to discuss and make recommendations on the reclassification of quantitative Cytomegalovirus (CMV) viral load assays from Class III (subject to Premarket Approval) to Class II (subject to General and Special Controls). A nucleic acid-based in vitro diagnostic device for the quantitation of CMV viral load, within the context of transplant patient management, is a post-amendment device classified into Class III under section 513(f)(1) of the Federal Food, Drug, and Cosmetic Act. To date, the following product code has been established for CMV viral load devices: PAB (Cytomegalovirus (CMV) DNA Quantitative Assay). This session of the meeting involves consideration of a particular matter of general applicability.

The use of CMV viral load measurements is chiefly for immunosuppressed patients following organ transplantation who are at risk for reactivation of latent infection or new onset primary infection by transmission through blood products. The overall benefit/risk of CMV viral load monitoring for transplant patients is well established and is the standard of care. Hence, it is not the topic for Panel deliberation. For the purpose of obtaining recommendations about possible reclassification, the Panel will be asked to discuss the types of evidence, including clinical evidence, which would be helpful to establish the appropriate controls necessary to mitigate the risks to health and assure the safety and effectiveness of new quantitative CMV viral load assays.

Type, Nature, and Magnitude of the Financial Interest(s):

Dr. Hayden is serving as a temporary non-voting member of the Microbiology Devices Panel. The Panel's function is to review and evaluate data concerning the safety and effectiveness of marketed and investigational *in vitro* devices for use in clinical laboratory medicine including microbiology, virology, and infectious disease, and make appropriate recommendations to the Commissioner of Food and Drugs. Dr. Hayden is Director of Clinical and Molecular Microbiology and Director of Pathology and Laboratory Medicine and International Outreach Program at St. Jude Children's Research Hospital in Memphis.

Dr. Hayden has provided advisory services to (b)(4) ., whose subsidiary (b)(4) , is an affected firm in the Panel's reclassification discussion of quantitative CMV viral load testing devices. Dr. Hayden participated in a June 2016 advisory board meeting for (b)(4) on the topic of the firm's new device platform for quantitative CMV viral load testing and problems of variability in CMV testing. He reported that the presentation he gave was focused on the subject of quantitative standards. It had more to do with the design of these quantitative standards materials than with the specific design of the (b)(4) assay or any other particular assay. Dr. Hayden received between $0 and $5,000 for his meeting participation. His agreement to attend the June 2016 meeting was covered by a 2-year contractual agreement ending May 2018.

Basis for Granting the Waiver:

There are very few U.S. scientists who have the in-depth expertise necessary for this meeting, i.e., knowledge of the clinical aspects of CMV infection as well as substantive knowledge of the laboratory methods for the measurement of CMV. For the purpose of reclassification, these knowledgeable experts are essential for the discussion of the benefit/risk of reclassification and potential mitigation of risks. How to address variability and non-commutability[1] across tests, and other concerns, through Special Controls, will be a significant aspect of the Committee discussion.

The relatively specialized area that is the subject of this meeting heightens the need for having experts supplement the standing Committee, as there are few standing members with such expertise. One major focus of discussion will be the use of standards as a factor in CMV reclassification. Both FDA-approved CMV viral load assays were developed independent of a

[1] Commutability is defined as equivalence of the mathematical relationships between the results of different measurement procedures for a reference material and for representative samples from healthy and diseased individuals. In practical terms, the property of commutability refers to the fact that a calibration material interacts with the test system in a manner similar to patient samples.

newly available WHO international standard. Although having a standard available would superficially appear to support reclassification, significant concerns still remain with commutability across assays. It is essential that the Committee have the relevant expertise on the Panel for discussion to be productive, as variability and non-commutability across tests is a major issue for reclassification.

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

Dr. Hayden earned his M.D. degree from the University of Illinois, College of Medicine. He is board-certified in anatomic and clinical pathology, with additional training and certification in medical microbiology. He is currently a member of the faculty of St. Jude's Children's Research Hospital. He is Director of Clinical and Molecular Microbiology, Director of the Pathology Quality Program, and also Director of the Laboratory Medicine Initiative, International Outreach Program. He is currently president-elect of the Pan-American Society for Clinical Virology and has held leadership positons in the Association for Molecular Pathology (past chair of the Infectious Diseases Subdivision). He is also a member of the College of American Pathologists Microbiology Resource Committee.

Dr. Hayden is an internationally recognized expert in the measurement of and the virologic aspects of CMV infection. He has over 50 peer-reviewed publications, including authorship of several chapters in well-recognized textbooks. He has published specifically on the evaluation of CMV measurements across different devices, and has recently published on the WHO international CMV standard, a subject of direct relevance to the meeting.

Dr. Hayden is essential for this Panel meeting because of his exceptional experience in the laboratory measurement of CMV, a critical aspect of the anticipated discussion. It would be impossible to replicate his knowledge and experience on the Panel.

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

As very few U.S. scientists have expertise in this area, it has been very difficult to locate individuals with the necessary expertise who are free of conflicts to attend this meeting. In the interest of public health, it is critical that Dr. Hayden participate to ensure fully-informed discussions and recommendations.

Furthermore, representatives of the Infectious Diseases Society of America published a position paper in early 2016 advocating reclassification. This led to a decision by agency management to exclude a number of individuals who might otherwise have been strongly considered for this meeting. The publication of this paper also led to exclusion of two standing Panel members, including the chairperson. These decisions had the effect of shrinking the pool of available experts even further.

In our Panel preparation process, we approached multiple individuals who have experience in these areas, but were unsuccessful in finding the range of expertise to match that of Dr. Hayden. Other possible Panelists with the relevant expertise who were contacted were ineligible due to financial conflicts or were unavailable due to scheduling conflicts. There is simply no other individual who could be found with Dr. Hayden's expertise for this particular meeting.

The particular matter is not sensitive.

The particular matter to be addressed by the Panel is not considered sensitive, as it will not change the standard of care for monitoring patients' CMV viral load post-transplantation. The subject of the meeting is whether these devices can be reclassified and Special Controls written, such that, these devices can safely be reclassified to Class II. The Panel discussion is very unlikely to affect current FDA recommendations for requiring clinical studies. FDA policy has evolved significantly since the first approval of a CMV viral load diagnostic test, and this policy is unlikely to be significantly affected by the discussion, as validation studies are likely to be required regardless of whether the regulatory pathway is Class III (subject to Premarket Approval) or Class II (subject to General and Special Controls). The particular matter to be discussed by the Panel may have an impact on the current market, as reclassification may encourage additional manufacturers to enter this market.

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

Dr. Hayden has an ongoing contractual relationship with (b)(4)., regarding quantitative CMV viral load testing and the problems of variability across sites when measuring CMV. (b)(4) has an approved CMV viral load measurement device and a device under development. This is a general, well-known issue and is relevant to all products within the affected class. Any potential conflict of interest created by this consultation is greatly outweighed by the need for Dr. Hayden's expertise in a field where such expertise is limited but imperative to the success of this particular matter.

Accordingly, I recommend that you grant a waiver for Dr. Randall T. Hayden, a temporary non-voting member of the Microbiology Devices Panel, from the conflict of interest prohibitions of 18 U.S.C. § 208(a).

Certification:

___X____ 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/_____ October 21, 2016

Janice M. Soreth, M.D. Date

Associate Commissioner for Special Medical Programs (Acting)

Office of Medical Products and Tobacco

Office of the Commissioner, FDA