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Division of Dockets Management (HFA-305)
U.S. Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Docket No. FDA-2016-N-2880] Microbiology Devices Panel of the Medical Devices Advisory Committee; Notice of Meeting; Establishment of a Public Docket; Request for Comments

Dear Sir/Madam:

On behalf of the Infectious Diseases Society of America (IDSAs) I write to thank the Food and Drug Administration (FDA) for scheduling a meeting of the Microbiology Devices Panel of the Medical Devices Advisory Committee Meeting to discuss reclassification of quantitative Cytomegalovirus (CMV) viral load devices from class III (Premarket approval or PMA) to class II (510(k)) and appropriate initial classification for qualitative or quantitative viral load devices for Epstein-Barr virus (EBV), BK virus (BK), JC virus (JCV), Human Herpesvirus 6 (HHV6), and Adenovirus infections. IDSAs greatly appreciates this opportunity to provide comments. We urge the FDA to classify viral load tests for these transplant associated viruses as Class II.

Over the past several years, IDSAs has stressed the importance of innovative diagnostic devices for the care of patients at risk for or suffering from infectious diseases (ID), including in our 2013 report, [Better Tests, Better Care: Improved Diagnostics for Infectious Diseases](#). Patients who receive solid organ, bone marrow or stem cell transplants are at greatly heightened risk of opportunistic viral infections, which can significantly complicate their clinical course. Viral load tests are critically important for managing these patients and providing them with the highest quality care possible. These tests provide invaluable information to allow for accurate diagnosis and monitoring of infections for transplant recipients.

IDSAs asserts that categorizing these viral load tests as high risk, as is currently the case for CMV viral load devices, is inappropriate and can limit the availability of these tests for patients who need them as well as testing innovation in this area. We encourage the FDA to reclassify CMV viral load devices to class II and to classify viral load tests for the other pathogens under consideration as class II as well.

Viral load tests for transplant viruses: routinely used, well supported by literature, risks easily mitigated

The management of the infections at issue has become routine for transplant specialists. Viral load tests for transplant associated viruses have been in use for many years by clinical laboratories, with well-documented data demonstrating clinical validity and peer reviewed literature supporting their use. The standardization of assays and clinical care for patients with transplant-related viruses has allowed for the establishment of strong expert guidelines for testing and managing these patients. Managing patients post transplant with viral load test is the standard of care.

The risk associated with the use of transplant viral load tests is further mitigated by additional factors. First, patients are typically tested multiple times, with clinicians regularly reviewing results for consistency. In fact, FDA could even consider requiring such sequential monitoring of patients when these tests are used. Second, clinicians utilize several additional factors beyond an individual test result to guide and inform clinical decisions. For example, a clinician will assess pathology, radiology, patient history and other data in a clinical context in order to optimally manage a patient.

In May, IDSA provided the FDA a [selection of literature](#) on viral load testing for transplant-associated viruses under the panel's consideration. The literature clearly demonstrates that the use of these tests is widely accepted and contributes to improved patient outcomes. Further, the literature supports IDSA's assertion that these tests are used in combination with several factors which, placed in a clinical context, provide the basis for patient care decisions. This context of use further mitigates the risk associated with these tests.

Greater risk to patient care posed by Class III designation

IDSA also encourages the panel and FDA to consider the risks posed by classifying these tests as Class III or high risk—namely significantly diminished patient access to testing. A Class III designation requires test developers to submit a PMA for any new commercial test. There are currently only two FDA-approved tests for CMV on the market, and there are no FDA-approved tests for many of the other transplant-related viruses

One reason for the paucity of FDA approved devices for transplant monitoring is the requirement for commercial companies to seek approval through the PMA process. A PMA would require multi-million-dollar, multi-site clinical trials, and often many years to complete depending on the rarity of the target analyte. This regulatory process can result in costs that could equal or surpass research and development costs that alone can range from \$20 million to \$100 million per device. Additionally, the overall volume of transplant testing is limited, making the return on investment difficult to attain. A reclassification of transplant testing to Class II (510k clearance process) should lead to a significant reduction in clinical trial costs, faster time to market, and therefore encourage commercial companies to seek FDA clearance. More FDA cleared devices would give laboratories options when selecting the device best suited for their testing and clinical needs.

In addition, by classifying viral load tests for transplant associated viruses as Class II or moderate risk, the FDA can delay and lessen the disruption to care for transplant patients that the proposed laboratory developed test (LDT) regulatory guidance would be likely to otherwise cause.

Loss of transplant virus viral load testing = severe patient impact

BK polyomavirus is one key example of a transplant associated virus for which access to rapid viral load testing is critical. Currently there are no FDA-cleared or approved assays for BK virus on the market. BK is the major cause of polyomavirus-associated nephropathy, putting 1-15% of kidney transplant patients at risk of premature allograft failure. Given the lack of effective antiviral therapies, screening kidney transplant patients for BK in urine and blood is the key recommendation to guide the reduction of immunosuppression in patients with BK viremia. This approach allows for clearance of BK infection in 70-90% of patients. Late diagnosis is accompanied by irreversible functional decline, poor treatment response, and graft loss. Guidelines published in 2013 in the *American Journal of Transplantation* recommend that screening for BK replication be performed at least every three months during the first two years posttransplant and then annually until the fifth year posttransplant. Using this strategy, at least 80-90% of patients at risk for serious BK infection and related complications can be identified before significant problems arise.¹ If physicians lose access to tests for BK as a result of these tests being classified as high risk and coming under increased FDA oversight, there is significant risk that many cases of BK infection will not be identified promptly and will thus lead to negative patient outcomes.

Conclusion

Classifying viral load tests for transplant associated viruses as high risk requires new tests in this area to undergo a costly and burdensome PMA submission. Many of the current tests in this space are laboratory developed tests (LDTs). Under the FDA's proposed LDT regulation, high risk LDTs would be the first to face FDA regulation. The vast majority of clinical laboratories would very likely be unable to bear the enormous cost of a PMA submission. This would likely lead to a situation in which few local testing options would exist to guide the care of transplant patients. Classifying transplant viral load assays as Class II or moderate risk devices should increase the number of commercial tests submitted for FDA clearance and ensure availability of these tests. Given their longstanding use and significant supporting data, tests for transplant-related viruses do not pose a high risk to patients and should be classified as Class II or moderate risk tests.

IDSA greatly appreciates the opportunity to provide comments on this important issue, and looks forward to continued dialogue with the FDA to guide policymaking in this area.

Sincerely,



Johan S. Bakken, MD, PhD, FIDSA
President, IDSA

¹Hirsch HH, et. al. [BK Polyomavirus in Solid Organ Transplantation](#). *American Journal of Transplantation*. 2013; 13: 177-188.