



## 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: Michael G. Ison, M.D., M.S.

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 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. Ison 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. Ison's (b) (4) [REDACTED], has a (b)(4) [REDACTED] (b)(4) [REDACTED] to study a (b)(4) [REDACTED] device, which is indicated for quantitative Cytomegalovirus (CMV) viral load detection in transplant patients. (b)(4) [REDACTED] is an affected entity for this meeting because their device is part of the class of devices under discussion by the Panel. Dr. Ison is Associate Professor of Medicine in the Department of Surgery, Division of Organ Transplantation. If the study goes forward, Dr. Ison will be the principal investigator. He will receive no remuneration for this work other than his university salary. It is estimated (b) (4) [REDACTED] (b) (4) [REDACTED] which will be the awardee, will receive between \$0 and \$50,000. The time period of the study will be 2016 to 2017.

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<sup>1</sup> 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 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

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<sup>1</sup> 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.

Panel for discussion to be productive, as variability and non-commutability across tests is a major issue for reclassification.

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

Dr. Ison received his M.D. degree from the University of South Florida, College of Medicine, and an M.S. degree in health evaluation sciences from the University of Virginia. He is currently Associate Professor in the Divisions of Infectious Diseases and Organ Transplantation at the Northwestern University Feinberg School of Medicine. He is currently the Medical Director of the Transplant & Immunocompromised Host Infectious Diseases Service at the Northwestern University Comprehensive Transplant Center. His research is focused on viral infections, including CMV, norovirus, and respiratory viral infections in transplant patients.

Dr. Ison is a member of numerous professional societies, including the Infectious Diseases Society of America, the American Society of Transplantation, the American Society of Microbiology, and the International Society for Influenza and Other Respiratory Virus Diseases. He serves on FDA's Center for Biologics Evaluation and Research Cellular Tissue and Gene Therapies Advisory Committee. Dr. Ison is an internationally-recognized expert in transplant infectious disease with over 100 peer-reviewed publications, and participation in numerous cooperative clinical trials.

Dr. Ison is being sought for participation in this Panel meeting because of his extensive experience in CMV infection and the additional viral infections to be discussed at the meeting. His expertise is amply demonstrated by the exceptional number of publications he has authored or co-authored in transplant infectious diseases, as well as his leadership position at Northwestern University. His unique experience and expertise in both clinical and laboratory aspects of CMV make him critically important for this meeting.

*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 free of conflicts to attend this meeting. In the interest of public health, it is critical that Dr. Ison 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 further 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. Ison. 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 that could be found to replace Dr. Ison'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. Ison's expertise in this matter.*

Dr. Ison's institution is negotiating for participation as part of a large, multicenter study, creating an imputed interest for him.

Because few U.S. scientists have expertise in this area, it is not uncommon that device manufacturers seek out the same experts for conducting studies for CMV diagnostics that FDA would seek for the upcoming Panel meeting. Although investigators participating in large, multicenter clinical studies are evaluating safety and efficacy of these devices for FDA submission, the committee discussion is very unlikely to affect current FDA recommendations for clinical studies. FDA policy has evolved significantly since the first approval of a CMV viral load diagnostic, and this policy is unlikely to be significantly affected by the discussion, as similar validation studies are likely to be required regardless of a Class II or Class III classification status (although in the former case these would be mandated by Special Controls). It should be noted that these studies are often blinded, and even if not, would be extremely unlikely to influence the committee as CMV viral load monitoring is firmly established as the standard of care post-transplantation. This is a general, well known issue and is relevant to all products within the affected class.

Moreover, if the negotiations go forward, Dr. Ison will not receive any remuneration for the study being conducted at Northwestern University other than his salary from the university.

Therefore, any conflict of interest created by this interest is greatly outweighed by the need for Dr. Ison'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. Michael G. Ison, a temporary non-voting member of the Microbiology Devices Panel, from the conflict of interest prohibitions of 18 U.S.C. § 208(a).

